UNIVERSIDADE DE LISBOA

Faculdade de Medicina de Lisboa

STUDIES ON THE IMPACT OF ASSISTIVE COMMUNICATION DEVICES ON THE QUALITY OF LIFE OF PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

Ana Rita Mendes Londral Gamboa

Orientador: Professor Doutor Mamede Alves de Carvalho
Co-Orientadores: Doutor Luis Manuel de Faria Azevedo
Professora Doutora Anabela Leuschner Pinto

Tese especialmente elaborada para obtenção do grau de
Doutor em Ciências Biomédicas (Neurociências)

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2016

Valeu a pena? Tudo vale a pena
Se a alma não é pequena.

Quem quere passar além do Bojador
Tem que passar além da dor.
Deus ao mar o perigo e o abismo deu,
Mas nele é que espelhou o céu.

Fernando Pessoa

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My process for developing this PhD thesis involved steps that were only possible due to the support of others, which I want to acknowledge.

I express my sincere gratitude to my supervisors. Dr. Mamede de Carvalho endorsed my research project since our first conversation. I thank him for giving me the opportunity to pursue this work in a faculty of Medicine, given my background in Engineering. His rigorous and constructive comments, his commitment with the supervision of my work, as well as his support and pragmatism made me go forward.

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My family and friends encouraged me and supported me everyday.

For my three daughters the time to fulfill this PhD thesis was almost a lifetime. I am grateful for their patience and love. For them, I daily learn to balance between home and work.

Hugo, with whom I share my choices, doubts, successes and errors, supported me with encouragement and love; with him I hope to work for a better world.

A note to the readers

Since my studies in Electrical Engineering, I have always been interested in technologies with which people interact to augment their abilities and to improve their quality of life. During my professional experience in the development of assistive technologies for disabled persons, I observed many patients with Amyotrophic Lateral Sclerosis (ALS) who sought for technologies that could help them to communicate. From my early interest in ALS, I produced a master thesis on input devices for severely disabled patients with ALS. However, I realized that, despite recent advances in assistive communication devices, many patients still do not use these devices. I believe that there are various reasons for this, but two are the most critical: the lack of specific assessment tools to implement the timely use of assistive devices; and the absence of well-defined clinical outcomes to determine the benefit of these technologies for the support of ALS patients and their families. My main motivation to proceed in this research area is to obtain novel scientific knowledge that could provide relevant advances in the two critical problems mentioned above, in particular to test the impact of assistive devices for communication in the quality of life of ALS patients, and to explore the use of these devices as tools to mark the disease progression that would be valuable for home-based clinical assessment.

This dissertation was developed under the Doctoral Program in Neurosciences, from the Faculty of Medicine, Universidade de Lisboa. Research was designed and developed in a common effort of researchers with Engineering and Medicine backgrounds. Assistive communication devices that were necessary for this research were funded by *Fundação Calouste Gulbenkian* and supported by the *Associação Portuguesa de Esclerose Lateral Amiotrófica* (APELA).

This thesis is structured in eight chapters. In the first chapter, a brief description of Amyotrophic Lateral Sclerosis is presented, with special emphasis on description of functional impairments that influence communication. Chapter 2 contains important concepts and definitions related to the field of Assistive Technologies. Moreover, this chapter describes the state-of-the-art of assistive technologies that support communication in ALS, during different stages of progression. Chapter 3 describes the objectives of the overall research presented in this thesis. Chapters 4, 5 and 6 describe the three studies performed in this research work, published in peer-reviewed scientific journals. Pertinent results of this research work are discussed in chapter 7, followed by a personal perspective on the presented contributions and future work, in chapter 8. After the References list, there are four appendices: appendix A, supports description of the study on speech monitoring; appendix B contains all the questionnaires used in the research; appendix C illustrates the use of ACD by some of the patients who participated in the research studies. Appendix D presents the facsimile of the published papers.

Complementing this organization and presented in the initial pages of this thesis, there are the acknowledgments, list of figures, list of tables, list of abbreviations and a summary of this thesis, both in Portuguese and English.

Table of Contents

Authorship

The results presented in this dissertation were presented in conferences and published in the following manuscripts:

Peer-reviewed Journals

Londral A, Pinto A, Pinto S, Azevedo L, de Carvalho M. Quality of life in ALS patients and caregivers: impact of assistive communication from early stages (2015). *Muscle & Nerve* (doi: 10.1002/mus.24659).

Londral A, Pinto S, de Carvalho M. Markers for upper limb dysfunction in Amyotrophic Lateral Sclerosis using analysis of typing (2015). *Clinical Neurophysiology* (DOI: 10.1016/j.clinph.2015.06.017).

Gómez-Vilda P, Londral A, Rodellar-Biarge V, Ferrández-Vicente JM, de Carvalho M. Monitoring amyotrophic lateral sclerosis by biomechanical modelling of speech production (2015). *Neurocomputing 151*: 130-138.

Londral A, Silva H, Nunes N, de Carvalho M, Azevedo L. A wireless user-computer interface to explore various sources of biosignals and visual biofeedback for severe motor impairment (2013). *Journal of Accessibility and Design for All 3*:118-134.

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Other publication sources

Londral A. (2015) As Tecnologias de Apoio à Comunicação na Esclerose Lateral Amiotrófica. *Revista ComunicActiva*, Associação Portuguesa de Terapeutas da Fala, 11: 7-15.

List of Figures *

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List of Abbreviations

AAC: Augmented and Alternative Communication;
ACC: Accelerometer;
Accpress: Mean acceleration in movements for pressing each key in a typing task;
Accrelease: Mean acceleration in movements for releasing each key in a typing task;
ACD: Assistive Communication Devices;
ADL: Activities of daily living;
ALS: Amyotrophic lateral Sclerosis;
ALSFRS-R: revised ALS functional rating scale;
ALSFRS-R-b: bulbar subscore of ALSFRS-R;
ALSFRS-R-ul: upper limb subscore of ALSFRS-R;
AT: Assistive Technologies;
ATd: Assistive Technology device;
BCI: Brain-computer interface
CETI-m: Communication Effectiveness Index-modified;
FCR: Formant Centralization Ratio;
FRS: Force Resistive Sensor;
G1: Group 1;
G2: Group 2;
LIS: Locked-in states
LMN: Lower Motor Neuron;
MNFS: Modulus of the normalized formant span;
MQoL: McGill Quality of Life Questionnaire;
nALS: ALS patients with normal upper limb function;
NIV: noninvasive ventilation
QoL: Quality of life;
t_hold: Mean time spent in holding down each key in a typing task;
t_p: Mean time spent between tapping a desired key and pressing it down, in a typing task;
UL: Upper limbs;

UMN: Upper Motor Neuron;

VSA: Vowel space area;

wALS: ALS patients with severe upper limb dysfunction.

WHOQOL-Bref: World Health Organization Quality of Life – Bref Questionnaire;

WPM: Words per minute;

Resumo

A Esclerose Lateral Amiotrófica (ELA) é uma doença neurodegenerativa, sem cura e de causa desconhecida. É a mais frequente entre as doenças do neurónio motor, causando progressiva fraqueza e atrofia muscular nas regiões bulbar, torácica, abdominal e membros. Sem terapias que travem o implacável processo neurodegenerativo, a insuficiência respiratória é a principal causa de morte. A média de idade da ocorrência dos primeiros sintomas é de 58 a 63 anos, com sobrevida de 2 a 5 anos e maior incidência para o sexo masculino (1:1,4). Apenas 5 a 10% de doentes sobrevive por mais de 10 anos.

As características de progressão da ELA podem variar, tendo um início focal com posterior difusão para outras regiões. Os doentes com ELA podem ser classificados pelos primeiros sintomas da doença: medular (afetando a função motora dos membros superiores e/ou inferiores), bulbar (afetando precocemente a fala e deglutição), respiratória (quando os primeiros sintomas caracterizam-se por dispneia), axial (afetando inicialmente os músculos do pescoço ou dorso) ou difusa (quando é difícil localizar os primeiros sintomas). Embora durante muito tempo se tenha considerado a ELA como uma doença que afetava apenas o sistema motor, há atualmente evidência de ser uma situação multissistémica. Estudos recentes indicam que cerca de metade dos doentes apresentam algum défice cognitivo quando avaliados por meios complementares; um reduzido grupo (2 a 15%) apresenta sinais clínicos de demência frontotemporal.

Devido à crescente incapacidade motora, o doente perde autonomia para as suas atividades da vida diária. A maioria dos doentes experimenta graves dificuldades de comunicação, com consequências para a sua qualidade de vida. Devido ao envolvimento da região bulbar, que causa rápido agravamento da disartria, estudos indicam que cerca de 90% dos doentes com ELA sofre de dificuldade em comunicar através da fala (caracterizada por perda de inteligibilidade). Por outro lado, a progressiva tetraparésia causada pelo envolvimento medular impossibilita a escrita. O doente com ELA vê-se então num crescente isolamento (do qual é consciente) com graves dificuldades (ou mesmo impossibilidade) em comunicar as suas necessidades, sentimentos ou decisões.

A falta de comunicação agrava a dependência entre o doente e cuidador, além de aumentar neste a frustração de não poder entender as necessidades do seu doente, com pressupostas consequências para a qualidade de vida de ambos.

As dificuldades de comunicação dos doentes de ELA tornam imperativo o suporte das Tecnologias de Apoio à Comunicação (TaC), à medida que estes perdem a fala e a escrita. Desde os sintetizadores de fala (para transformar qualquer texto escrito em fala), atualmente presentes em qualquer *smartphone*, aos avançados sistemas de controlo pelo olhar ou as interfaces cérebro-computador, as TaC possibilitam ao doente com ELA comunicar no seu contexto social, nomeadamente com o cuidador, familiares ou amigos e profissionais de saúde, independentemente da sua incapacidade motora e características da progressão da doença.

Contudo, pelas suas características neurodegenerativas e rapidez de progressão, a ELA constitui um desafio a quem se dedica à investigação, desenvolvimento e aplicação de TaC: as características físicas do doente e as suas necessidades de comunicação alteram-se com o avanço da doença. A perda progressiva, mas não simultânea, da fala e da mobilidade nos membros superiores e inferiores faz com que seja necessária uma contínua avaliação das capacidades funcionais e das necessidades de comunicação do doente, para que a escolha e utilização de TaC seja adequada a cada fase da doença.

Apesar dos enormes avanços nas TaC, durante a última década, persistem várias dificuldades em apoiar a sua utilização por doentes com ELA. Algumas das razões para estas dificuldades são: falta de evidência científica do benefício da utilização destas tecnologias para a qualidade de vida dos doentes e cuidadores; falta de ferramentas de avaliação, que permitam apoiar os profissionais de saúde na escolha atempada das tecnologias que melhor se ajustam às necessidades de comunicação e ao contexto de cada doente; e o apoio tardio, muitas vezes sugerido ou procurado apenas quando o cuidador já tem muita dificuldade em comunicar com o doente. Com frequência, em algumas fases da ELA, o doente e o cuidador têm de gerir complicações clínicas relacionadas com o suporte vital (nomeadamente, a disfagia e a insuficiência respiratória) que se tornam prioritárias e fazem com que o problema da comunicação seja negligenciado. No entanto, as graves limitações físicas do doente (logo, a elevada dependência das decisões do cuidador), bem como a crescente depressão ou sobrecarga do

cuidador, tornam a adaptação às TaC muito difícil, quando adiada para fases avançadas da doença. Também relacionado com as dificuldades de apoio dos doentes para utilizar TaC, é discutido neste trabalho a perspetiva limitada que é colocada nestas tecnologias. As modernas TaC não devem ser consideradas apenas como *alternativas à fala*, mas como um importante meio tecnológico que potencia a integração dos doentes com ELA nos modernos paradigmas da Saúde.

A presente tese tem como principal objetivo estudar o impacto que a utilização de TaC tem na qualidade de vida dos doentes e seus cuidadores, desde as primeiras dificuldades em comunicar através da fala. Como objetivos secundários, pretende-se (1) estudar novas ferramentas de avaliação e medição da capacidade de comunicação nos doentes com ELA, que possam contribuir para um melhor acompanhamento dos doentes ao longo das diferentes fases da doença; (2) validar a hipótese de que as TaC podem ser instrumentos para implementar ferramentas clínicas de telemonitorização, desde a casa do doente.

Um grupo de 30 doentes com ELA e 17 cuidadores, de início bulbar, foi selecionado na consulta de ELA do Hospital de Santa Maria. Os doentes e cuidadores foram avaliados longitudinalmente, na consulta de Neurologia do hospital, durante 2 a 29 meses. Em cada sessão de avaliação, os instrumentos utilizados para o estudo da qualidade de vida foram: para os doentes, o questionário McGill Quality of Life questionnaire (MQoL); para os cuidadores, o MQoL e o World Health Organization quality of life-BREF (WHOQoL-bref). Para a avaliação do desempenho na comunicação foi usada a métrica de *número de palavras por minuto*, e registaram-se as funções da fala e escrita (manual e num teclado). Para o estudo de novas ferramentas de monitorização, foi gravada fala dos doentes (utilizando o microfone de um computador) e os movimentos de escrita num teclado (através de um acelerómetro colocado na parte posterior do dedo indicador).

Um grupo de 15 doentes (selecionados aleatoriamente) recebeu TaC baseadas em computadores tipo *tablet*, desde as primeiras dificuldades em comunicar. Verificou-se que estes doentes aprenderam facilmente a utilizar as tecnologias, e melhoraram o desempenho de utilização da escrita com teclado. Observamos neste grupo de doentes um impacto positivo das TaC em alguns

domínios específicos da qualidade de vida dos doentes (Psicológico e Bem-Estar) e seus cuidadores (Psicológico e Suporte).

Estudamos a função do membros superiores, no que se refere ao desempenho na comunicação escrita. Observamos que as TaC podem suportar a comunicação dos doentes com ELA durante mais tempo do que a escrita manual, muitas vezes utilizada como única alternativa à fala (ficando o doente impossibilitado de comunicar quando perde a função motora necessária para agarrar a caneta).

Com base na metodologia definida para registo da fala e da escrita no teclado, observamos em dois estudos exploratórios que as TaC podem ser utilizadas como ferramentas para monitorizar a progressão dos sintomas da ELA, nomeadamente os que dizem respeito à comunicação. Num primeiro estudo com 19 doentes de ELA, observamos que o tempo médio que o doente demora a pressionar cada tecla do teclado pode ser utilizado como marcador precoce de disfunção nos membros superiores. Também verificamos que a aceleração dos movimentos ao premir e libertar as teclas indicam aumento da disfunção dos membros superiores na ELA. Num segundo estudo, baseado na análise longitudinal de fala gravada de quatro doentes de ELA, observamos a possibilidade de utilizar fala corrente para avaliação e detecção precoce da progressão da ELA. As metodologias utilizadas neste trabalho de investigação para o registo e avaliação da comunicação podem ser replicadas em ambiente doméstico, e fazem parte das contribuições desta investigação. A implementação de ferramentas de telemonitorização suportadas nas TaC, é discutida nesta tese.

Com o objetivo de explorar novas ferramentas de avaliação e novos canais de comunicação em doentes que recebem apoio tardio na utilização de TaC, desenvolvemos uma ferramenta de deteção e controlo de movimentos residuais, simples de controlar. Foram testados movimentos captados por sensores de acelerometria, eletromiografia e força (que podem ser utilizados pelo doente para acesso a ferramentas de comunicação), em três doentes de ELA com grave incapacidade motora.

Em conclusão, os resultados deste trabalho de investigação contribuem com ferramentas de Engenharia para a melhoria da comunicação e do acompanhamento dos doentes com ELA e seus cuidadores na utilização de TaC. As metodologias desenvolvidas para o desenvolvimento deste estudo podem ser

aplicadas para estudar o impacto das TaC em outras doenças neurodegenerativas que afetam o controlo motor da fala e membros superiores.

Palavras-chave
Esclerose Lateral Amiotrófica; Comunicação; Tecnologias de Apoio; Qualidade de Vida; Condições neurodegenerativas.

Abstract

Amyotrophic Lateral Sclerosis (ALS) is a progressive neuromuscular disease with rapid and generalized degeneration of motor neurons. Patients with ALS experiment a relentless decline in functions that affect performance of most activities of daily living (ADL), such as speaking, eating, walking or writing. For this reason, dependence on caregivers grows as the disease progresses. Management of the respiratory system is one of the main concerns of medical support, since respiratory failure is the most common cause of death in ALS.

Due to increasing muscle weakness, most patients experience dramatic decrease of speech intelligibility and difficulties in using upper limbs (UL) for writing. There is growing evidence that mild cognitive impairment is common in ALS, but most patients are self-conscious of their difficulties in communicating and, in very severe stages, locked-in syndrome can occur. When no other resources than speech and writing are used to assist communication, patients are deprived of expressing needs or feelings, making decisions and keeping social relationships. Further, caregivers feel increased dependence due to difficulties in communication with others and get frustrated about difficulties in understanding partners' needs. Support for communication is then very important to improve quality of life of both patients and caregivers; however, this has been poorly investigated in ALS.

Assistive communication devices (ACD) can support patients by providing a diversity of tools for communication, as they progressively lose speech. ALS, in common with other degenerative conditions, introduces an additional challenge for the field of ACD: as the disease progresses, technologies must adapt to different conditions of the user. In early stages, patients may need speech synthesis in a mobile device, if dysarthria is one of the initial symptoms, or keyboard modifications, as weakness in UL increases. When upper limbs' dysfunction is high, different input technologies may be adapted to capture voluntary control (for example, eye-tracking devices).

Despite the enormous advances in the field of Assistive Technologies, in the last decade, difficulties in clinical support for the use of assistive communication devices (ACD) persist. Among the main reasons for these

difficulties are lack of assessment tools to evaluate communication needs and determine proper input devices and to indicate changes over disease progression, and absence of clinical evidence that ACD has relevant impact on the quality of life of affected patients. For this set of reasons, support with communication tools is delayed to stages where patients are severely disabled. Often in these stages, patients face additional clinical complications and increased dependence on their caregivers' decisions, which increase the difficulty in adaptation to new communication tools.

This thesis addresses the role of assistive technologies in the quality of life of early-affected patients with ALS. Also, it includes the study of assessment tools that can improve longitudinal evaluation of communication needs of patients with ALS.

We longitudinally evaluated a group of 30 patients with bulbar-onset ALS and 17 caregivers, during 2 to 29 months. Patients were assessed during their regular clinical appointments, in the Hospital de Santa Maria-Centro Hospitalar Lisboa_Norte. Evaluation of patients was based on validated instruments for assessing the Quality of Life (QoL) of patients and caregivers, and on methodologies for recording communication and measuring its performance (including speech, handwriting and typing).

We tested the impact of early support with ACD on the QoL of patients with ALS, using a randomized, prospective, longitudinal design. Patients were able to learn and improve their skills to use communication tools based on electronic assistive devices. We found a positive impact of ACD in psychological and well-being domains of quality of life in patients, as well as in the support and psychological domains in caregivers.

We also studied performance of communication (words per minute) using UL. Performance in handwriting may decline faster than performance in typing, supporting the idea that the use of touchscreen-based ACD supports communication for longer than handwriting. From longitudinal recordings of speech and typing activity we could observe that ACD can support tools to detect early markers of bulbar and UL dysfunction in ALS.

Methodologies that were used in this research for recording and assessing function in communication can be replicated in the home environment and form

part of the original contributions of this research. Implementation of remote monitoring tools in daily use of ACD, based on these methodologies, is discussed.

Considering those patients who receive late support for the use of ACD, lack of time or daily support to learn how to control complex input devices may hinder its use. We developed a novel device to explore the detection and control of various residual movements, based on sensors of accelerometry, electromyography and force, as input signals for communication. The aim of this input device was to develop a tool to explore new communication channels in patients with generalized muscle weakness.

This research contributed with novel tools from the Engineering field to the study of assistive communication in patients with ALS. Methodologies that were developed in this work can be further applied to the study of the impact of ACD in other neurodegenerative diseases that affect speech and motor control of UL.

Keywords

Amyotrophic Lateral Sclerosis; Assistive Communication; Assistive Technologies; Quality of Life; Neurodegenerative conditions.

Chapter 1 - Amyotrophic Lateral Sclerosis

1.1 **Introduction**

Amyotrophic Lateral Sclerosis is in the group of the *motor neuron disorders*. It was considered as a muscular condition until the French neurobiologist and physician Jean-Martin Charcot published, in 1869, a number of clinico-pathological studies identifying neuromotor degeneration as cause of muscle wasting (Goetz, 2000). For his fundamental contributions, ALS is still known as “Charcot’s disease”.

This motor neuron disease is distinguished by the combination of degeneration of upper and lower motor neurons (Figure 1). Upper motor neurons (UMN) are in the motor cortex and project down to connect to lower motor neurons (LMN). LMN reside in brainstem and spinal cord; they project to the peripheral nerves to connect directly to the muscle fibers. Spasticity is a well-known manifestation related to UMN involvement in ALS, while muscle weakness, muscle wasting and fasciculations are related to LMN degeneration that occurs in this disease.

Symptoms are progressive weakness and wasting of bulbar, limb, thoracic and abdominal muscles. Most patients experiment a dramatic and progressive loss of muscle function. Motor neurons controlling the eye movements and sphincters are commonly spared, as also the sensory and autonomic nervous system. For a definitive diagnostic of ALS it is important to identify the presence of concomitant signs of UMN and LMN degeneration in multiple body regions (Shaw & Quinn, 2006; Brooks et al., 2000).

ALS is rapidly progressive and fatal, with no available treatment to interrupt the motoneurone death; its cause is still unknown. The mean age of onset is 58-63 years old in sporadic cases of ALS. Lifetime risk of developing ALS is 1 in 350–500, for male sex (Miller et al., 2013); the incidence is higher for male sex (1:1,4) (Miller et al., 2013; Logroscino et al., 2010). Only 5% of cases have an onset before the age of 30 years (Haverkamp et al., 1995), but young-onset sporadic cases are increasingly recognized (Gouveia & de Carvalho, 2007). Due to fast progression, death occurs in average 2-4 years after the first symptoms, due to

respiratory failure, but 5-10% may survive for a decade or more (Andersen et al., 2012; Miller et al., 2013).

The management of ALS is supportive, palliative and multidisciplinary (Wijesekera & Leigh, 2009). Riluzole is the only approved drug that has been shown to have a modest effect in prolonging life (Bensimon et al., 2002; Bellingham, 2011).

Respiratory failure and other respiratory complications account for the majority of deaths in ALS. Although respiratory function is a frequent late complication, it may be a presenting feature (de Carvalho et al., 1996). Several different factors have been shown to predict survival in ALS. The most consistent negative predictive factors for survival are: elderly age, low body-mass index, short diagnostic delay, bulbar and respiratory presentation, rapid clinical and respiratory decline (Pinto et al., 2009; Chiò et al., 2009).

Non-invasive ventilation (NIV) is widely used to improve alveolar hypoventilation in ALS. Several studies indicate a longer survival when NIV is used. Health-related QoL is improved in patients under NIV, in particular in those with none to moderate bulbar dysfunction (Pinto et al., 2010; Bourke et al., 2006; Vrijsen et al., 2013). Forced vital capacity, vital capacity, nasal inspiratory pressure obtained during a sniff, the size of the phrenic nerve motor response and mean nocturnal oxygen saturation have been considered as respiratory markers related to prognosis in ALS (S. Pinto & Carvalho, 2014; S. Pinto et al., 2009).

Most ALS cases (approximately two thirds of patients with typical ALS) have a spinal form of the disease: symptoms may start either distally or proximally in the upper or lower limbs. Nearly 25% of the patients have bulbar-onset ALS: dysarthria as initial symptoms. In this group of patients, limbs symptoms can develop almost simultaneously with bulbar manifestations or, for most of the cases, will occur later within 1–2 years. All patients with bulbar symptoms will develop dysphagia and sialorrhea due to difficulty in swallowing saliva, as well as mild UMN type bilateral facial weakness, which affects the lower part of the face. 'Pseudobulbar' symptoms such as emotional lability are seen in a significant number of cases (Wijesekera & Leigh, 2009). About 5% of cases with ALS present with respiratory weakness without significant limb or bulbar symptoms (de Carvalho et al., 1996). These patients present with symptoms of respiratory failure or nocturnal hypoventilation (dyspnea, orthopnea, disturbed sleep, morning

headaches, excessive day time somnolence, anorexia, decreased concentration and irritability or mood changes) (Polkey et al., 1999; Wijesekera & Leigh, 2009).

Bulbar-onset is more common in women and in older age groups; 43% of patients over the age of 70 present bulbar symptoms, compared to 15% below the age of 30 (Forbes et al., 2004; Haverkamp et al., 1995). In general, death is due to respiratory failure within 2–3 years for bulbar onset cases and 3–5 years for spinal onset ALS cases. Most ALS cases are sporadic but 5–10% of cases are familial, and of these 10-20% have a mutation of the SOD1 gene and about 20-40% have mutations of the C9Orf72 gene, in Europe (Wijesekera & Leigh, 2009; Cooper-Knock et al., 2015).

The deterioration of the neuromotor system involved in respiration, phonation, swallowing, and lingual and oro-facial muscle functions leads to a rapidly progressing dysarthria in ALS. Dysarthria occurs in more than 80% of patients and is manifested as an early symptom in patients with bulbar-onset, often leading to anarthria. It also affects 70% of patients with spinal onset; 25 to 30% of patients have dysarthria within initial symptoms (Tomik & Guiloff, 2010).

Dysphagia is a common symptom of ALS, leading to malnutrition, weight loss, dehydration and the need of aspiration (Kühnlein et al., 2008). Percutaneous endoscopic gastrostomy is the standard procedure for alternative feeding; evidence suggests that it should be placed before vital capacity falls below 50% of predicted (Wijesekera & Leigh, 2009).

ALS is characterized by functional decline related to muscle weakness, affecting most activities of daily living (Cedarbaum et al., 1999). Dependence on caregivers grows as disease progresses (Brownlee & Bruening, 2012). Increasing dependence and general dysfunction of patients with ALS cause strong negative social and economic impact. Patients and caregivers may suffer from depression and anxiety, from diagnosis and as disease progresses. Psychological support and palliative care should be offered to the families since early symptoms (Averill et al., 2007). Most patients will experiment dramatic decrease of speech intelligibility and great difficulties in writing due to increasing muscle weakness. For this reason, one of the concerns of persons with ALS is the fear of losing ability to communicate (Gruis et al., 2011).

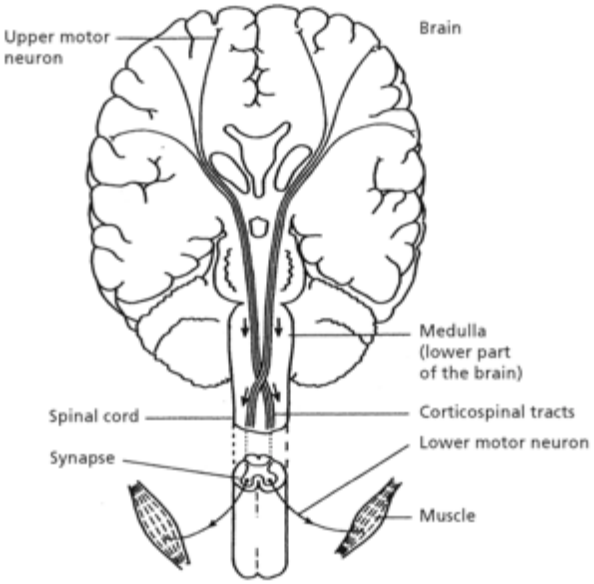

Figure 1 – Pathways of Upper Motor Neuron and Lower Motor Neuron systems (in (Shaw et al., 2006)*, p.2)*

1.2 **Functional progression**

ALS may be identified by the functional involvement of one or more central nervous system region (bulbar, cervical-upper limbs, lumbosacral-lower limbs or thoracic-diaphragmatic) evaluated by manifestations of weakness, wasting or spasticity. First symptoms spread to other contiguous anatomic regions, in a progressive order. Time of progression can vary according to survival rates, and be influenced by clinical, demographic, and genetic features (Simon et al., 2014).

Brownlee & Bruening (2012) describe ALS as a *disease of losses*. In fact, a dramatic decrease in patients' autonomy is caused by a cascade of functional losses. ALS Functional Rating Scale revised (ALSFRS-R) (Cedarbaum et al., 1999) is a widely applied tool for research and routine clinical evaluation, that measures in a single score the severity of the functional status. The ALSFRS-R measures bulbar function, gross motor tasks, fine motor tasks, walking, and respiratory function. Maximum score (48) corresponds to normal function; this score declines as disease progresses (minimum is 0). Quality of life is correlated to ALSFRS-R scores, indicating that *function* is important in the QoL of ALS patients and their caregivers (Bourke et al., 2006; Cedarbaum et al., 1999). This score has been used as a self-report form (Montes et al., 2006), for telephone administration (Kaufmann et al., 2007; Kasarskis et al., 2005) and online assessment (Maier et al., 2012). For these characteristics, this tool was used for

clinical functional assessment in this research, and is further described in section 4.2.4.

A staging system proposed by Roche et al. (2012), characterizes ALS progression in four stages: (1) Symptom onset (involvement of one single region); (2) Involvement of a second region; (3) Involvement of a third region and (4) A- Need for gastrostomy, B- Need for respiratory support (non-invasive ventilation). Quantitative outcome measures of functional progression in ALS, used in clinical trials, mainly rely on muscle strength assessment, respiratory and bulbar function tests as well as on general functional rating scales (Brinkmann et al., 1997). Emerging imaging technologies are contributing to further insights of the disease, in particular related to the study of UMN abnormalities in ALS (Simon et al., 2014).

1.3 **Upper and Lower limbs dysfunction**

Symptoms of ALS include difficulties of movements and reduced strength in upper and lower limbs. Due to lower limbs dysfunction, patients may fall and progressively become unable to walk. Loss of physical independence related to upper limbs dysfunction is characterized by progressive difficulties in performing most activities in daily living, as handwriting, handling utensils and dressing (Cedarbaum et al., 1999).

Figure 2 depicts a simplified model for dysfunction, considering a simplified linear progression: walking with autonomy, moving on a wheelchair and, finally, living mainly at home. For the scope of assistive communication devices in ALS, this simplified model represents three stages where significant changes in communication needs and individual social contexts can occur.

Figure 2 – A suggested model of the progression of limbs dysfunction, considering a simplified and linear progression of ALS. Three stages where significant changes in communication needs and individual social contexts can occur are represented: (i) the patient can walk normally (with independence for most ADL), (ii) the patient moves on a wheelchair and has difficulties in moving upper limbs (becomes more dependent on the caregiver and loses autonomy for several ADL) and (iii) finally, the patient is severely impaired and dependent on the caregiver (lives mainly at home, on a chair or bed).

1.4 Speech dysfunction

Different types of dysarthria occur in ALS, according to systems that are affected. Frequently it has mixed characteristics due to multisystemic involvement. Degeneration of LMN results in flaccid bulbar palsy with denervation of muscles of face, oropharynx, larynx and tongue (muscle wasting and weakness with proportional slowness of movements). Involvement of cortical areas and corticobulbar tracts (UMN) causes spastic bulbar palsy (slowness of movement with variable weakness and no wasting) (Darley et al., 1969). Figure 3 resumes dysarthria characteristics in ALS disease, as suggested in (Tomik & Guiloff, 2010).

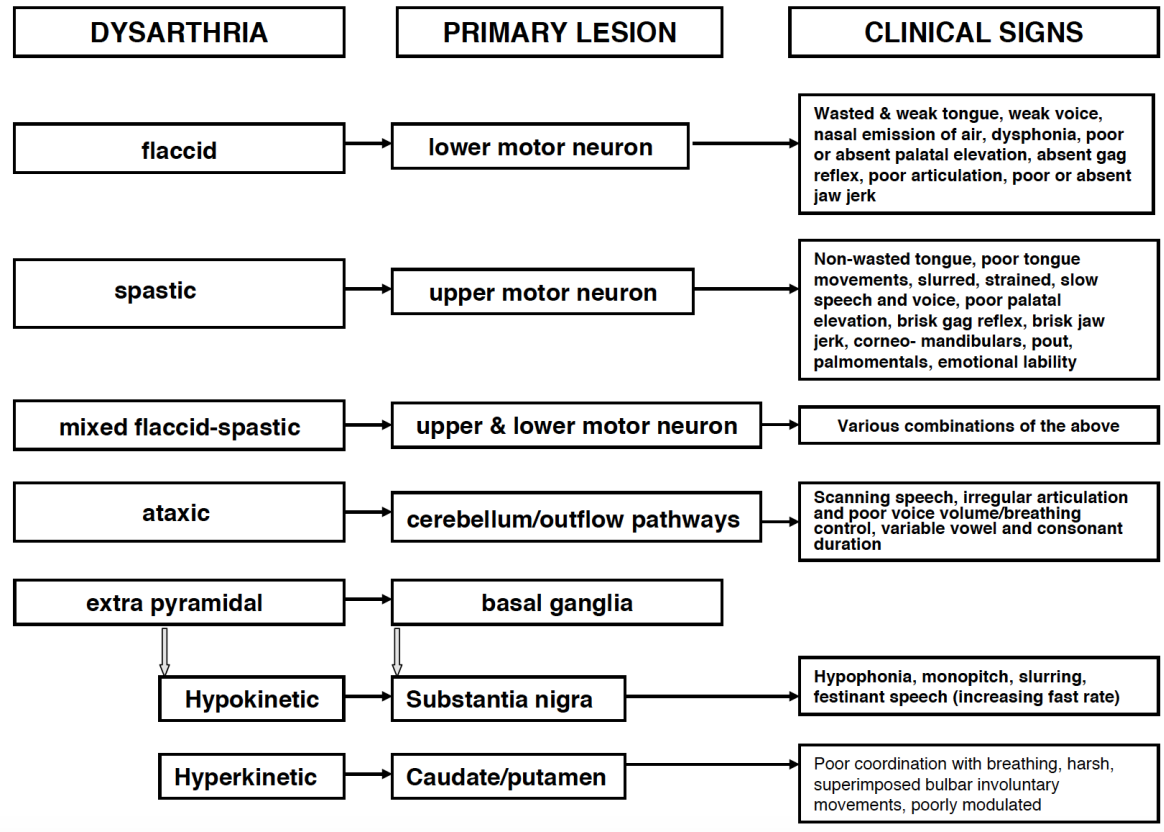

Figure 3 – Type, mechanisms and clinical signs of Dysarthria in ALS (from Tomik & Guiloff, 2010)

Decline of functional speech is characterized by decrease in speech intelligibility. Patients experiment progressive difficulties in being understood by others, increasing need to repeat words, reduction of the group of listeners who understand their speech, until they are unable to use speech for communication. In a longitudinal analysis, Beukelman et al. (2007) observed that 80 to 95% of ALS patients were prevented from communicating without any alternative strategy, in

some stage during disease progression. Ball et al. (2004) studied 158 patients, in 3 months intervals, since diagnosis until death concluding that speech rate is a valid predictor for decrease of speech intelligibility. According to Ball et al. (2007), a speech rate of 125 words per minute (65% of normal speech rate) is a valid marker for rapid decline in speech intelligibility.

1.5 **Cognitive impairment**

It is now evident that ALS disease affects multiple systems, with a significant impact for cognitive deficits. High incidence of mild cognitive impairment (up to 50%) has been reported (Phukan et al., 2007; Lomen-Hoerth et al., 2003; Barson et al., 2000); frontotemporal dementia (FTD) is found in a reduced group of ALS patients (with prevalence ranging from 15 to 41%) (Strong et al., 2009). Although cognitive impairment manifestations are heterogeneous, its decline has been described by personality change, irritability, obsessions, poor insight and pervasive deficits on frontal executive functions (i.e. verbal fluency, mental flexibility, attention, working memory, planning, and abstract reasoning) (Phukan et al., 2007; Cipresso et al., 2012). Different longitudinal studies indicate that cognitive decline is slow in the absence of dementia (Phukan et al., 2007; Robinson et al., 2006), but progresses more rapidly in bulbar-onset patients, when compared to spinal-onset (Schreiber et al., 2005). Motor and speech impairments raise difficulties for studying neuropsychological aspects of the disease. In stages where patients have lower functional scores, assessment with neuropsychology tests need modifications that accommodate physical impairment and the possibility to use ACD to answer to *digital* modified neuropsychology test. However, heterogeneity of physical impairment and difficulty in collecting large samples are obstacles to validation of these test modifications (Hill-Briggs et al., 2007). Some authors suggested the use of Brain-computer interface (BCI) or *eye-tracking* systems to assess cognition by neuropsychological tests in patients with severe motor impairment. Nevertheless, the lack of research in test modifications adapted to different devices reduces the possibility of studying cognition in later stages of ALS disease (Cipresso et al., 2012; Iversen et al., 2008).

Chapter 2 - Assistive Technologies for Communication and Control in ALS

2.1 Definition of Assistive Technology

The term *Assistive Technologies* is defined by Cook & Polgar (2013) as a broad range of devices, services, strategies and practices that are conceived and applied to ameliorate the problems faced by individuals who have disabilities. In the same perspective, Cowan & Turner-Smith (1999) define *Assistive Technologies* as "any device or system that allows an individual to perform a task that they would otherwise be unable to do, or increases the ease and safety with which the task can be performed".

According to Rehabilitation Engineering Society of North America (RESNA), the term *AT Device* (ATd) means *"*any item, piece of equipment, or product system, whether acquired commercially, modified, or customized, that is used to increase, maintain, or improve functional capabilities of individuals with disabilities*"*. This definition is adopted from Assistive Technology Act of 2004, P.L. 108-364 (http://www.gpo.gov/fdsys/pkg/STATUTE-118/pdf/STATUTE-118-Pg1707.pdf). The same document defines *AT Service* as "any service that directly assists an individual with a disability in the selection, acquisition, or use of an assistive technology device*"*. AT services include evaluation of individuals' needs (which includes functional evaluation), support in acquisition of ATd, customization and technical support for ATd, coordination between the use of ATd and rehabilitation services; training users, professionals and caregivers; among others.

2.2 Assistive Communication Devices (ACD)

Different ATd are developed to assist different functional disabilities. Assistance in communication, mobility, cognition, manipulation, vision, audition and tact are the targets of the ATd (Cook & Polgar, 2013). For example, a wheelchair is developed and used to improve patients' mobility; an infrared transmitter that is controlled by eye-tracking system can allow a severely motor disabled patient to choose TV channels from the bed; an application in a smartphone that alerts for daily tasks can help a person with memory problems; screen readers in the computers help individuals with vision impairment to access

to information; auditory prosthesis allow individuals with auditory impairments to improve listening performance; an electromyographic interface can allow a severely disabled individual with motor speech impairment to write on a screen keyboard and use text-to-speech to communicate with others. All these examples refer to ATd that are developed to assist in different functional needs.

The present work is devoted to AT for support in communication. In this scope, the term ATd will be replaced by *assistive communication devices* (ACD). We refer to ACD as any device or system that enables an individual to communicate when they would otherwise be unable (or have difficulties) to do it, due to functional impairments. A unique reference to the field of Augmentative and Alternative Communication (AAC) is done in this paragraph. According to ASHA, "*Augmentative and alternative communication includes all forms of communication (other than oral speech) that are used to express thoughts, needs, wants, and ideas.*" In fact, all the present research work is in the scope of the field of AAC. However, a special focus is given on the technology (electronic devices) and effects of the use of ACD.

In this context, ACD aim at enhancing communication of those patients who have difficulties in speaking or writing. In ALS, as also in several other neurological conditions, difficulties in communication appear due to physical dysfunction in speech and in upper limbs. Depending on physical dysfunction and individual needs, different technologies can support communication, as tablet devices or computers with software-based communication tools (e.g. speech synthesis), simple devices that record and reproduce voice, eye glasses with embedded gaze control or even intracortical brain computer interfaces.

It is important to note that, in opposition to most clinical equipment, which is controlled by the professionals, ACD are to be used by patients. This fact makes them distinct from other technologies for clinical support and has important implications:

i) expertise in the use of ACD belong to the patient.

ii) outcomes from the use of ACD are difficult to obtain in clinical settings, as these technologies are designed to enhance patients' function in daily living, out of the clinical environment.

iii) use and selection of ACD must follow a *patient-centered approach* (Stewart, 2001), taking into account the individual context and decisions of each

patient. As Gosnell et al. (2011) advocate, while ACD must “represent a reasonable match to the strengths and needs of some individuals, it is important that the needs of an individual be considered on a case-by-case basis using a thorough and clinically based approach.”

2.2.1 Input devices

As aforementioned, ACD are operated by the patient. Operation is done using an *input device* (most commonly named as *access interface*), i.e. a mean of interaction between the body functions (input signals) and the ACD. Most commonly, interaction between a person and a personal electronic device is done through motor control of upper limbs. For example, touchscreens or keyboards are input devices that are used by the patient (requiring motor control of upper limbs) to *access* to an ACD (Figure 4).

Figure 4 – Input devices (accessibility tools) are controlled by body functions and translated into commands for controlling communication tools of the AT device.

Input devices have particular importance in ALS in the context of patients with upper limbs impairment. In a neurodegenerative process of losing motor control, as is the case of ALS, use of upper limbs to control a device may become limited or impossible. As disease advances and functional limitations increase, patients’ support in Communication includes searching for alternative resources (body functions and input devices) to access to ACD. Miyasaka et al. (2013, p.165) illustrate an example where they observe the finger joint movements required to perform a left click on a computer mouse input device and problems that arise as ALS progresses:

“To click the left mouse button, the hand rests on the mouse while maintaining a longitudinal and lateral arch in the palm and the four fingers and thumb envelop and grip the mouse. Then, with the distal interphalangeal and proximal interphalangeal joints of the left-side finger slightly flexed, the angle of each joint is maintained and the metacarpophalangeal (MP) joint is flexed to perform the clicking operation. After clicking, the flexion of the MP joint is relaxed to cease the clicking operation. Clicking the left mouse button thus involves the complex operation of simultaneously holding the mouse and clicking the button, which requires the coordination of

several joint muscles. Because muscle strength throughout the body deteriorates as ALS progresses, input methods, such as the mouse, requires the use of multiple muscles and therefore become unusable after the early stages of the disease."

As these same authors refer, as disease progresses, input devices that minimize the number of joint movements are selected. Figure 5 illustrates body sites and input signals that are most commonly used by ALS patients for access to ACD, depending on disease symptoms and stage.

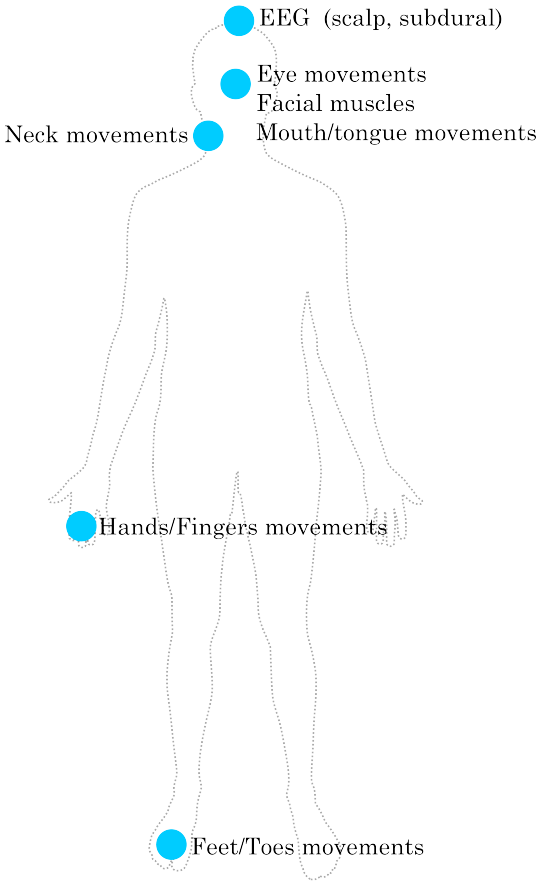

Figure 5 - Body sites and signals commonly used to control input devices by ALS patients.

2.2.2 Access Methods

Depending on the input signals (Figure 4) and the body functions that are used to access to ACD, two main access methods may be used:

(i) **Direct selection** – in this access method, patient can choose a function in the ACD directly. For example, when using a keyboard with finger selection or an eyetracking system with eye control, the patient can select any letter at any

instance. Motor control allows the user to reach any option in the keyboard directly.

(ii) **Scanning method** – when physical disability prevents the patient to access to all functions in ACD, an alternative method must be used. For example, a patient with ALS may not be able to move upper limb to reach all keys in a keyboard, thus be able to press a switch using hands or head movements, as depicted in Figure 6. A single switch (a simple 0/I signal) may be used to select a device with a scanning method: all options in an onscreen keyboard are highlighted in a sequential order and defined frequency (e.g. 1 option/sec). When the desired option is highlighted, user will press the switch and select that option (Figure 6). Scanning process continues for further selections. Despite of being a slow process

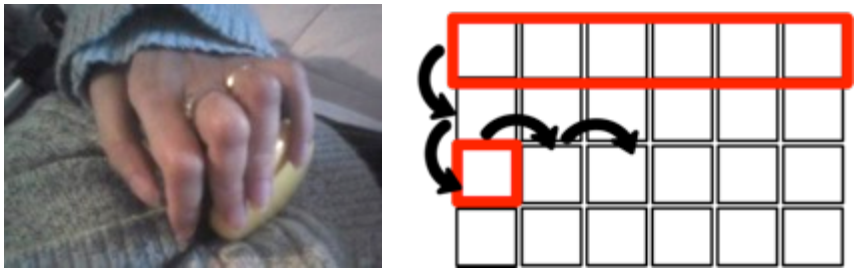

Figure 6 - (left) Switch being used by a patient with ALS for accessing to communication tools in an ACD using a scanning method. (right) Scheme illustrating scanning method (in Encarnação et al. (2015), p.61).

of selection, scanning method is used by many ALS patients, with the support of acceleration techniques (e.g. text prediction or different scanning sequences). It is important to refer that, in particular for patients in late stages of ALS, easiness for setup and learning of the input device may be more important for the patients than the communication rate. Birbmauer (2006) describes difficulties to find volunteers for implanting intracortical brain computer interfaces: "*Even when informed about the possibilities and advantages of the surgical implantation, 16 patients refused the procedure and preferred the slow and error-prone noninvasive device. An important argument of patients was that time is not an issue if one is completely paralyzed*". In fact, acceptance of assistive technologies is dependent on other factors than velocity, as is discussed in chapter 4.

There is also another specific scanning method that is used on some brain computer interfaces. In this specific case, which further described in section 2.3.2.3, scanning is not sequentially driven. Instead, options are highlighted in a random order and patients have to look at their option until it highlights.

2.3 **Assistive communication and dynamic needs in ALS**

When assessing to communication needs in ALS, and generally in progressive neurological conditions, three important aspects should be considered:

(i) Communication support must include assessment of input devices and ACD (access and communication tools). In ALS, both speech and upper limb functions are severely affected. As so, patients will need communication tools (for example, a speech synthesizer) and specific access tools to compensate functional impairment in upper limbs (for example, an input device to access a keyboard using eye movements) (Fager et al., 2012).

(ii) Time and characteristics of symptoms and progression deeply influence communication and access needs. Some characteristics that are specific of ALS are determinant for the specification of ACD that should best match to patients' communication and control needs. It is then especially important to estimate the rate of progression and know the stages of the disease, to plan ACD according to expected advance of the symptoms.

(iii) Communication needs depend on each patient's individual needs and context and may not be restricted to replacing speech dysfunction. Communication needs of the patients may go beyond dysfunction of speech. Solving communication problems in today's digital world requires consideration of multiple functions, depending on the age, circumstances, interests, and preferences of each person. Interpersonal communication, information, online services, entertainment, education, health and safety, are different functions of present communication tools, services and facilities (Shane et al., 2012).

In the following sections, we describe the state-of-art of assistive technologies that are used for supporting communication in ALS. Firstly, we describe technologies that are used in initial phases of disease progression (depending if main disability is in bulbar or upper limbs), and then those technologies that are used when patients are severely affected.

2.3.1 ACD in moderately affected patients

2.3.1.1 Initial speech impairment

When patients experiment speech intelligibility decay, though keeping functional upper limbs, the most inexpensive communication aids are pen and notepad (handwriting) or printed boards, as depicted in Figure 7. Though, generation of *tablet devices* is having a tremendous impact on the possibilities of communication for these patients (McNaughton et al., 2013; RERC, 2011). Simple and inexpensive applications can allow a patient to communicate with others, for example by using a simple touchscreen-activated keyboard and voice output (based on text-to-speech technologies). The possibility of using Internet applications as communication tools included in any tablet device is also an opportunity for patients to avoid social isolation caused by decreased speech intelligibility (Shane et al., 2012).

Handwriting and pointing to printed alphabetic boards are communication tools that are limited to peer-to-peer communication and can be used until functional impairment in upper limbs does not definitely prevent its use (Figure 7 and Figure 8). Digital ACD, such as the tablet devices, have the advantage of allowing the patient to use the same communication tools, as new input devices can be connected to these devices, to adapt to functional changes imposed by disease progression. Moreover, patients may be able to write using direct selection on a keyboard for more time than handwriting (as described in Chapters 4 and 5). Several authors defend the use of handwriting or printed boards in parallel to digital ACD, for being practical instruments, easy to use in any context (Brownlee & Bruening, 2012; Bongioanni, 2008; Kühnlein et al., 2008; Miyasaka et al., 2013).

2.3.1.2 Initial upper limbs impairment

When muscle weakness first affects UL function, patients may experiment early difficulties in using writing (handwriting or typing in an electronic device) or grabbing/controlling devices (for example, difficulties in using a cell phone). These difficulties may occur before any perceived symptom of dysarthria. One of the main overwhelming problems of losing UL function is loss of autonomy in daily living and consequent restricted participation in social and leisure activities (Sveen et al., 1999; Bongioanni, 2008).

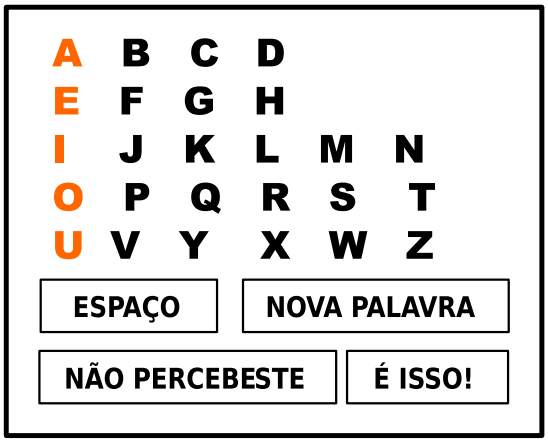

Figure 7 - Alphabetic Board printed in paper; the user points to the desired letters, words, phrases or pictures to communicate. This alphabetic board can also be used when patients are severely disabled: the caregiver points to the letters and patient indicates the selection by eyeblink or other gesture. In Encarnação et al. (2015), p.89.

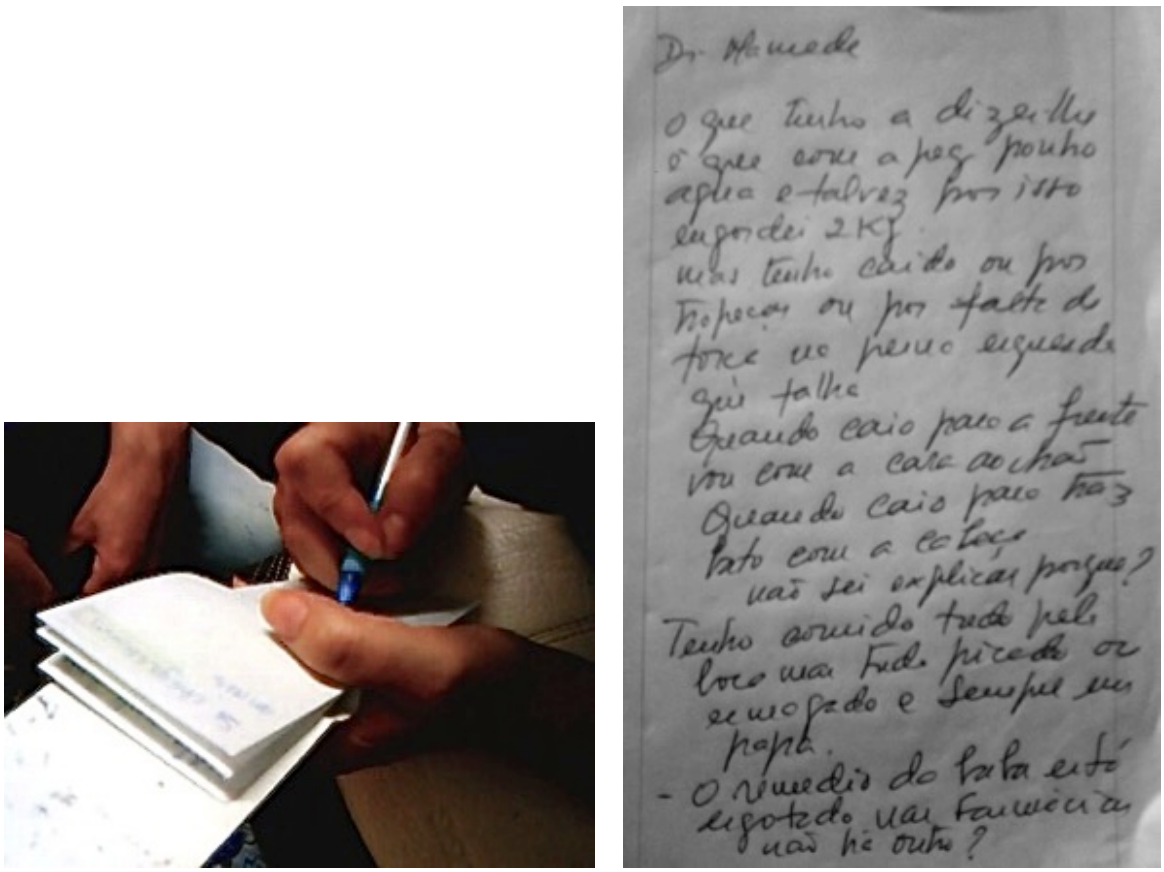

Figure 8 – (Left) Example of handwriting as a replacement of speech function. (Right) This note was written by a patient with ALS (bulbar onset) participating in this study; due to low intelligibility of speech, this woman wrote about her symptoms to communicate with her neurologist.

As muscle weakness increases, the use of alternative input devices for accessing communication tools becomes progressively important, as depicted in

Figure 9. Lack of understanding of UL functional progression in ALS, in what refers to access to ACD, limits support in early stages (Londral et al., 2013). Instead, access tools that do not rely on UL movements have been extensively explored in ACD research. In section 2.3.2, we describe input technologies that have been developed for ALS patients with severe UL dysfunction.

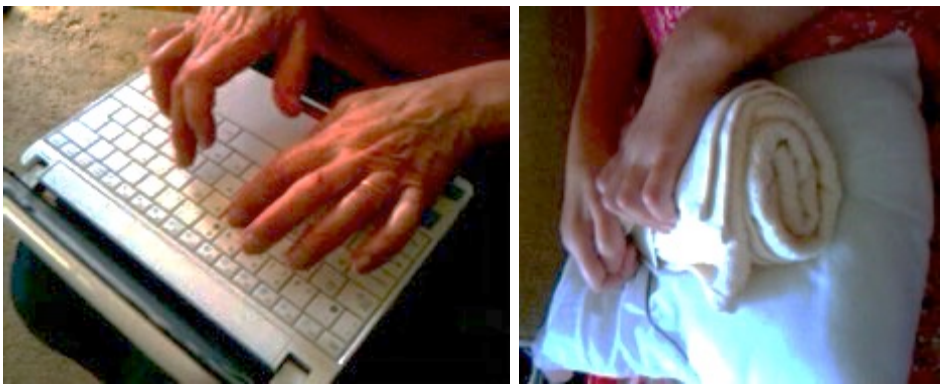

Figure 9 – One of the participants in this research: (left) she could type on the keyboard using both hands; (right) six months later, the same patient could not perform more than slight movements with left hand fingers (with the hand closed).

Wicks et al. (2009) proposed an extension for ALSFRS-R, in which there is a new item related to ULs and the use of assistive devices:

> *Compared to the time before you had symptoms of ALS, has your ability to use your fingers been affected when using the keys of a computer, speech device, remote control, or environmental controls?*
> *4: no change; able to type or press buttons quickly with any finger*
> *3: can press buttons or type but at a reduced rate*
> *2: can only press some buttons or type very slowly*
> *1: can only activate one key or switch at a time*
> *0: Am unable to activate any key or switch with fingers*

When accessing to keyboards or switches, some difficulties may be observed:

(i) Increasing difficulties in pressing or releasing a button or key. When this happens, it is important to allow patients to press the key or switch for a longer period, by eliminating the function of repetition (often, pressing for a longer time will activate the command to repeat the command; this option should be turned-off), as illustrated in Figure 10.

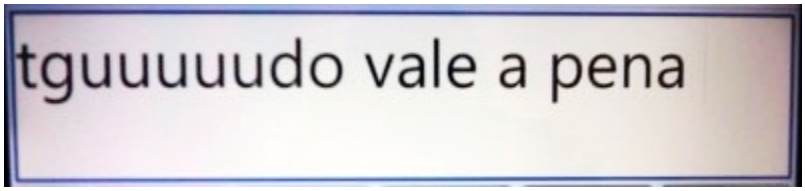

Figure 10 - Repetition of letters in a typing task of an ALS-patient participating in this research. Repetition is caused by abnormal delay in releasing the finger from the key

(ii) Patients may have difficulties in raising and moving the arm to point and select items on a keyboard or an alphabet board. Some patients may use arm supports to augment distal function of upper limbs (Londral et al., 2009): if forearm is supported higher that the keyboard, the hand will drop over the keyboard and patient will be able to select and press the keys (Figure 11).

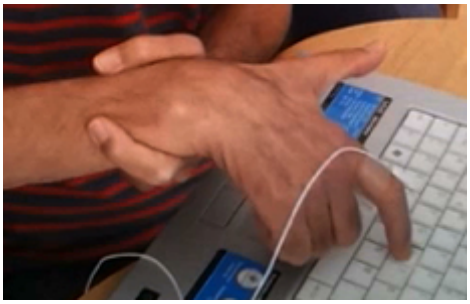

Figure 11 – (left) A patient who participated in our study is using the left hand to support his right forearm and enhance upper limb function in typing; (right) Representation of the distal function of UL when forearm is supported.

2.3.1.3 Voice banking

At this early stage, when bulbar symptoms are not perceived, ALS patients have the opportunity to anticipate speech dysarthria. Voice banking is an increasing practice for communication support in ALS. Patients record speech/voice for later incorporation in assistive communication device. Recorded voice allows personal and more authentic expression, when comparing to the inexpressive voice of speech synthesizers (Costello & Dimery, 2014). Guidelines for voice banking of patients with ALS are available online (for example in http://www.alsforums.com/guides/documents/Voice-Banking-Guidelines.pdf).

A very promising technology for ALS patients is the personalized speech synthesis. Voice features are extracted from the user and combined with a surrogate voice, generating a synthesizer with vocal identity of the user (Mills et

al., 2014; Yamagishi et al., 2012; ACAPELA, 2014). Despite voice banking should be done while ALS patient has no perceived speech disorder, there are techniques in which *disordered* speech can be repaired after recorded to be used in personalized synthesis; voice banking from familiar voices was also proposed to be used as a complement of patient's voice (Yamagishi et al., 2012).

2.3.2 Input signals and ACD in severely disabled patients

2.3.2.1 Eye movements

Advances in eye tracking technologies were responsible for the outbreak of eye-gaze input devices occurred in last two decades, also denominated by *eyecontrol*. Generalization of these devices brought new communication tools for those with severe upper limbs impairment, in particular ALS patients with decreased upper extremity motor function.

Many different methods have been developed to detect and track eye movements. The first methods were developed more than 100 years ago for research of reading. Initial methods for tracking the location of eye fixations involved direct mechanical contact with the cornea (Javel, 1878). Non-invasive techniques development to track eye movements started in the first half of 20th century. The first attempt was based on the use of light reflected from the cornea and recorded onto a photographic plate; further techniques based on combination of cornea reflection and motion picture techniques were developed by several scientists interested in studying eyes movements. Jacob and Karn (2003) describe in detail the history of eye-tracking systems, since the pioneer study with cornea reflection (Dodge & Cline, 1901) until precise and accurate systems of our days. The discovery that multiple reflections from the eye could be used to dissociate eye rotations from head movement (Cornsweet & Crane, 1973) improved tracking precision and also prepared the ground for further developments that today allow greater freedom of movements from users.

Most of the commercially available eye-gaze input devices are based on optical methods to measure eye motion, particularly one called "corneal-reflection/pupil-center" (Poole & Ball, 2005). This method is based on an infrared light that is generated by a LED in a camera (usually this camera is below the computer screen). Infrared is used for being invisible to humans eye. It is directed to the eyes, to create a strong reflection. Two images are captured by the camera

of the eye tracking system: the pupil is captured as a large bright dot and the cornea reflection (the first *Purkinje image*[1]) is detected as a small glint (as depicted in Figure 12). Vector formed from the center of the pupil and the corneal reflection gives accurate information on the eye position (*point-of-regard).* Techniques using multiple reflections from the eye, firstly proposed by Cornsweet and Crane (1973), increase accuracy by allowing to dissociate eye rotations from head or camera movements (Kolakowski & Pelz, 2006).

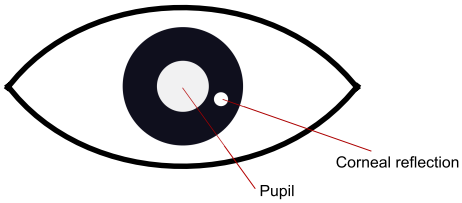

Figure 12 - Most common method for detecting eye movements for computer control in ACD are based on two images: the pupil and cornea reflection.

Using eyes as an input device (i.e. *eyecontrol*) for an ACD has some inherent difficulties. As Jacob & Karn (2003) describe in detail, the eye moves very differently from the intentional way the hand moves to perform a voluntary movement. Idea of using eye movements to choose options on a screen (e.g. choosing letters in an onscreen keyboard) and performing other pointing tasks is not as trivial as it may seem. On one hand, eyes can be used as a high-speed pointing device with no need for training, since brain dominates the control of this input. On the other hand, eye gaze is a sensory input that is related to complex cognitive tasks - eyes movements are often performed non-intentionally and not consciously. Typically, the user looks at the target on the screen and fixes gaze for a specific time (*dwell time*). This time acts like a threshold for a selection. As this input device is always "turned on" (a problem denominated as *Midas Touch*[2]) it can be frustrating and fatiguing to use it as input device for a specific task (for example, writing in the computer). Some methods were implemented in these input devices to avoid this problem. For example, using a different input device to perform selection (a switch or eye blink), instead of fixing eyegaze; another option

[1] Also named *Purkinje-Sanson images* due to Czech anatomist Jan Evangelista Purkyně (1787–1869) and French physician Louis Joseph Sanson (1790–1841).

[2] Everywhere you look another command is activated; you cannot look anywhere without issuing a command. (Jacob e Karn, 2003, pp.589-590)

is to use a mode of “standby” that user can activate and deactivate using eye-gaze based commands.

Good cognitive capabilities, few involuntary movements and absence of motor neuron degeneration in ocular motor nuclei related to eye muscles makes ALS patients one of the most important target group for eye-gaze access technologies. Input devices based on these technologies are small cameras that are placed on the screen of the computer, to track eye movements and translate them as a pointer to select any item in the screen. Recent advances in eye tracking devices integrated in augmented reality glasses are promising *wearable* communication tools for ALS-patients who are severely disabled.

Nevertheless, there are some drawbacks. Despite that muscles related to eye movements are usually spared in ALS, there can be problems with reliability in using eye-gaze access in late stages of ALS. Sellers et al. (2010, p.3) report the case of a patient who had a proficient use of the ACD: “*However, as his eye movements weakened, the device became unreliable, and he and his family despaired of his being able to continue the independent communication essential to his quality of life and to his professional productivity*”. Problems in system calibration or the need to repeat it often, difficulties due to inexperience in the use of a keyboard, previous vision problems, too many head or body movements or the need to have an ideal positioning (body and camera positions) were reported in other studies as difficulties in using this technology with ALS patients (Ball et al., 2010; Calvo et al., 2008). For its technological complexity, eye tracking systems may need more support for troubleshooting than other systems, which is a drawback for those patients living in long-term care facilities, where support for AT is scarce (as discussed in Chapter 6).

Technologies to detect eye movements that are based on non-optical methods are less used in the context of ALS patients. Electro-oculogram (EOG) is one of these non-optical technologies. It is based on detecting electrical muscle signals from the eye movements, as depicted in Figure 13. This technique has been developed by many researchers and proposed as input device for those with no upper limbs movements. As advantages, EOG signals have relatively high amplitude (when comparing to EEG), relationship between EOG and eye movements is linear, and eye movements are simple to detect (Lv et al., 2008).

Advantages that are related to the use of biosignals are further discussed in Chapter 6 . The EOG is the electrical signal obtained from potential difference between a positive pole, the cornea, and a negative pole, the retina (where there is a large number of nerve cells) and the cornea. Signal from this ocular dipole can thus be estimated by measuring the voltage induced across a system of electrodes placed around the eyes.

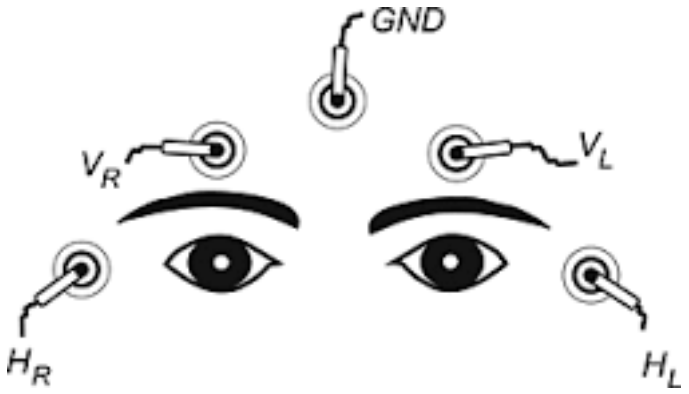

Figure 13 – Picture of an input device based on EOG capture (in Fricke et al. (2014), p. 196).

As the eye gaze changes, EOG can vary from 50 to 3500 μV, with a frequency range of about 100 Hz DC. It varies practically linearly for gaze angles of ±30º (Barea et al., 2002; Siriwadee et al., 2012). The amplitude of pulse will be increased with the increment of the rolling angle. EOG signals have certain patterns for each kind of eye gaze movement (horizontal movements: left, right; vertical movements: up, down; blink or wink) (Uşaklı, 2012). Several authors suggest EOG techniques for communication of ALS patients with severe motor impairment (Tsai & Chen, 2009; Dhillon et al., 2009; Park et al., 2005; Murakami et al., 2012). Using classification of different patterns in the EOG signal (corresponding to different eye movements), various methods are suggested, as writing on an onscreen keyboard by moving a cursor in two directions or blinking for switch input. Uşaklı (2012) developed an EOG system to ALS patients, reporting better accuracy, speed, applicability, and cost efficiency, when comparing their EOG system with a P300-based BCI system. In spite that EOG has been suggested as accurate input devices and potentially useful for patients with ALS or other severe motor disorder, results reported from experimental research were performed in healthy persons.

Miyasaka et al. (2013) refer to systems using this technique as having the advantage of detecting eye movements regardless the positioning of the patient or the opening angle of eyelids. Nevertheless, main problems of this technique are: the setup, as depicted in Figure 13, is not practical to implement in real scenarios of ALS and it is dependent on movements' speed to detect an input signal. Furthermore, occulomotor dysfunction, as slower saccades, vertical gaze palsy or abnormal eyelid movements have been observed in ALS patients (Okuda et al., 1992; Abe et al., 1995).

2.3.2.2 Head and neck movements

Although it is observable that slight head and neck movements are generally preserved until late stages, in the majority of patients, these are not evaluated for a functional perspective. However, Wicks et al. (2009) suggest a new item to add to ALSFRS-R:

> *To what extent have there been changes in your ability to move your head?*
>
> *4 - no change; can move head in all directions from a vertical position without head support*
> *3 - can move head in all directions from a vertical position with head support*
> *2 - can move head in all directions from a reclined or tilted back position with head support, and can nod or tilt head*
> *1 - can move head from left-to-right from a reclined or tilted back position with head support but have a very limited range of motion*
> *0 - cannot move head*

Frequently, when patients cannot use ULs to access communication tools, they are still able to control head movements to activate a head mounted switch or, in some cases, a *headmouse*.

The switch activated by head movements is often used by ALS patients with no UL movements (as depicted in Figure 14). Despite that this input device relies on scanning method (section 2.2.2), which is slower than other input devices (for example, comparing to eye-tracking input devices), it has the advantage of being simple and easy to use and to setup. Especially for those patients with lack of support for AT use, for example if a patient is living in a long-term care residence, the head mounted switch is a valid, feasible and efficient input device to use communication tools.

Figure 14 – A patient with severe dysfunction of upper limbs (ALSFRS-R-ul=0) using a head activated switch to control a keyboard based on the scanning method.

A *headMouse* is an input device that tracks head movements. Most common systems use a camera with an infrared transmitter, placed below or above the computer screen. Users wear a small and discrete infrared reflector (like a small dot) that is placed on the forehead, glasses or hat (Figure 15). As user moves their head, the camera tracks head's movements and translates them to pointing (mouse) control. Selections (mouse clicks) are performed either by a *dwell time* or by an external switch, as similar to eye-gaze input devices. Other approaches for *headmouse* use computer vision methods to visually track body features from real-time video. Eye, nose, lip, chin, thumb or dark light tracking were suggested by Betke et al. (2002) as body segments that can be used for tracking head movements to voluntary control a pointing input device.

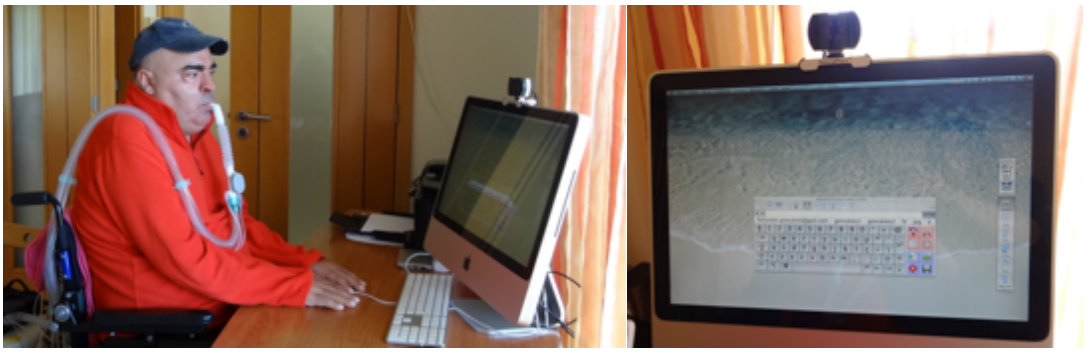

Figure 15 – (up) A man with ALS (who cannot move his upper limbs to control a computer mouse or to type) using an input device based on head movements. (down) Picture of the computer screen showing a virtual keyboard that this patient can use by head movements.

Despite the high sensitivity of head tracking, the necessary range of neck motion and the potential fatigue may reduce performance, when comparing to eye tracking systems. Bates and Istance (2003) found, in an experiment with healthy participants, that headmouse had shorter learning times and required lower workload with higher comfort to low experienced users, when compared to eye tracking pointing devices. Though, uncertainty in time of use due to the disease progression is the reason for preference of eye-tracking systems for ALS patients. Despite the lack of studies on the effectiveness of headmouse devices in ALS, these input devices are mentioned in various sources in Internet related to ALS, as ALS Associations websites or reports of patients' testimonials (for example in Wolf (2007), a patient testimonial refers: "*because of its flexibility and the excellent support (…), the HeadMouse served me well for about three and a half years*". Ball et al. (2010) refer to the example of an ALS patient who progressively did transition from head mouse to *eye tracking* due to extensive fatigue when using head movements.

2.3.2.3 Brain activity

A BCI is an input device that is controlled solely by brain activity. In last two decades, there was a rapid growth in BCI research, motivated by the hope that this technology can be a new communication channel for those who are severely disabled and cannot rely on muscle control for communication. Brain signals are recorded by BCI and transmitted as a control signal to an ACD, to external prosthetic devices or even directly to muscles (Figure 16).

Invasive BCIs use brain signals that are recorded from inside the body including: (1) action potentials from nerve cells or nerve fibers (2) synaptic and extracellular field potentials, and (3) electrocorticograms. Noninvasive BCIs are those that record brain signal with sensors placed out of the body. The brain signals recorded by this type of BCI are: (1) slow cortical potentials (SCP) of the EEG, (2) EEG and MEG oscillations, mainly sensorimotor rhythm (SMR), also called mu-rhythm, (3) P300 and other event-related brain potentials, (4) BOLD response in functional magnetic resonance imaging, or (5) near-infrared spectroscopy (NIRS) measuring cortical blood flow (Birbaumer, 2006; Marchetti & Priftis, 2015).

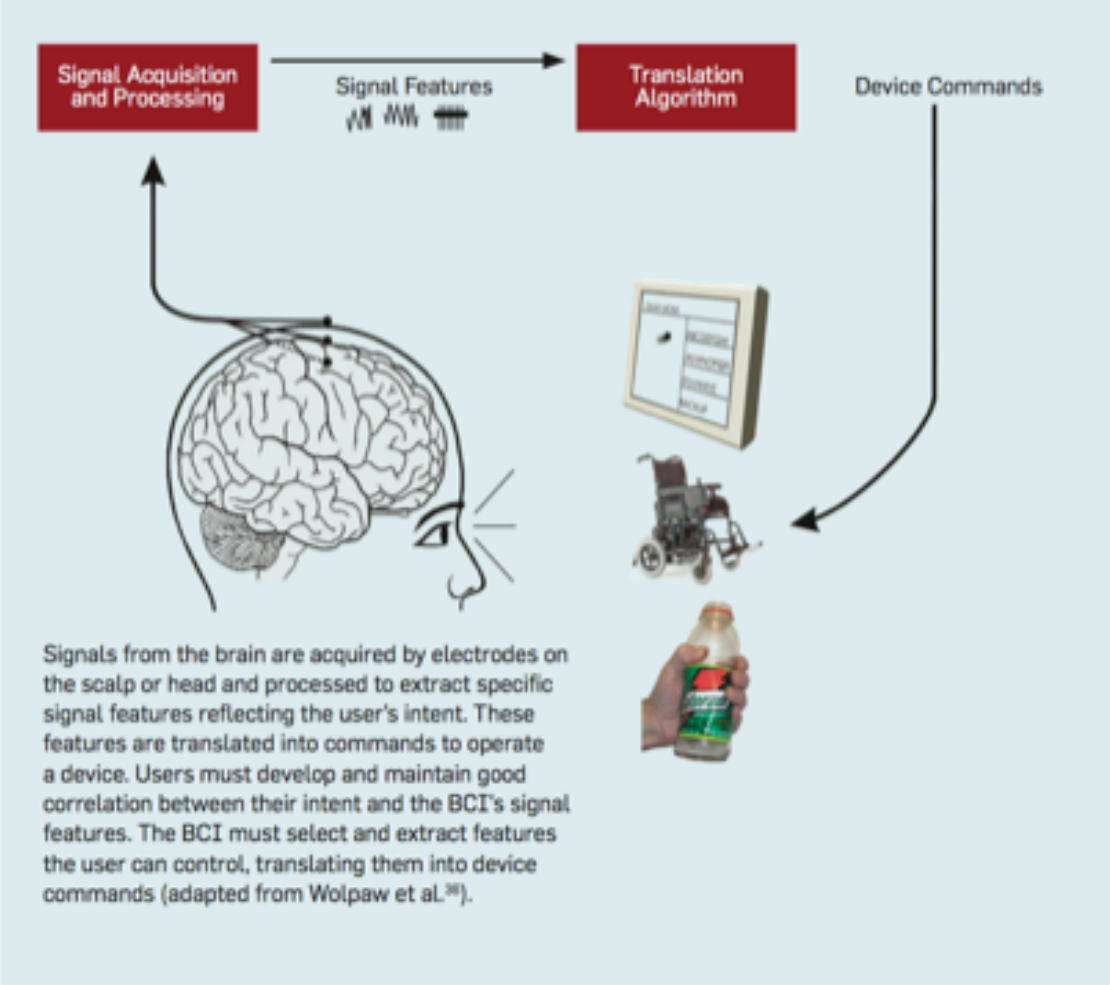

Figure 16 - Brain computer interface (McFarland & Wolpaw 2011, p.62).

Mainly those ALS patients who opt for artificial respiration may reach a state of *locked-in state*, with sparse (or any) voluntary muscle control. Visual P300 and SMR are the brain signals that showed better results in ALS (Birbaumer, 2006), but the first is the most mentioned in studies related to use of BCI by ALS patients. When patients have vision problems, auditory stimuli are an alternative to visual stimuli in P300-BCI (Nijboer et al., 2010).

Despite the promising results of this technology and the effort in developing simple and reduced cost devices and other applications than spelling (Holz et al., 2013; Schreuder et al., 2011; Bai et al., 2010; Münßinger et al., 2010; Mugler et al., 2010), some drawbacks persist. Training periods are long, professionals need to give continuous support due to its complex setup; signal-noise ratios are low; several electrode and skin problems occur due to long recording times; spelling speed is slow; choice of communication tools that can respond to individual needs

of BCI users is reduced; and ultimately, it demands high effort from the user, who must be very focused during spelling and spend many hours in training until they reach a reasonable success rate (Blain-Moraes et al., 2012; Sellers et al., 2010; Birbaumer, 2006).

Invasive BCI are attractive because using subdural implanted electrodes, signal to noise ratio is higher and success rate may improve significantly. Nevertheless, experiments with ALS patients or other in locked-in states (LIS) have been scarce and not successful, in part due to lack of persons in such conditions who agree to go through surgical implants. Wilhelm et al. (2006) report that 16 in 17 ALS patients in late stages (using invasive ventilation) rejected to implant macroelectrodes, even after being informed on the advantages of invasive BCI. Those patients preferred to use a slower input device for communication than going through surgical implantation. Furthermore, it is still not clear the influence of the disease and its progressive conditions in BCIs performance, when comparing patients with ALS in late stages to LIS due to other neurological conditions. Slow and inconsistent responses from ALS patients in late stages observed in invasive BCI may be caused by deterioration of cognitive functions or other disease constraints, as episodes of anoxia (Sellers et al., 2010; Birbaumer, 2006).

Combination of non invasive BCI with other input technologies, as eye tracking, *headmouse* or switch input devices, in multimodal or combined approaches have been reported as methods to reduce error rate, improve user performance and increase user acceptance as ALS disease progresses (Gürkök & Nijholt, 2012; Cincotti et al., 2008; Zander et al., 2010).

2.3.2.4 Other input signals

Mouth and tongue movements. Mouth-controlled text input devices (Cheng-Hong et al., 2003; Wu et al., 2010) and tongue-operated computer input devices (Huo et al., 2008; Yousefi et al., 2011) were proposed to the severely impaired. In spite that patients with ALS are referred as eligible candidates for these technologies, we found no reports on experiments with these patients.

Electromyography and other biosignals. Input devices based on electromyography have been proposed by several authors, for interaction with computer. These methods are attractive because sensors can be placed in any part of the body where minor muscle activity exists. Also, the effort to generate

voluntary EMG signal is lower than for pressing a mechanical switch. These have also been proposed as input signals for rapid selection (like a *mouse click*) in eye-tracking pointing devices (Surakka et al., 2004; Chin et al., 2008). As main problems of the EMG-based input devices are the noise from involuntary muscle activity that may generate false commands, difficulties related to sensors fixation or complex setup procedures (Pinheiro et al., 2011). In ALS, muscles in upper limbs and face may be good candidates for EMG control, despite lack of research studies on electrodes position for EMG control in ALS. Nöjd et al. (2008) presented a study on optimal position of electrodes for facial EMG and EOG, although results were performed with healthy subjects. As ALS is a neuromuscular disease, EMG control must be assessed for each patient, since there may be no general conclusions on optimal body region to place the electrodes. Moreover, it is expected that neurodegeneration process will lead to the need to change body region to place the electrodes. Concerning other input biosignals, Moore & Dua (2003) report the development of an input device based on the Galvanic Skin Response. This input device was tested in one patient with ALS. Mariano et al. (2014) developed an input device based on accelerometry to detect residual movements in severely disabled patients, though experiments were undertaken with healthy subjects.

2.4 **Impact of cognitive impairment on the use of ACD**

Until recently, ALS patients were elected as ideal candidates for assistive communication because it was thought that patients had no cognitive deficits. Despite that cognitive functional decline has been identified in the last two decades, its influence in AAC acceptance is still not clearly understood.

Some studies identify difficulties in the use of AAC possibly related to cognitive impairment. Ball et al. (2004) considered that primary reason for AAC rejection was early FTD symptoms, as observed in 2 (out of 50) participants in their study. Rejection was associated to spinal onset and rejection was not just in technological solutions but in any kind of communication support. These authors pointed-out resistance to change, inflexibility of thought and rigid personality trait, reported by Lomen-Hoerth et al. (2003) and Strong et al. (2009), as the main limitations for AAC acceptance. In another study, Cipresso et al. (2012) concluded that poor concentration, distractibility, and short-term memory difficulties, should

be taken into account, in order to adequately plan and realize AAC sessions to ALS patients for the use of P300-BCI technology.

However, other studies report that cognitive deficits in ALS seem to have a negligible effect in the use of technological devices for communication. Beukelman et al. (2011) prospectively analyzed a database of 87 patients supported in the same hospital. Multidisciplinary clinical screen revealed 18.4% and 4.6% patients with mild cognitive impairment and FTD, respectively; 77% did not reveal cognitive impairment. According to the authors, just 2 patients with mild cognitive impairment and 2 patients with FTD were not successful in the use of AAC. The same authors report that, while their ALS clinical team manifested concern on patients' cognition when referring to communication support, this seem to have not affected those patients' acceptance and successful use of AD to meet their communication needs.

Brownlee & Bruening (2012) pointed-out to the fact that executive function interferes with decision-making – a resource need when selecting the AAC device or in the learning/training process for using the device or for deciding new access strategy. However, in accordance to results in the study of Beukelman et al. (2011), it is critical to distinguish between cognitive impairment scores resulting from neuropsychological standardized assessment and functional cognitive skills in daily living. Each individual with ALS reacts to the loss of communication in a unique way and may change over time, depending on many personal, physical or social factors. A close support to the patients in their decisions and in anticipating their relevant impairments is essential.

Chapter 3 - Rationale, objectives and methods

3.1 **Rationale**

Recent mass marketing of tablet and smartphone devices, as well as advances in novel input technologies (such as touchscreens, eye tracking devices or BCI) observed in the last decade, represent a new generation of ACD with enormous potential impact in support of patients with ALS and other neurological conditions (McNaughton et al., 2013; Fager et al., 2012b; Beukelman et al., 2011). These ACDs provide not just an alternative to speech, but also communication tools connected to a new generation of Internet services that may remotely support patients in health and social care (Shane et al., 2012; van den Broek et al., 2009). As reported by INTEL (2008), "*technologies that can improve and enhance* [patients' and caregivers'] *social connectedness will be at an advantage"*. For example, using the internet for online assessment of ALSFRS-R, as suggested by Maier et al. (2012), or using the computer for supporting advanced care planning, as suggested by Hossler et al. (2011), are examples of the potential benefits of modern ACD as tools to access to clinical support. Further, as the benefits of home telemonitoring of non-invasive ventilation have been demonstrated for ALS (A. Pinto et al., 2010), ACD could potentially augment these benefits by allowing remote communication between health professionals and the patient, along the whole course of the disease.

Despite the technological advances, several main difficulties related to the support for ACD in ALS persist: (1) the lack of clinical outcomes that could confirm the expected positive impact related to the use of these technologies; (2) the lack of clinical assessment tools to evaluate the progression of patients' functional impairment that specifically affects the use of ACD; (3) late referral (when patients are severely disabled and extremely dependent on others' decisions); and (4) a limited perspective on ACD, often solely considered as an alternative to speech.

Communication is a concern in recent clinical guidelines for ALS management (Miller et al., 2013; Andersen et al., 2012), though lack of clinical evidence on the benefits of ACD for ALS patients may hinder its general use and funding. Two recent prospective studies indicated a positive impact of ACD in the

QoL of ALS patients. Körner et al. (2012) studied the impact of ACD on the mood and quality of life of a group of ALS patients who used ACD, compared with a group of patients who did not use ACD. Caligari et al. (2013) studied the impact of using ACD based on eyetracking interaction on the QoL of a group of ALS patients. However, there is limited evidence documenting how the use of ACD from the early stages of disease progression affects QoL of patients and their caregivers.

As speech dysfunction increases, ALS patients move from speech to written communication (Murphy, 2004a). While speech has been extensively studied in ALS, in particular concerning characteristics and progression of dysarthria, written communication, in terms of function of UL movements, is not well characterized. Ball et al. (2001) indicated speech rate as a predictor of deterioration of speech intelligibility in ALS. However, taking into consideration that most of the ALS patients will have difficulties in using UL for handwriting or accessing to mainstream devices to write (e.g. a *smartphone*), further research on how long can a patient rely on UL movements for communicating is needed.

Most of the studies related to the use of ACD rely on groups of patients that are already severely disabled. One example is the high enthusiasm from the research community for BCI specifically oriented for ALS patients. In fact, late referral is a common practice, since patients, caregivers and health professionals tend to postpone decisions on the use of ACD until no other alternatives are possible. Nevertheless, late referral has been studied as a difficulty for successful use of ACD by ALS patients (Beukelman et al., 2011; Brownlee & Bruening, 2012). Light & McNaughton (2014) refer to motivation and confidence as general psychosocial factors involved in the competence to using ACD. These factors may be affected in late stages of ALS (Nijboer et al., 2010), in particular when input devices are difficult to set up or need a significant time to learn. Further studies on the impact early support in the use of ACD are necessary to improve patients' communication during the whole course of disease progression.

3.2 **Objectives**

The overall purpose of this PhD thesis is threefold: (1) to investigate the impact of ACD on QoL of early-affected patients with bulbar-onset ALS and on their caregivers; (2) to test the hypothesis that ACD can support tools for remote

functional monitoring; and (3) to identify novel methods to assess quantitatively the functional performance of patients in communication, in different stages of ALS.

Our contribution is expected to:

i) Reveal scientific evidence that early support with ACDs has a positive impact on the QoL of ALS patients and their caregivers, even in a population with poor experience with the use of computer devices;

ii) Identify novel methodologies to monitor UL function, related with the use of ACD.

iii) Broaden the classical perspective of ACD as technologies with the single purpose of improving communication, by demonstrating its potential application as in-home clinical remote monitoring tool.

iv) Show how to explore the potential of input biosignals generated by residual muscular movements in the body, to enhance communication in very affected ALS patients.

v) Contribute with methodologies for the development of new input devices, based on the concept that ACD should be changed over disease progression, taking into account the necessary flexible adaptation to the patient and caregivers conditions.

3.3 **Organization of the research**

The research work is organized in three chapters: chapter 4 - Quality of life in ALS patients and caregivers: impact of assistive communication; chapter 5 - Monitoring disease progression with assistive communication devices: speech and typing activity and chapter 6 - Communication during stages of severe dysfunction: development of a new input device to assess novel input signals.

3.4 **Methods**

Most research was based on longitudinal data collected from a homogeneous population of 30 early-affected bulbar-onset ALS patients followed at the ALS outpatient consultation of the Department of Neurosciences (Hospital de Santa Maria-Centro Hospitalar Lisboa Norte), over a period of 29 months. As there were no previous studies including our outcomes, we could not calculate the number of patients required to attain the expected results. We estimated that recruitment of 30 patients would be appropriate to our goals.

Patients with bulbar-onset symptoms were selected for the following reasons: (a) they present early speech dysfunction; (b) this group is understudied (concerning the use of ACDs); (c) they represent 25-30% of total number of ALS patients, in general with a faster progression rate.

All data presented in this dissertation was collected in clinical environment, both by myself and by medical doctors in Neurology and Rehabilitation, co-authors in the main publications supporting this thesis.

Quality of life, methodologies for assessment of communication performance and markers of disease progression were the main clinical outcomes in this research. Other outcomes related to behavioral dysfunction in the use of technology, assessment tools and new input devices are of interest for the engineering field, where new technological instruments should be developed.

Chapter 4 - Quality of life in ALS patients and caregivers: impact of assistive communication

4.1 Introduction

Recent recommendations for clinical management in ALS indicate that patients' autonomy and ability to communicate should be promoted (Miller et al., 2013; Andersen et al., 2012). Accordingly, communication has been rated by ALS patients as one of the most important domains for their own independence (Gruis et al., 2011).

Severe dysarthria has great impact on the QoL of ALS patients, since most patients become unable to communicate through speech at some stage of the disease, in spite of speech therapy interventions (Tomik et al., 1999; Körner et al., 2012).

In bulbar-onset patients, early deterioration of speech intelligibility (Ball et al., 2001) leads to rapid replacing of speech by handwriting (often a pen and a notepad for peer-to-peer communication), until UL muscle weakness demands new strategies for communication (Brownlee & Bruening, 2012; Bloch & Clarke, 2013). In any case, as the disease progresses, most patients must replace speech by communication based on text input (handwriting, use of computer or paper-based letter board).

Modern tablet devices used as tablet-based assistive communication devices, with touchscreen input, can allow bulbar-onset patients to maintain autonomy in communication, through simple applications with speech synthesizers. Nevertheless, its use is strongly dependent on the decision and expectations of patients, their caregivers and health professionals. As long as residual capacity for communicating through speech or handwriting is present, the use of communication devices may not be considered. When communication alternatives lack (severe dysarthria associated with severe UL dysfunction), technologically more advanced methods have to be explored. Timely referral and economic burden remain critical issues in decision-making for communication support in ALS. Besides, late referral is one of the main causes for low acceptance; indeed, the adaptation of patients with marked generalized weakness

to new strategies (e.g. eye-tracking or even brain-computer interfaces) can be a difficult process, especially when there is lack of experience or support for continuous training in the use of these ACD (Brownlee & Bruening, 2012; Beukelman et al., 2011).

Particularly, when patients' disability is severe, the use of ACD relies on the caregivers' support for daily setup and maintenance. For this reason caregivers' needs, skills and expectations must be considered as important factors in clinical intervention with ACD (Beukelman et al., 2011; Murphy, 2004b). Difficulty to understand patients' needs and feelings is the chief caregivers' motivation for supporting intervention with ACD (Fried-Oken et al., 2006). Furthermore, patient´s autonomy regarding communication has been reported as an essential *family caregiver need* that may influence their own quality of life (Williams et al., 2008).

The main outcome of the present study is to explore, longitudinally, the impact of the introduction of tablet-based ACDs on the quality of life of early-stage bulbar-onset ALS patients and their caregivers. Secondary outcomes are self-perceived communication and performance of writing (handwriting and typing) in order to monitor UL function regarding their use in ACD based on touchscreen input.

4.2 **Materials and Methods**

4.2.1 Patients

ALS patients were included with the following inclusion criteria: probable or definite disease according to the revised El Escorial criteria (Brooks et al., 2000); bulbar-onset, as defined by initial symptoms of dysarthria and/or dysphagia; bulbar score of dysarthria of 3 or 2 (mild or moderate impairment) as given by the first question of the ALSFRS-R; informed consent. Patients with other medical conditions, respiratory symptoms or clinical evidence of dementia were excluded. Main caregiver was identified by the patient as the person providing daily support and accompanying them in the clinical visits (frequently the husband/wife or a sibling). The caregiver did not change over the duration of this study.

The research was approved by joint Ethics committee Centro Hospitalar Lisboa Norte-Faculdade de Medicina de Lisboa and patients and caregivers gave written informed consent.

4.2.2 Procedure

Patients were assessed three times: at entry (T0); 3-4 months later (T1); 7-10 months after entry (T2). Caregivers were assessed 2 times, at T0 and T2. Assessments were made at our clinic, exceptionally at the patient's home. At each visit, patient and caregiver were interviewed separately. The duration of the complete assessment was 30 minutes, approximately. At T0 patients were also randomized in 2 groups according to the intervention time (Group 1, G1 - Early intervention, patients received a ACD just after baseline assessment; Group 2, G2 - late intervention, patients were followed and received communication devices according to the conventional approach in our centre (referral when dysarthria score is 0 or 1 on the ALSFRS-R, meaning anarthria or severe dysarthria). ACD consisted in a small and light touchscreen-tablet device (approximately 200x130mm), commercially available in the market. We used a software based on a simple onscreen keyboard for text-to-speech communication with text prediction (Figure 17). This software was commercially developed for the specific purpose of text-to-speech communication and is available to download from the internet; for our choice, an important feature was that this software included the possibility to be used with different access strategies, alternative to touchscreen. Patients and caregivers were trained and supported, during local clinical appointments, for using this ACD. Those patients who had internet connection at home were instructed to use email communication through the ACD. Email communication was tested and stimulated by sending emails (demanding reply) periodically, during the period of this study.

Figure 17 – A participant of this study using an assistive communication device: writing on a touchscreen-accessed keyboard with speech synthesis.

Patients underwent the following questionnaires: McGill Quality of Life questionnaire (MQoL), ALSFRS-R and modified Communication Effectiveness

Index (CETI-m). Caregivers completed the questionnaires MQoL and World Health Organization quality of life-BREF (WHOQoL-bref), related to their own QoL. All these tests have been used in ALS, as well as they have been translated and validated in Portuguese.

Both patients and caregivers answered to a self-designed questionnaire, rated on a 0 to 5 Likert-type scale, to assess to previous experience with computer devices (Table 1).

4.2.3 Quality of Life

4.2.3.1 McGill Quality of Life questionnaire

The MQoL (Cohen et al., 1995) consists in a questionnaire with 16 items, each rated on a Likert-type scale from 0 to 10. Questions include two health-related domains (Physical symptoms and MQoL-Phys: Physical well-being), three non-health related domains (MQoL-Psych: Psychological symptoms, MQoL-Exist: Existential well-being and MQoL-Support: Support (related to the feeling of being cared), a single-index score (MQoL-SIS) and a descriptive section (MQoL-part D), where the inquired can list what had greatest impact (positive or negative) on their QoL in the past two days. This instrument has a total score (MQoL-tot) and subscores for each domain, range 1 to 10 (higher scores indicate greater QoL). It is sensitive to psychological, supportive and spiritual factors, more than to health related QoL measures (Epton et al., 2009). MQoL has been used in various studies related to QoL of ALS patients (Gauthier et al., 2007; Chiò et al., 2004; Robbins et al., 2001).

4.2.3.2 World Health Organization quality of life-BREF (WHOQOL-BREF)

WHOQOL-BREF (Skevington et al., 2004; WHOQOL Group, 1998) is a 26-item questionnaire for measuring QoL in four domains: (1) physical health and well-being; (2) psychological health and well-being; (3) social relations; (4) environment (related to financial resources, health and social services, home and physical environment, among others). Items are rated on a 1 to 5 Likert-type scale and scores are calculated for a 100 points scale (greater scores correspond to better QoL). Ratings range from 1 (very poor) to 5 (very good). This questionnaire has been extensively used to investigate QoL of patients and caregivers in

different chronic diseases, including ALS (Baumann et al., 2012; Lo Coco et al., 2005).

4.2.4 Functional Measurements

ALSFRS-R was applied at each visit. It is an instrument used for monitoring progression of functional disability of patients with ALS (Cedarbaum et al., 1999). Each question in ALSFRS-R (total of 12 questions) is rated from 4 (normal function) to 0, according to progressive functional impairment. We registered the total score (ALSFRS-R), which is rated from 48 (normal) to 0, and two subscores: bulbar function (ALSFRS-R-b) (Pinto et al., 2009) and upper limb function (ALSFRS-R-ul) (Kollewe et al., 2011). Subscores are rated from 12 to 0 and were calculated by summing the first three questions and the fourth to sixth questions of ALSFRS-R, respectively. ALSFRS-R-b rates speech, salivation and swallowing functions; ALSFRS-R-ul rates UL function related to handwriting, handling utensils in daily activities and dressing.

The modified Communication Effectiveness Index (CETI-m) (L. Ball et al., 2004b) is an adaptation from the original CETI designed for persons with aphasia. It is a valid measure of functional communication and is sensitive to changes in performance over time (Lomas et al., 1989). The CETI-m rates self-perceived limitation of a person when communicating; it consists of 10 questions related to communication in different contextual situations rated on a visual Likert-type scale. Total score is given by the sum of the individual scores, presented on a 100-point scale, representing the minimum (0) to maximum (100) communication effectiveness.

4.2.5 Performance measures

To monitor performance of UL in written communication, at each evaluation session, patients were asked to write, sequentially, three different sentences with two different modalities: handwriting and using a keyboard (Figure 18). Both performance of handwriting and typing on a keyboard were calculated as the mean rate of the writing tasks, measured as words per minute (wpm).

Figure 18 - Assessment of performance in handwriting (left); assessment of performance in typing (right).

4.2.6 Statistical Analysis

Primary outcomes were scores from MQoL (single index item, total score, physical, psychological health, existential well-being and support) and WHOQoL scores (four domains: physical health and well-being; psychological health and well-being; social relations and environment). Secondary outcomes were ALSFRS-R total, ALSFRS-R-b, ALSFRS-R-ul, CETI-m, typing rate and handwriting rate.

Descriptive statistics was used to characterize participants and results of the self-designed questionnaire. Pearson and Spearman correlation coefficients were used to examine associations among different variables, for normal and non-normal data distribution, respectively. Changes in outcome variables, between T0 to T2, were analyzed by paired sample T-test and Wilcoxon Signed Rank test. T-Test and Mann Whitney U for independent samples were used to test differences between the two different groups (G1 vs G2). A *p*-value of <0.05 was considered for statistical significance. For each of the statistical analysis, we used Bonferroni adjustment of the p value for multiple comparisons. However, taking into account the exploratory profile of this study, we considered $p<0.05$ without correction for multiple comparisons as a trend that was worth reporting.

4.3 **Results**

Twenty-seven ALS patients with a mean age of 64.8 (SD=10.2; range: 39 to 83) were included. From these, one declined immediately after baseline assessment and 5 were evaluated only twice due to rapid disease progression (Figure 19). Only 17 caregivers were interviewed (4 patients came to clinical visits alone or with different persons; 6 caregivers declined to fill-in the questionnaires).

Most of patients were women (81.5%), the previous experience in the use of computers, rated by patients from 0 to 5, was, generally, low (median: 2). Low school education and poor previous experience with technology of most of the participants is in agreement with the demographic characteristics of the Portuguese population within this age group. Table 2 describes demographic data of participants.

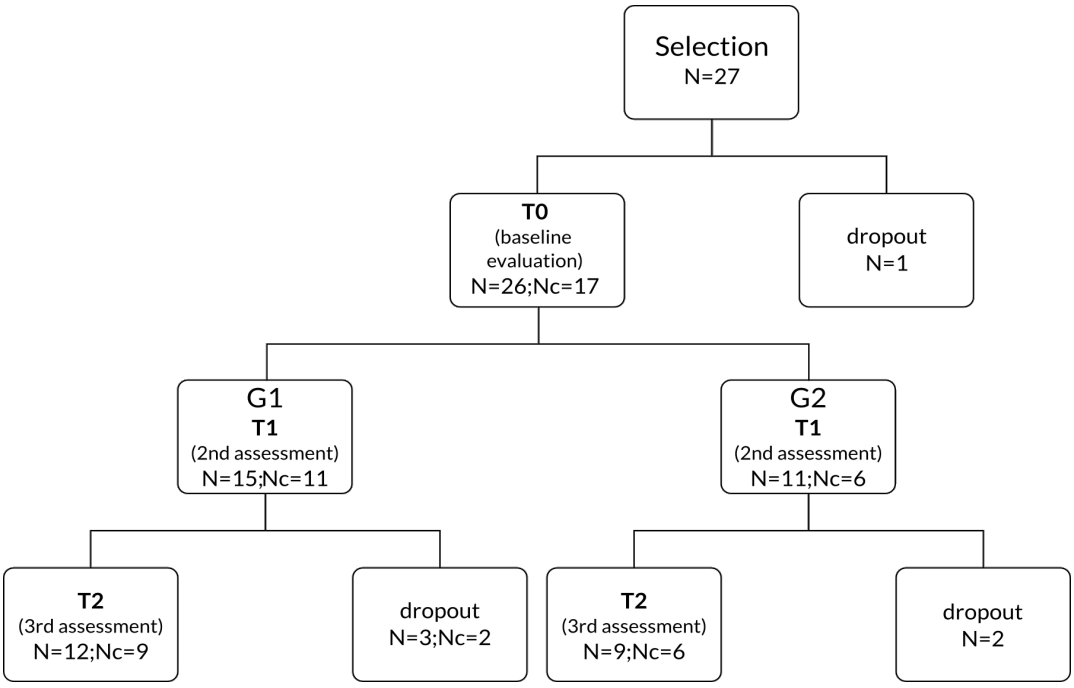

Figure 19 - Flowchart of the recruitment process. N, number of patients; Nc, number of caregivers.

Patients in G1 started to use the ACD after baseline assessment (Figure 17). There was no record of spontaneous use of assistive communication devices in patients randomized to G2. Table 3 presents mean scores of the outcome variables of this study, for each time of assessment.

We analysed each domain of QoL questionnaires and compared scores between different assessments and groups of patients and caregivers. No significant result was found when considering the adjusted p-value for multiple comparisons (Table 3 and Table 4). However, we observed a trend in favor of the influence of ACD on the QoL.

Table 1. Questionnaires and tests applied and respective ranges.

Test/questionnaire	Range	Time
ALSFRS-R	0 (max disability) to 48 (normal)	T0,T1,T2
ALSFRS-R-b	0 (max disability) to 12 (no bulbar symptoms)	T0,T1,T2
ALSFRS-R-ul	0 (max disability) to 12 (no upper limitations)	T0,T1,T2
WHOQoL-BREF	0 (poorest QoL) to 100 (max QoL)	T0,T2
MQoL MQoL-sis (single item score)	0 (lowest QoL) to 10 (highest QoL) 0 (very bad) to 10 (excellent)	T0,T1,T2
Communication Effectiveness Index (CETI-m)	0 (no communication) to 100 (normal)	T0,T1,T2
Performance in typing Performance in handwriting	words per minute (wpm)	T0,T1,T2
Self designed questionnaire for patients and caregivers: How much are you familiar to computer devices?	0 (I never used a computer) to 5 (I am an expert)	T0

4.3.1 Quality of Life

4.3.1.1 Patients

Mean values calculated for all patients (through MQoL) showed a decrease in total, physical and existential domains of quality of life ($p<0.05$), as described in Table 3. Single-index score, psychological symptoms and support domains did not change with time ($p>0.05$). In descriptive parts of MQoL (physical symptoms and part D), twenty three patients (88.5%) referred, in one or more assessments, to speech problems or difficulty to be understood by others, as negative factors in QoL; two patients in G1 referred to communication device as having a positive impact in QoL.

Table 2. Characteristics of all participants at baseline (T0): patients and caregivers.

	Patients	Caregivers
Total (N)	27	17
Gender *(f/m)*	22/5	6/11
Mean age (standard deviation)(range)	64.8±10.2 (39-83)	57.52±13.9 (26-81)
Education		
- Primary school	12 (44.4%)	5 (22.7%)
- Elementary/High school	10 (37%)	6 (27.3%)
- University	5 (18.5%)	6 (27.3%)
Relation of caregiver		
- Husband/wife	-	10
- Sibling	-	7
Previous computer experience		
(Level 0 to 5) *median(mode)*	2(0) (range: 0-4)	3(4) (range: 0-5)
Internet access at home	12 (44%)	-

Table 4 shows comparison between scores obtained for patients in G1 and those in G2, in the three periods of evaluation. Patients with early intervention with ACD had higher MQoL scores than the other patients, in particular for existential well-being domain at T1 (p=0.045), and psychological symptoms domain, both at T1 (p=0.047) and T2 (p=0.032) – when considering p-values without correction for multiple comparisons.

Table 3. Mean values of dependent variables tested in this study, for the whole population of patients considering the time of assessment (T0, T1, T2) as the independent variable. Statistical significance was calculated for adjusted p-value for multiple comparisons (Bonferroni method). However, p-values <0.05 without correction for multiple comparisons were accepted as a trend.

	T0		T1		T2		
	Mean	SD	MEAN	SD	MEAN	SD	p (T0,T2)
ALSFRS-R	27.18	8.54	22.15	8.96	15.50	7.88	<0.001*† ‡
ALSFRS-R-b	6.32	2.71	4.75	2.47	2.75	2.05	<0.001*‡
ALSFRS-R-ul	9.45	3.04	8.25	4	6.44	4.34	0.002*† ‡
Handwriting rate	16.2	6.6	14.1	9.8	10.7	9.8	0.002* ‡
Typing rate	9.2	5.2	8.5	5.4	6.7	4.9	0.317
CETI-m	67.17	28.6	45.50	23.65	39.53	20.9	<0.001 ‡
MQoL-tot (patient)	6.64	1.18	6.32	1.12	5.75	0.95	0.010 ‡
MQoL-SIS (patient)	6.04	1.69	5.64	1.75	5.10	1.84	0.054 †
MQoL-Phys (patient)	5.50	2.10	4.92	1.82	4.42	1.5	0.027 ‡
MQoL-Psych (patient)	5.06	1.96	4.91	2.02	4.35	1.57	0.141
MQoL-Exist (patient)	7.15	1.76	7.03	1.41	6.12	1.62	0.025 ‡
MQoL-Sup (patient)	8.46	1.78	8.52	1.91	8.63	1.05	0.710 †
MQoL-tot (caregiver)	5.64	1.48	NA	NA	5.21	1.56	0.177
MQoL-SIS (caregiver)	5.13	1.51	NA	NA	3.73	2.12	0.030 ‡
MQoL-Phy (caregiver)	5.5	2.37	NA	NA	5.21	2.36	0.675
MQoL-Psych (caregiver)	4.76	2.12	NA	NA	4.15	2.24	0.398
MQoL-Exist (caregiver)	6.42	1.03	NA	NA	6.16	1.67	0.624
MQoL-Sup (caregiver)	5.92	1.81	NA	NA	5.42	2.23	0.428
WHO-phys (caregiver)	65.85	15.92	NA	NA	49.74	19.59	0.009* ‡
WHO-psych (caregiver)	63.28	18.89	NA	NA	54.72	18.89	0.038 ‡
WHO-social (caregiver)	60.42	23.86	NA	NA	60.12	17.04	0.749
WHO-envir (caregiver)	63.09	10.35	NA	NA	48.75	13.3	0.003* ‡

** indicates statistical significance for adjusted p-value (Bonferroni method), paired-t test*
† indicates statistical significance for adjusted p-value (Bonferroni method), calculated for comparison between T0 and T2, by Wilcoxon Signed Rank Test;
‡ indicates p<0.05, without correction for multiple comparisons (trend)
NA = not applicable

4.3.1.2 Caregivers

Mean scores of caregivers' quality of life (MQoL) (Table 3) decreased from T0 to T2, though just the single-index score (MQoL-SIS) attained a difference with

p<0.05. Mean scores of WHOQoL-bref showed a decrease (p<0.05) in all domains, from T0 to T2, except for Social Relations domain (p=0.749). In descriptive item of MQoL (part D), eight (47%) caregivers referred to patient´s speech problems as having a negative impact in their own quality of life; 5 out of 11 (46%) caregivers of patients in G1 considered ACD as having a positive impact in their quality of life.

Table 4. Mean values of dependent variables tested in the three evaluation periods (t0, t1, t2), comparing results between G1 and G2. There were no statistical significant differences between the two groups, considering adjusted p-value for multiple comparisons (Bonferroni method). Statistical comparisons with p-value less than 0.05 are indicated in the table as significant.

	T0					**T1**					**T2**				
	G1		**G2**		**p**	**G1**		**G2**		**p**	**G1**		**G2**		**p**
	MEAN	SD	MEAN	SD		MEAN	SD	MEAN	SD		MEAN	SD	MEAN	SD	
ALSFRS-T	25.86	9.30	29.50	6.99	**0.207†**	21.23	7.81	23.86	11.26	**0.201**	15.17	7.00	16.50	11.36	**0.136**
ALSFRS-B	5.57	2.24	7.63	3.11	**0.070**	4.31	2.04	6.14	2.73	**0.088**	3.00	2.22	3.83	3.06	**0.516**
ALSFRS-R-ul	9.21	3.47	9.88	2.23	**0.192†**	8.15	3.48	8.43	5.13	**0.715†**	6.25	4.22	7.00	5.29	**0.776**
Handwriting rate	16.67	6.86	13.4	2.96	**0.326**	14.28	9.53	8.51	8.06	**0.831**	11.8	9.97	10	8.96	**0.778**
Typing rate	9.05	5.50	9.46	5.10	**0.716†**	8.34	4.68	8.80	7.10	**0.337**	7.99	5.02	7.09	6.53	**0.761**
CETI-m	64.67	27.26	71.33	31.92	**0.592**	44.53	20.63	47.11	29.31	**0.570**	48.83	16.24	17.20	11.80	**0.027‡**
MQoL-tot (patient)	6.82	1.10	6.37	1.42	**0.382**	6.69	1.04	5.76	1.17	**0.063**	5.97	0.93	5.07	0.97	**0.205**
MQoL-SIS (patient)	5.73	1.62	6.44	1.81	**0.329†**	6.00	1.84	5.00	1.73	**0.255**	5.00	1.81	5.40	2.70	**0.792**
MQoL-Phys (patient)	5.45	2.16	5.53	2.13	**0.927**	5.00	1.92	4.82	1.78	**0.811**	4.50	1.51	3.80	1.30	**0.774**
MQoL-Psych (patient)	5.34	2.21	4.68	1.57	**0.405**	5.61	2.20	4.01	1.39	**0.047‡**	4.93	1.59	3.18	1.10	**0.032‡**
MQoL-Exist (patient)	7.25	1.60	7.00	2.03	**0.728**	7.52	1.37	6.40	1.24	**0.045‡**	6.53	1.65	5.02	1.15	**0.155**
MQoL-Sup (patient)	8.77	1.62	8.05	1.98	**0.318**	8.79	1.67	8.18	2.21	**0.456†**	8.54	1.10	8.80	1.15	**0.639**
MQoL-tot (caregiver)	5.39	1.38	5.97	1.37	**0.423**	NA	NA	NA	NA	NA	5.10	1.57	5.37	1.68	**0.766**
MQoL-SIS (caregiver)	5.00	1.48	5.33	1.37	**0.650†**	NA	NA	NA	NA	NA	3.56	2.13	4.00	2.28	**0.706**
MQoL-Phy (caregiver)	4.73	2.24	6.67	2.25	**0.109**	NA	NA	NA	NA	NA	4.00	1.93	6.83	1.94	**0.019‡**
MQoL-Psych (caregiver)	5.05	2.41	3.65	1.38	**0.212**	NA	NA	NA	NA	NA	4.23	2.09	4.05	2.62	**0.892**
MQoL-Exist (caregiver)	6.05	0.84	6.80	1.17	**0.148**	NA	NA	NA	NA	NA	6.23	1.71	6.07	1.77	**0.869**
MQoL-Sup (caregiver)	6.30	1.44	4.42	1.83	**0.633**	NA	NA	NA	NA	NA	6.71	1.41	3.92	2.13	**0.016‡**
WHO-phys (caregiver)	68.57	17.56	61.31	12.86	**0.396**	NA	NA	NA	NA	NA	44.44	16.76	59.28	22.53	**0.184**
WHO-psych (caregiver)	62.08	19.09	65.28	20.18	**0.756**	NA	NA	NA	NA	NA	50.46	17.73	61.11	20.36	**0.392**
WHO-social (caregiver)	60.00	26.87	61.11	20.18	**0.932**	NA	NA	NA	NA	NA	58.33	15.02	63.33	21.73	**0.530†**
WHO-envir (caregiver)	63.13	10.91	63.02	10.35	**0.662†**	NA	NA	NA	NA	NA	48.27	8.72	49.48	19.31	**0.870**

† corrected p-value < 0.05, by Mann-Whitney U Test and by t-test for independent samples
‡ indicates p<0.05, without correction for multiple comparisons (trend)
NA = not applicable

Comparing results from caregivers of patients in G1 vs G2, no statistically significant difference was found for the corrected p-values. However, considering the uncorrected p-value < 0.05 as a trend, we identified a higher quality of life in G1, for the following domains: physical well-being (p=0.019) and support (p=0.016) (Table 4). No differences between the two groups (p>0.05) were found in any of the WHOQoL-bref domains (Table 4).

Caregivers' MQoL scores and patients' MQoL scores were not correlated in any of the periods (p>0.05).

4.3.2 Functional Measurements

As expected, evaluation of bulbar function (ALSFRS-R-b score) decreased significantly over time (Table 3); decline was linear as showed no difference in the percentage of change between T0-T1 and T1-T2. We found no significant difference between the two groups of patients, regarding bulbar score decline (Table 4). The higher the bulbar impairment (lower ALSFRS-R-b scores), the lower the self-perceived communication effectiveness index (CETI-m) of patients in G1 (r=0.419, p<0.001) and G2 (r=0.809, p<0.001). However, when considering data from patients in G1, after they started to use ACD (T1 and T2), patients with lower bulbar functional scores did not necessarily have lower self-perceived communication (r=0.101, p=0.629).

In general, we found positive correlations between patients' quality of life, bulbar function and self-perceived communication: the higher the bulbar dysfunction (lower ALSFRS-b score), the lower the quality of life, both in total score (r=0.297, p=0.019) and in single-item score (r=0.280, p=0.028). Patients with higher scores in self-perceived communication effectiveness had higher quality of life, both in total score (r=0.268, p=0.027) and in psychological symptoms domain (r=0.265, p=0.029).

No correlations were found between caregivers' QoL scores and patients' bulbar function (ALSFRS-R-b) or communication (CETI-m) scores, for the whole group of caregivers. However, when analyzing caregivers of patients who received early ACD intervention, we found that patients with higher self-perceived communication had caregivers with higher scores in quality of life, for psychological symptoms domain of MQoL (r=0.515, p=0.011).

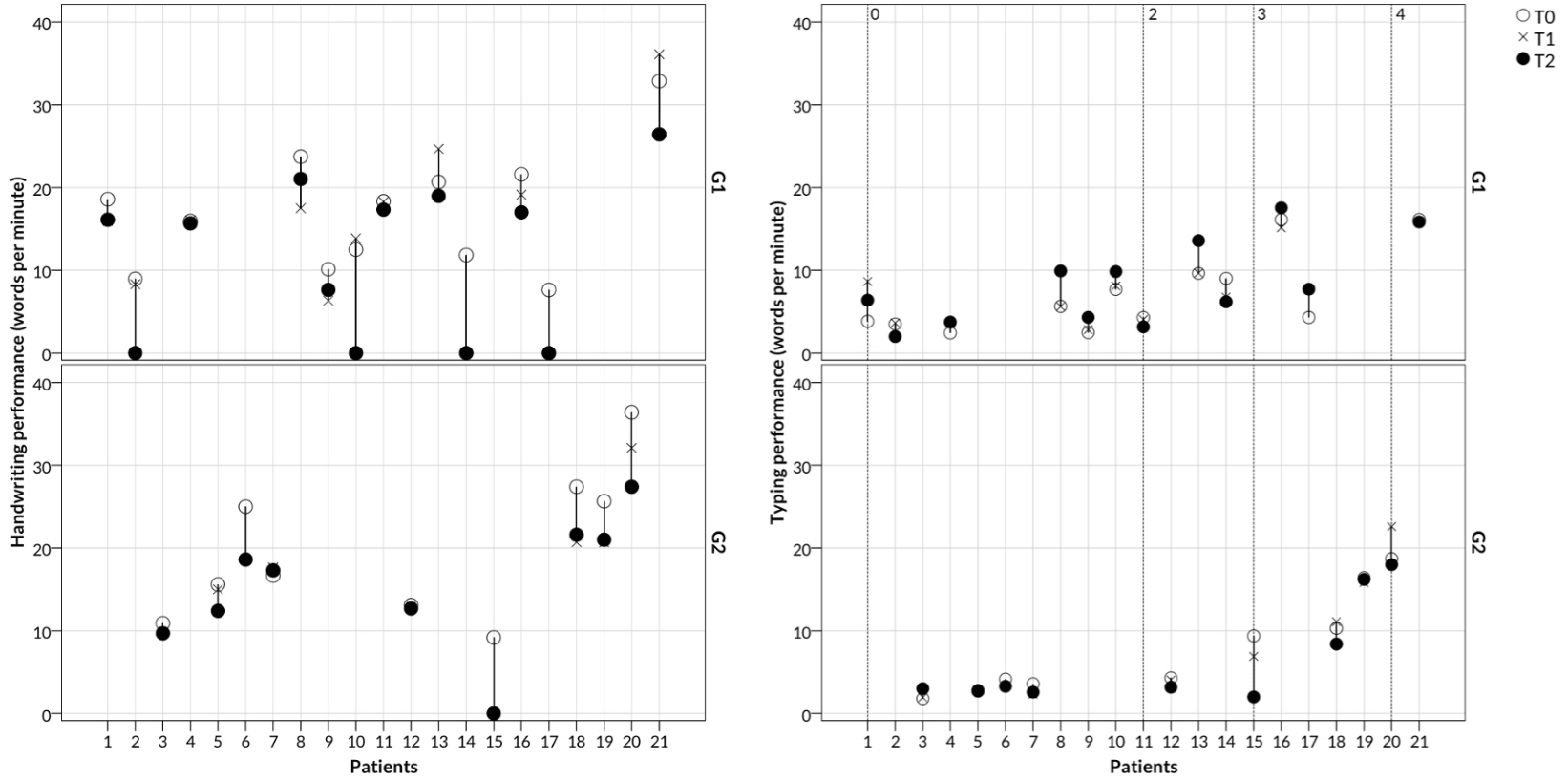

Figure 20 – Graphs represent performance (y axis) of handwriting (A) and typing (B) for each patient (N=21, patients are ordered by self-rated experience in the use of computers).

Vertical dotted lines indicate patients' experience in the use of computers (patients 1-10 had no experience:0; patients 11-14, 15-19, 20- 21 rated experience as 2,3,4, respectively). Results from patients in G1 (using ACD) and G2 are represented in separate. Performance is indicated for each patient with a different symbol for each period of evaluation (1,2,3). Performance in handwriting dropped from baseline to T2 in all patients (mean: -5.1±3.8 wpm), except for patient 7. Five patients could not perform handwriting anymore in last assessment (2,10,14,15,17). Typing rate did not drop significantly, but it was higher for patients with higher self-rated experience in the use of computers. All patients were able to type during the three evaluation periods; it can be observed that performance in typing increased more than 1 wpm (mean: 2.5±1.8 wpm), in 8 patients from G1 (1, 4, 8, 9, 10, 13, 16, 17) and one from G2 (3)

4.3.3 Performance measures

Performance of handwriting had a mean of 17.5 wpm (SD=8.1; range: 7.6 to 36.4), at T0, and it decreased significantly (p=0.002) from baseline assessment to T2 (mean=12.4; SD=10; range: 0 to 27.4) (Table 3). The lower the UL function (ALSFRS-R-ul), the lower the measured performance of handwriting (r=0.693, p<0.001). Due to disease progression in UL, 5 patients were unable to perform handwriting at T1 or T2, although could still use ACD for typing. These patients had difficulties in grasping a pen but were able to use one finger to select on the keyboard or touchscreen.

Performance in using a keyboard strongly varied among patients due to different previous experience of using computer devices (mean=9.2; SD=5.2; range: 2.4-18.7 wpm), at baseline assessment. During the period of this study, patients' performance of typing had no significant changes in time, as described in Table 3. Interestingly, we could observe that 8 out of 11 patients in G1 with low experience (≤3) in the use of computers have improved typing rate, from T0 to T2 (Figure 20). During the period of this study, decrease in UL function (ALSFRS-R-ul) did not alter performance of typing (r=0.09, p=0.52), in contrast to performance of handwriting, which decreased with UL dysfunction.

4.3.4 Internet

Patients in G1 who had internet connection at home were able to learn how to use the email and replied to the emails sent by one of the authors (AL), independently of previous experience with email. Communicating with family (in particular siblings living abroad and grandchildren) was the main motivation expressed by patients to use internet.

4.4 Discussion

We present a longitudinal study on the effect of early intervention with assistive communication devices in quality of life of bulbar-onset ALS patients and their caregivers. Most studies regarding the impact of assistive communication on the QoL address ALS patients with severe UL dysfunction, but not much research focuses on its specific impact when introduced from early stages.

4.4.1 Quality of life

In this study, when investigating on the effect of communication in patients and caregivers' quality of life scores, we cannot ignore that other factors may have had impact on these scores; moreover, since we explored several scores and subscores of quality of life, statistical significance was not attained considering multiple comparisons between the two groups of patients. Nevertheless, our results support that communication difficulties affect quality of life and that early intervention with ACD has a positive impact on some of its domains.

Problems in communication were reported as negative factors in quality of life, by both patients and caregivers, and some patients and caregivers referred to ACD as having a positive impact on their quality of life. Indeed, Körner et al. (2012) reported that the use of communication devices improves or stabilizes quality of life and mood of ALS patients with dysarthria. Accordingly, in our study we observed that in the second assessment, Psychological Symptoms and Existential well-being domains of quality of life were higher for patients using ACD. However, in the third period of assessment, differences between groups were reduced to Psychological symptoms. We hypothesize that, as disease progresses, Existential well-being domain of quality of life might be influenced by other symptoms related to disease progression. In particular, in this population of bulbar-onset, patients' dysphagia had a major negative impact in the period of the third assessment.

In our study, quality of life of both patients and caregivers decreased overtime. Further, patients with lower bulbar function had lower quality of life. These results contradict other longitudinal studies that demonstrated independence of patients' quality of life on disease symptoms progression (Robbins et al., 2001; De Groot et al., 2007; Olsson et al., 2010; Chiò et al., 2004) or stability of quality of life with time (Gauthier et al., 2007; Trail et al., 2003). This contradictory result may be related to the homogeneity of selected patients in our study. In particular, in bulbar onset ALS, rapid progression could influence quality of life in the early stages.

General decrease in caregivers' quality of life scores, which we observed between the baseline and the final evaluation, compares with other studies (Robbins et al., 2001; Lo Coco et al., 2005). In our study, the early intervention

with ACD had a positive impact on caregivers´ support domain of quality of life, indicating an increased feeling of being cared for and supported. Moreover, for caregivers in the group of early intervention, patients with higher communication effectiveness index had caregivers with higher psychological quality of life. We hypothesize that this result is related to a positive experience of support, due to training and specific follow-up of patients with ACD, as well as the experience of improvement of communication with the patients.

Caregivers and patients' quality of life scores were not correlated; they were higher for patients comparing with their caregivers. Accordingly, Lo Coco et al. (2005) suggest that patients and caregivers do not represent a single psychological entity. Following these findings, different motivation and expectations for the use of ACD should be considered between patients and caregivers, depending on each individual context.

4.4.2 Caregivers

A special attention to caregivers is important in intervention with ACD. Caregivers have an important role as primary facilitators in the use of communication devices (Ball et al., 2005); the use of ACD by patients is strongly dependent on caregivers' support, in particular when patients' disability is major. In agreement to the positive association between the psychological domain of quality of life and patients' self-perceived communication (observed in the group with early support) it is expected that caregivers who are supportive of enhancing communication will raise patients' confidence in the use of ACD. Nevertheless, we have observed that the initial expectations for the early use of ACD were generally lower in caregivers than in patients. Encouragement from researchers or siblings was an important factor in raising the motivation of both patients and caregivers, in particular those who had no past experience in technology.

4.4.3 Evaluating the use of assistive communication devices

One limitation of our study is that we did not quantify the number of hours/day of using the selected application in ACD. However, UL performance for using the ACD did not drop significantly overtime, even for patients with lower ALSFRS-R-ul scores, suggesting its persistent use. Despite the initial slower communication performance by typing when compared to handwriting, we

emphasize that some patients could still rely on typing using the touchscreen access after being unable to perform handwriting and speaking. Therefore, we suggest that touchscreen-based ACD preserves better autonomy in communication for longer periods than handwriting.

Interestingly, we could observe improvements in the performance of typing in patients with early support for the use of ACD and with previous experience in using computers scored as lower than 3 (average age: 65.42±11.94 years). We hypothesize that improvement in performance was related to the process of memorizing key positions in the keyboard due to the regular use of ACD. Also, patients who had internet at home successfully learned to use email communication. This result indicates that, in this early period of the disease, patients can effectively learn and improve skills for using communication devices, independently of the disease's progression. This period may be particularly important for patients with little experience with computer devices. Another limitation of our study is that the selected population had a low education level and poor technology training, in general. This could limit generalization of the positive results. But, we would expect better or similar outcomes when applying early intervention in a more educated population (Czaja & Lee, 2008). Our population was formed by bulbar-onset patients, with a typical female gender predominance. Women tend to have a lower experience with technology. This later issue was associated with poor literacy and low pension income, which could be critical to interventions, like the use of ACD. The vast majority of our patients had no access to a computer, smart-phone or tablet devices. From our results we consider that even in this set of ALS population, timely intervention permit successful learning and adaptation to new communication tools, with positive impact on the quality of life.

When studying intervention with ACD, it is difficult to assess how patients use the communication tools out of the research environment. Further, we cannot reject that, while possible, patients use handwriting jointly with ACD at the very early stage. In this study, we considered typing rate improvement and self-reported communication effectiveness index as outcome measures for evaluating the use of ACD. As previously discussed, improvement of typing rate in inexperienced patients was most probably due to regular practice in the use of the communication device. Besides, patients using ACD reported higher scores in

communication effectiveness index, when comparing to patients with no early intervention. Indeed, after intervention with ACD, we found that the self-perceived communication of these patients was not related to their bulbar functional score. This can be explained by the effectiveness of ACD to compensate communication difficulties related to speech. In our perspective, it is not important to detail how each patient uses communication tools, since it may strongly depend on each person and their social environment, but to confirm the impact it has on self-perceived ability to communicate. For example, some patients reported the use of ACD to participate in internet social networks and others just wanted to communicate with close family. Accordingly, we suggest that the evaluation of intervention with ACD should consider self-perceived ability to communicate an important outcome, from early stages.

4.4.4 Duration of use

Although there is a growing offer of communication tools based on touchscreen tablet devices that can be easily accessed by patients, anticipation of UL severe dysfunction raises the question on whether an ALS patient should be supported in communication with these devices. As an additional part of this study, we investigated on the duration of use of ACD based on touchscreen access, in our group of patients. We monitored the use of ACD in 14 of our participants after the end of this study, until the end of life or when they were unable to use touchscreen ACD due to severe muscle weakness in ULs. These devices were used for a mean duration of 11 months (SD=3.4, range: 2-24 months). Eight out of the 9 patients who have died were able to use ULs to communicate with the ACD (using the touchscreen) until the end of life; these patients had preserved UL function for access to a touchscreen-based keyboard, and did not need any other access strategy. Even for patients who had fast progression in UL dysfunction, shorter use of touchscreen was important for learning how to use assistive communication tools. Their transition to alternative access (patients used head movements or eye-tracking control), was easily learned and accepted as important by both these patients and their caregivers. We suggest that touchscreen access is valid for early intervention in communication, as long as communication tools are prepared to integrate other access strategies to accommodate UL dysfunction. Further research is needed on predictors for upper limb function that are relevant

to anticipate the need of new access strategies for the use of assistive communication devices.

4.4.5 From early to late stages

Research in advanced technologies that allow late-stage patients to communicate and control the environment has gained high relevance, indicating communication as determinant for patients' quality of life (Caligari et al., 2013; Lulé et al., 2008) in those stages. However, late referral is still described as a common reason for low acceptance of technology in late stages of ALS (Brownlee & Bruening, 2012; Beukelman et al., 2011). Moreover, patients' age or intrinsic motivation (which may be related to mastery confidence or incompetence fear) have been studied as factors influencing performance of ALS patients using BCIs (Nijboer et al., 2010; Silvoni et al., 2013) or as general psychosocial factors (motivation and confidence) involved in competence to use ACD (Light & McNaughton, 2014). In our study, patients with early intervention for using ACD improved skills to use communication devices, particularly in those with low experience with informatics and low education. Both patients and caregivers' motivation for using ACD was progressively higher. Text-to-speech and onscreen keyboard for writing are valid communication tools both in early and late stages, regardless of the need to adapt ACD for replacing UL function. Particularly in fast progression, early intervention may reduce negative factors that influence acceptance of ACD in later stages and potentially will improve communication in overall disease progression.

4.5 Conclusions

Our results suggest that assistive communication tools based on touch screen-tablet devices (including text input, speech synthesizer and internet access) should be introduced in early stages of bulbar-onset ALS, particularly when dysarthria score in ALSFRS-R is between 2 and 3. Our study indicates a positive impact of assistive communication on quality of life in early stages of bulbar-onset ALS, both for patients and caregivers. We suggest that early intervention will improve patients' skills for using communication devices in later stages, when more complex alternative access strategies are necessary. Future

research is needed to investigate on the effect of early intervention on general performance of communication in later stages.

4.6 **New findings and their importance under research goals**

We found that ACDs show a strong trend towards a positive impact on the QoL on both early-affected bulbar-onset ALS patients and on their caregivers. This study was original in two ways:

(1) we applied a randomized, prospective, longitudinal design to test the impact of ACD on quality of life in early affected ALS patients and their caregivers, which is contrary to previous studies that included advanced patients very affected regarding speech and UL function;

(2) we demonstrated that early ACD support based on touchscreen input can preserve self-perceived communication for longer than handwriting, in bulbar onset ALS patients.

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Chapter 5 - Monitoring disease progression with assistive communication devices: speech and typing activity

Two studies were conducted including the following research goals: (1) to explore novel methods to objectively characterize disease progression in speech and in ULs function; (2) to test the hypothesis that ACDs can be used as tools to remotely monitor ALS progression.

Typing activity and speech were collected during longitudinal assessments of ALS patients, in the same setup as for the study of quality of life (Chapter 4). For the purpose of testing this hypothesis with data that would be possible to collect in an in-home environment, procedure was designed to be simple and non-exhausting. Typing activity and speech were recorded with a standard laptop computer. Length of recordings (both in speech and typing) was restricted to one short and well-known Portuguese 10-word sentence: *Tudo vale a pena quando a alma não é pequena*.

5.1 **Introduction**

Assistive devices usually rely on keyboards (physical or virtual). As disease symptoms progress, UL weakness leads to increasing difficulties in using a keyboard (either physical or touchscreen-based) until the use of input devices that do not rely on UL movements (e.g. eye tracking and brain computer interfaces) are needed for communication and environment interaction (Caligari et al., 2013; Lightbody et al., 2014). Moreover, speech intelligibility decreases until communication using natural speech is very difficult and frustrating (Green et al., 2013).

Identification of markers of disease progression is important to monitor ALS patients, with potential application in clinical trials (de Carvalho et al., 2005; Simon et al., 2014). As previously mentioned in section 1.2, ALSFRS-R is broadly used for assessment of ALS symptoms during the course of the disease. This scale includes a subscore for UL function (ALSFRS-R-ul) and Bulbar function (ALSFRS_R_b), as described in section 4.2.4. In spite that this scale can be

reliably administered remotely by patients or caregivers, over the phone or the internet by online assessment (Maier et al., 2012), two limitations of this assessment tool are addressed in our research: it does not give a continuous objective scoring (since it does not rely on physical examinations or instruments (Cedarbaum & Stambler, 1997; Tramacere et al., 2015) and it may not be enough sensitive to change, considering that it has been criticized for having a relatively small slope of decline (Wicks et al., 2009; Traynor et al., 2004). Bulbar motor dysfunction starts before perceived changes in speech intelligibility. For example, speech rate decreases prior to a perceived impact on speech intelligibility, but the first may be a marker for the later, as studied by Ball et al., (2001). In addition, results in section 4.3.3 showed that ALSFRS-R may be not sensible to functional decline in the use of UL for specific activities related to control of assistive devices (mostly involving movements to *select*, *tap* or *press* and *release* keys).

The goal of this research was to develop new methodologies intended for the design of non-invasive instruments, supported on ACD, for early detection, monitoring of disease progression and clinical trial applications. We developed methodologies for objective and longitudinal functional assessment of speech and ULs, based on simple procedures for recording typing activity and speech. Our main objective is to contribute for the development of in-home monitoring tools (to be implemented in ACD) that can assist in-clinic assessment of communication in patients with ALS.

5.1.1 Upper limb dysfunction and typing activity

Typing activity with a computer keyboard has been suggested by Austin et al. (2011), as a surrogate for the *finger-tapping test*, which could be used as a continuous in-home tool. Finger tapping test has been widely used in research of several neurological conditions, for characterization and quantitative assessment of the UL motor function (Bowden and McNaulty, 2013; Shima et al., 2014; Buracchio et al., 2010; Jimenez-Jimenez et al., 2010).

In the present study, we used a simple setup with inertial sensors to explore features related to UL function in typing activity. To keep independence of users' experience in the use of keyboards for writing, frequency of typing (analogous to tapping frequency in finger-tapping test) was not considered. Alternatively, we

analyzed time and movement features related to key press and key release actions.

Study aims related to typing activity were:

(a) Characterization of UL impairment progression in ALS patients for using assistive devices, by analysis of finger movements in keyboard typing;

(b) Identification of typing activity markers that could provide a new tool for disease monitoring.

5.1.2 Bulbar dysfunction and biomechanical modeling of speech production

The deterioration of the neuromotor system involved in respiration, phonation, swallowing, and lingual and oro-facial muscle function degenerates in a rapidly progressing dysarthria. As ALS progresses, speech movements become smaller in extent and slower in speed (Green et al., 2013). Perceptual and acoustic features of dysarthria in ALS have been well studied (Tomik & Guiloff, 2010; Bongioanni, 2008).

Turner et al. (1995) studied the relationship between speech rate, speech intelligibility and vowel space area (VSA) in a group of 9 patients with ALS. These authors suggested that VSA was an important component of global estimates of speech intelligibility (accounting for 45% of the variance in speech intelligibility). The VSA and the Formant Centralization Ratio (FCR) are parameters defined to estimate the vowel span range and positioning produced by a given speaker (Sapir et al., 2011). In this exploratory study, we assume that the relative deviation of VSA and FCR in a specific patient with ALS, from a control or normative statistics, may be used to evaluate the distortion of the formant space, in terms of independent formant span ranges (ΔF2 vs ΔF1). This deviation can be expressed as a vector in the formant space showing speech deterioration related to disease progression. We use a method based on speech articulation biomechanical modeling, from the level of signal processing to neuromotor activity inference (Gómez-Vilda et al., 2011). Estimated parameters in common speech are associated to specific neuromuscular complexes involved in articulation, more specifically the masseter, the stylo-glosus and the genio-hyo-glosus muscles - as described in Gómez-Vilda et al. (2015).

We performed longitudinal study cases in patients with ALS, to study the evolution of the vowel space as disease progresses. We aimed at exploring early

detection and monitoring of speech dysfunction in ALS, based on running speech and low-cost voice recording instrumentation.

5.2 Materials and Methods

5.2.1.1 Materials

For data collection of finger movements in keyboard typing, we used a wireless 4-channel acquisition system with a 3-axis accelerometer sensor (range ±3 g, with a relation of 300 mv/g at the output) and a sample rate of 1KHz. The sensor was placed on the posterior part of the index finger of the dominant hand, as depicted in Figure 21. There was one exception: one patient used the non-dominant hand due to severe dysfunction of the right upper limb. Data was acquired via Bluetooth to a common laptop computer, to be processed offline. A second laptop was used for the typing tasks. Due to its very low weight, the sensor did not interfere with the finger typing activity.

For data collection of speech, we used the laptop where patients performed the typing task. Voice was recorded at 44 kHz and 16 bits.

5.2.1.2 Methods

ALS patients were assessed at study entry and every 2-6 months for a variable period depending on disease progression. Assessments were made during clinical appointments. At each session, patients were asked to record speech: reproducing a familiar Portuguese 10-word sentence "*Tudo vale a pena quando a alma não é pequena"* (Figure 21). Then, the accelerometer was placed on the participant´s index finger. Patients were asked to type the same 10-word sentence using just the finger with the accelerometer (Figure 21). All tasks were recorded throughout accelerometer signal acquisition, a video camera and a log text editor. A complete assessment session had the duration of 20 minutes. In the first assessment we asked each participant to classify previous experience in using a computer by applying a Likert-type classification of 0 (I have no experience) to 5 (I am very skilled in the use of computers).

Typing and speech analysis was blind to the functional rating scores of the patients; ALSFRS-R scoring was done after recordings, on the same day, by an independent researcher.

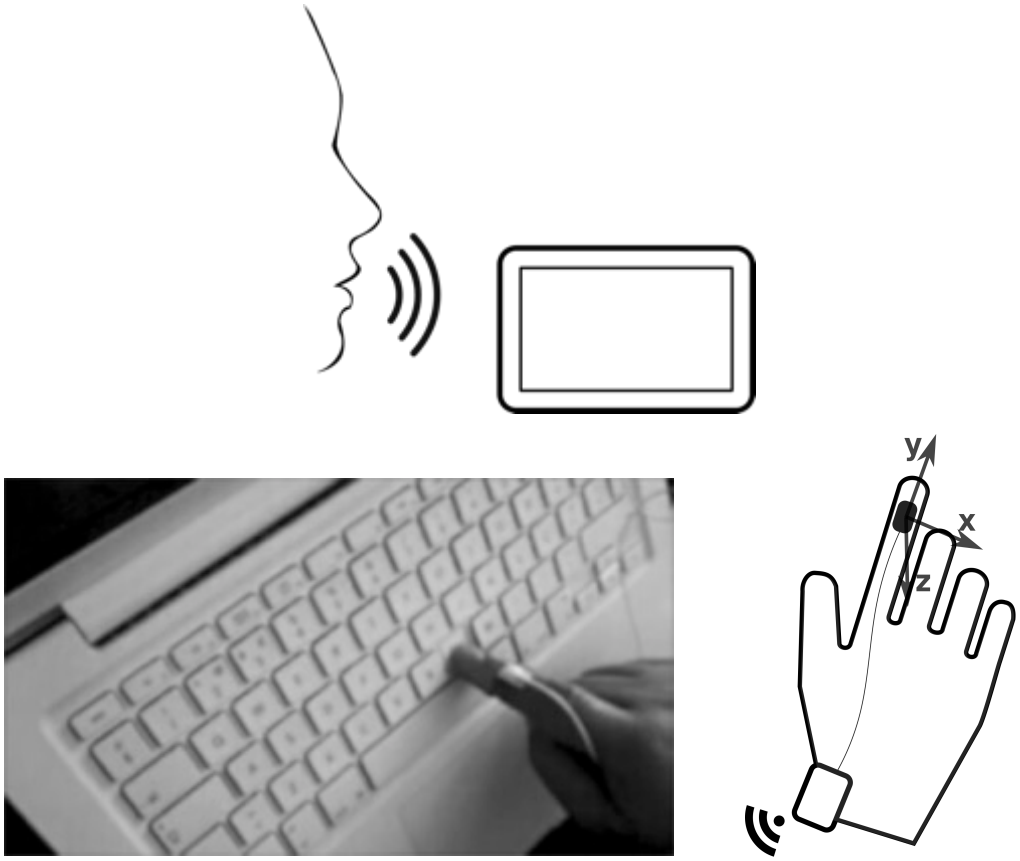

Figure 21 - Experimental setup (up) speech recording in a simple voice recording system included in a common laptop. (down-left) An accelerometer was placed on the typing index finger of the subject. Accelerometer was connected to the acquisition module. Data was sent via bluetooth connection to a computer where it was saved. Participants did the typing tasks in a laptop using a simple text editor. (down-right) The three axes of the accelerometer sensor were measured, as illustrated.

5.2.1.3 Participants

Nineteen ALS patients were consecutively recruited, with the following criteria: probable or definite disease according to the revised El Escorial criteria (Brooks et al., 2000), bulbar onset disease (as bulbar-onset patients presenting with dysarthria were previously included in a study evaluating the impact of communication devices in quality of life), no other neurological disorder (in particular no clinical signs of dementia or polyneuropathy), absence of mechanical limitation using hand or fingers (as associated with arthritis, edema or pain) and agreement to participate. The joint Ethics Commission of the Centro Hospitalar Lisboa Norte and Faculdade de Medicina de Lisboa approved this research and patients gave written informed consent. Four of these patients with low perceived dysarthria (*Speech* item in ALSFRS-R-b ≥3) were selected for speech longitudinal analysis.

Controls

A total of 26 controls were included: six patients with other neuromuscular disorders causing moderate UL weakness (3 with demyelinating neuropathy with predominant motor impairment and 3 with spinal muscle atrophy) and 20 healthy subjects. The six patients with other neuromuscular disorders had ALSFRS-R-ul scores between 9 and 11.

For reference of speech data, two of the healthy subjects were recorded under the same conditions described for the patients.

5.2.1.4 Typing signal and outcome measures from typing activity

For feature extraction we used the Euclidean norm of the 3-axis (ax,ay,az) acceleration signal (Equation 1).

(Equation 1) $$a_{norm} = \sqrt{a_x^2 + a_y^2 + a_z^2} \quad (m/s^2)$$

We extracted four features from the acceleration signal (related to finger typing a keystroke), as described in Figure 22: ***mean keyhold time*** (*t_hold*) - mean time spent in holding down each key, in a typing task; ***time to press*** (*t_p*) – mean time spent between tapping a desired key and pressing it down, in a typing task; ***acceleration to press*** (*accpress*) – mean acceleration in the movement of pressing each key during the typing task; ***acceleration to release*** (*accrelease*) – mean acceleration in the movement of releasing each key during the typing task.

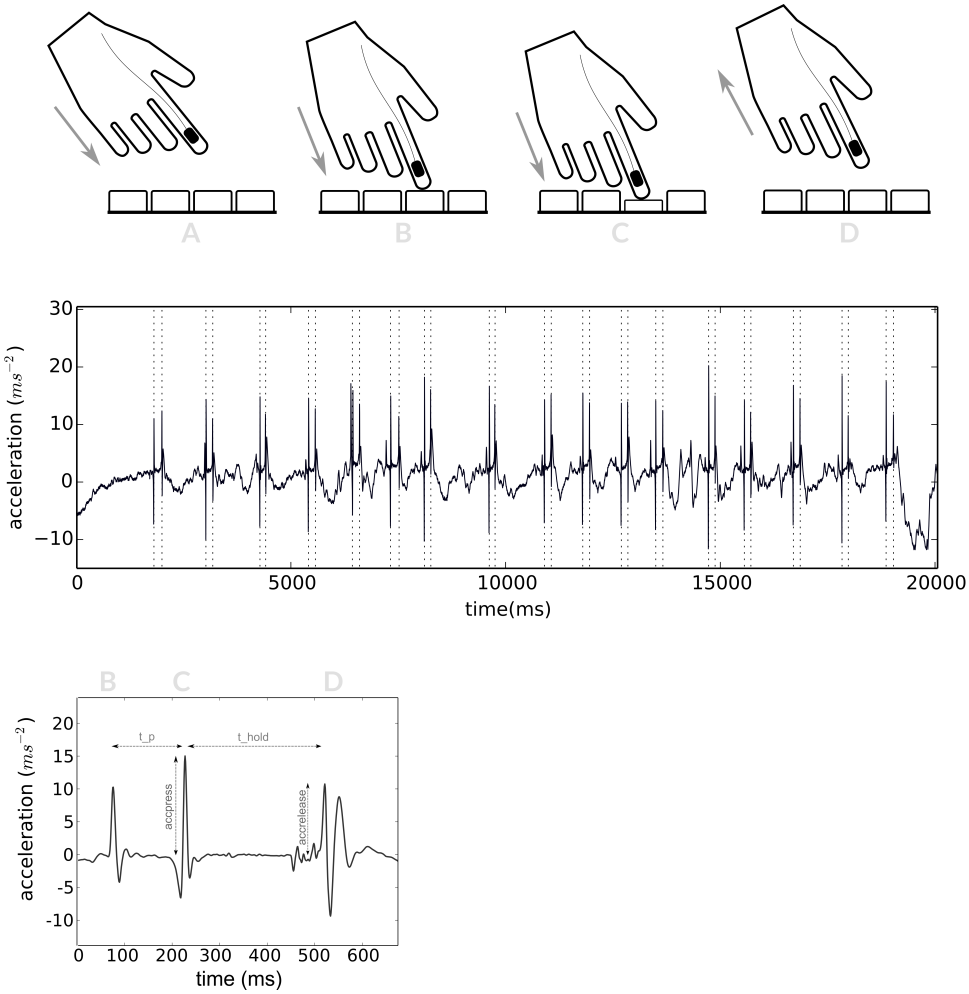

Figure 22 - Recording of finger movements in typing activity. (top) User finds and points to the desired key (A), touches the desired key (B), then presses it down (C) and finally, the user releases the key (D). (middle) Signal showing 20 seconds (17 keystrokes) of typing activity from a healthy participant. Vertical dotted lines indicate events of pressing (C) and re- leasing (D) a key. (bottom) Signal showing two consecutive keystrokes. Features extracted from the accelerometer signal are marked: t_hold: time from C to D, while user holds down the key; t_p: time delay between touching the key (B) and pressing it (C); accpress: maximum acceleration at key press (C); accrelease: maximum accel- eration at key release (D).

5.2.1.5 Phonation modeling and outcome measures from speech

Recordings were originally saved with 44kHz sampling rate and 16 bit resolution, on the laptop. For feature extraction of speech recordings, we used the formant-like pattern detection on LPC spectrograms produced from the speech signal using a Phonation Model Inversion (Gómez-Vilda et al., 2011). Recordings were undersampled at 8kHz before being processed; formant positions F1-F2 in each 2 ms were extracted using a 11-pole LPC lattice-ladder inverter to separate vocal tract and glottal source components (Gómez-Vilda et al., 2013). Segments with no phonation were removed from the estimations. A synoptic vowel triangle

similar to the one defined in Figure 26 was produced from the F1-F2 positions obtained from each utterance.

Outcome measures, inferred from this Phonation Model Inversion, were: the vowel triangle (F1-F2), the formants span (ΔF1 and ΔF2) in relation to an ideal vowel triangle, the modulus of the normalized formants span (MNFS), the vowel space area (VSA) and the formant centralization ratio (FCR) (see Appendix A).

5.2.1.6 Statistical Analysis

Pearson correlation was used to study association between variables. For the analysis of typing activity, unpaired and paired t-Test for dependent variables, and one-way ANOVA were used to test differences between groups. Repeated-measures ANOVA was used in longitudinal analysis (three assessments) of each patient. For ANOVA, post-hoc analysis with Tukey HSD was used to find significant differences between pairs. A *p*-value lower than 0.05 was considered for statistical significance.

5.3 **Results**

Median age of the ALS population was 64 years (ranging from 38 to 81) and median disease duration was 14 months (ranging from 2 to 34). Healthy control subjects were matched for age and gender ($p>0.05$). Most ALS patients (84%) were women, due to specific clinical characteristics of this group of ALS patients (bulbar onset). Twelve healthy controls (60%) and 5 controls with other neuromuscular disorders had poor experience in using computers (score ≤2). Ten ALS patients (62.5%) were using a personal tablet or computer device for assistive communication, due to speech difficulties, during this study. ALS patients were followed during 2 to 20 months, in intervals of 2-6 months (2 to 6 assessments), the period of regular clinical appointments. Number of assessments performed for each patient varied due to progression rate of speech or UL function (fast progressors lost ability to type a few months after entry) or death (or late stage conditions).

5.3.1 Analysis of typing activity

Table 5 shows a summary of the ALS patients and assessments. Due to variability between patients in number of assessments, we selected 2 to 3 assessments of each patient. For patients with more than three assessments, we

selected the baseline, the last and the assessment closer to the mean time within first and last assessments.

Table 5. Characterization of patients and longitudinal assessments used for the study of typing activity

P#	Experience[a]	ACD	T_ASSESS	Total time[b]	ALSFRS-R	ALSFRS-R-ul	Group
1*	3	Y	4	12.5	26/17/14	10/7/5[c]	W
2	4	N	2	4.2	15/5	8/3[c]	W
3	0	Y	2	5.9	17/10	5/0[c]	W
4	2	Y	3	5.4	36/31/25	12[c]/11/10	N
5*	2	N	5	13.2	30/22/15	11/10/6[c]	W
6	0	Y	6	14.9	36/27/22	12[c]/12/10	N
7	4	N	2	2	35/31	12[c]/9	N
8	0	Y	2	6.9	24/14	9/4[c]	W
9	4	N	3	5.6	6/7/3	3[c]/3/0	W
10	3	Y	4	8.7	20/17/14	11[c]/9/8	N
11	0	Y	6	19.7	32/16/14	12[c]/8/7	N
12	4	Y	6	15.6	27/23/13	12[c]/10/8	N
13	0	N	3	7	29/27/25	12[c]/12/12	N
14*	0	Y	5	16	36/31/20	12[c]/12/9	N
15	1	N	2	2.1	19/15	7/4[c]	W
16*	2	Y	3	7.6	26/28/23	9/9/7	-
17	4	Y	2	3	22/15	9/2[c]	W
18	2	N	3	7.7	12/6/2	4[c]/1/0	W[d]
19	2	N	2	6.2	32/27	12[c]/9	N

ACD: using an ACD (Yes or No); T_ASSESS: Total number of assessments; *ALSFRS-R = ALSFRS-R score (from 0 to 48, normal); ALSFRS-R-ul = ALSFRS-R upperlimbs subscore (from 0 to 12, normal); N: nALS-normal UL (no UL dysfunction when performing typing task); W: wALS (marked UL dysfunction when performing typing task)*
** Patients evaluated for speech analysis*
(a) Experience with computers rated by the patient (0:min to 5:max).
(b) in Months.
(c) Assessments that were considered for comparison between groups Normal/ Weak UL function.
(d) This patient used left hand for typing – as ALSFRS-R-ul was not sensitive to this function of the left hand, we followed video analysis to classify typing performance group.

Outcome variables were calculated for each typing task as the mean value of all keystrokes. Average number of keystrokes performed in each typing task was 38.1 (SD=10.6) (variation on the number of keystrokes for typing the same 10-word sentence depended on the spelling errors, missing spaces and punctuation).

5.3.1.1 Test-Retest Reliability

Fourteen participants performed a second task: typing a free sentence (like writing their names or what they did during that morning). This second task was performed in the same evaluation session, after typing the standard 10-word sentence. Number of keystrokes in the second task was 31.6 (SD=18.62). Measurements obtained from the first task were highly correlated to those obtained in the second task, as presented in Table 6.

Table 6. Test-Retest reliability comparing performance with a standard sentence vs free sentence

Measure	Mean±SD (task 1)	Mean±SD (task 2)	R	Paired t-test
t_hold	221.49±94	233.40±108.44	0.963*	p=0.210
Accpress	20.71±8.83	22.31±10.10	0.957*	p=0.093
Accrelease	13.26±3.84	13.58±4.09	0.841*	p=0.635
t_p	103.14±56.11	115.82±65.90	0.908*	p=0.062

R = Pearson product-moment correlation coefficient
* p<0.001

5.3.1.2 Test independence of user experience

To test the independence of previous user experience (in the use of keyboards) on the measured variables, we tested healthy controls and ALS patients with no or mild UL dysfunction. Those who had a good experience in using computer or assistive communication devices (score >2, 11 subjects) were compared to those who had low experience (score ≤2, 13 subjects). There were no significant differences between both groups (Table 7).

Table 7. Comparing subjects with vs without previous experience with computer or assistive communication devices.

Measurement	Mean±SD (experience)[(a)]	Mean±SD (no experience)[(b)]	T-test
t_hold	182.10±80.57	179.32±65.69	p=0.920
Accpress	24.17±9.15	21.33±8.99	p=0.425
Accrelease	16.05±6.37	15.46±4.59	p=0.779
t_p	63.13±55.21	60.06±48.46	p=0.885

(a) 4 healthy controls and 7 patients; (b) 4 healthy controls and 9 patients.

5.3.1.3 Sensitivity of measurements to test progression

To evaluate the sensitivity of measurements in evaluating the progression of UL dysfunction, we compared data from patients with low and severe dysfunction in UL. We defined 2 subgroups of ALS patients: **normal UL** (nALS) - patients with no significant UL dysfunction (ALSFRS-R-ul subscore >10) and **weak**

UL (wALS)- patients with marked UL dysfunction (ALSFRS-R-ul subscore ≤ 6). All the assessments of each patient were classified in one of these subgroups. When one patient was classified in more than one group, the wALS was chosen for statistical analysis (indicated in Table 5).

Table 8. Results from typing activity distributed by classification of upper limb dysfunction. Description of outcome variables (mean±standard_deviation).

	HE (n=20)	NM (n=6)	nALS (n=109)	wALS (n=9)	*p-value*
t_hold (ms)	110.5±43.79	222.86±37.35	173.26±70.80	304.88±40.35	$p_{(HE,NM)}$ >0.05 $p_{(HE,nALS)}$ <0.01** $p_{(HE,wALS)}$ <0.01** $p_{(NM,nALS)}$ >0.05 $p_{(NM,wALS)}$ <0.01** $p_{(nALS,wALS)}$ <0.01**
accpress (m/s2)	25.71±6.49	16.11±7.40	29.83±6.49	13.08±6.69	$p_{(HE,NM)}$ <0.01** $p_{(HE,nALS)}$ >0.05 $p_{(HE,wALS)}$ <0.01** $p_{(NM,nALS)}$ >0.05 $p_{(NM,wALS)}$ <0.01** $p_{(nALS,wALS)}$ <0.01**
accrelease (m/s2)	17.99±4.66	11.16±6.35	18.30±3.56	10.07±4.57	$p_{(HE,NM)}$ <0.01** $p_{(HE,nALS)}$ >0.05 $p_{(HE,wALS)}$ <0.01** $p_{(NM,nALS)}$ <0.05* $p_{(NM,wALS)}$ <0.01** $p_{(nALS,wALS)}$ <0.01**
t_p (ms)	26.11±25.36	15.56±3.83	52.83±35.27	161.13±76.20	$p_{(HE,NM)}$ >0.05 $p_{(HE,nALS)}$ >0.05 $p_{(HE,wALS)}$ <0.01** $p_{(NM,nALS)}$ >0.05 $p_{(NM,wALS)}$ <0.01** $p_{(nALS,wALS)}$ <0.01**

HE: healthy controls; NM: controls with other neuromuscular diseases; nALS: ALS patients with normal UL function; wALS: ALS patients with marked UL dysfunction.

5.3.1.4 Keyhold time

Mean values of *t_hold*, calculated for each group, are described in Table 8. Comparisons between groups indicate significant differences between healthy controls and all groups of patients (p<0.01) and between wALS and the other groups (p<0.01) (Figure 23). Mean *t_hold* from patients with other neuromuscular diseases was similar to nALS - Figure 23.

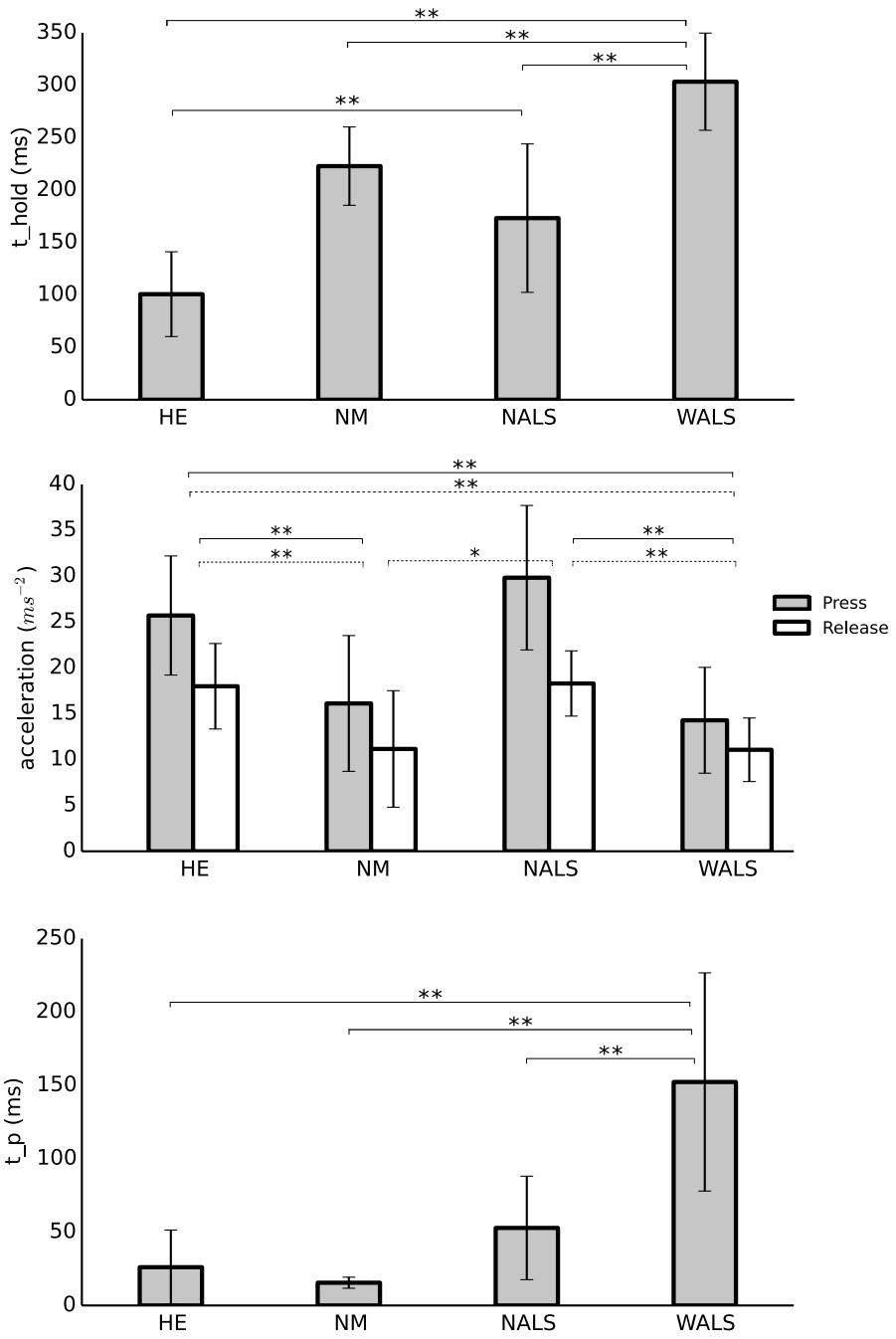

Figure 23 - Mean values of outcome variables in the different groups: HE (healthy participants); NM (other neuromuscular diseases); nALS (ALS patients with normal UL function) and wALS (ALS patients with marked UL dysfunction).

5.3.1.5 Longitudinal analysis of keyhold time

For the longitudinal analysis of t_hold in patients with slower progression in UL, we selected a subset of patients with three assessments (N=12) (Table 5). We observed significant differences in t_hold between assessments (p=0.008). Increase in t_hold was found between the first (mean difference of 64.0 ms, p=0.03) or middle (mean difference of 44.1 ms, p=0.04) and the last assessment,

but not significant between the first and the middle assessment (mean difference of 19.9 ms, p=0.211). Fig. 4 represents t_hold and ALSFRS-UL scores obtained for the three assessments.

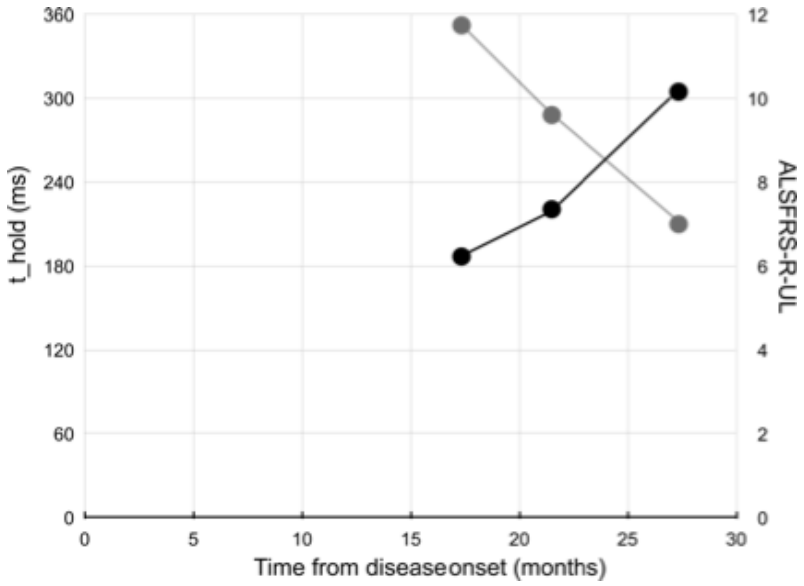

Figure 24 - Longitudinal assessments. Plots represent median values of t_hold and ALSFRS-UL scores, in each of the three assessments.

5.3.1.6 Delay to press

As ALSFRS-R-ul decreases, there is an increasing delay between touching the key and the movement for pressing it down (*t_p*). Figure 25 illustrates this increasing delay observed in 9 months on one patient and comparing it with a healthy control. This delay to press down the key (after touching it) was higher in the wALS group compared with nALS and controls (p<0.01) – Table 8 and Figure 23.

5.3.1.7 Acceleration in movements for pressing and releasing each key

Mean values for acceleration at key press (*accpress*) and key release (accrelease) are described in Table 8. Both acceleration at key press and at key release decreased with UL dysfunction: *accpress* and *accrelease* were significantly lower in the group of wALS comparing with healthy controls or with patients with normal UL (p<0.05). We found no differences between healthy controls and nALS; patients with other neuromuscular disorders had lower acceleration amplitude for releasing keys, when comparing to ALS patients with normal UL (p<0.05) (Figure 23).

5.3.2 Analysis of speech production

Speech of four ALS patients (all were women and are marked in Table 5) was recorded in 3 to 5 evaluation sessions, separated by 2 to 6 months intervals. Healthy controls were selected from the control set: two women with 36 (CF36) and 63 (CF63) years old. An *ideal* vowel triangle inferred from the control subject CF36, was defined for comparisons between different assessments of each patient (Figure 26).

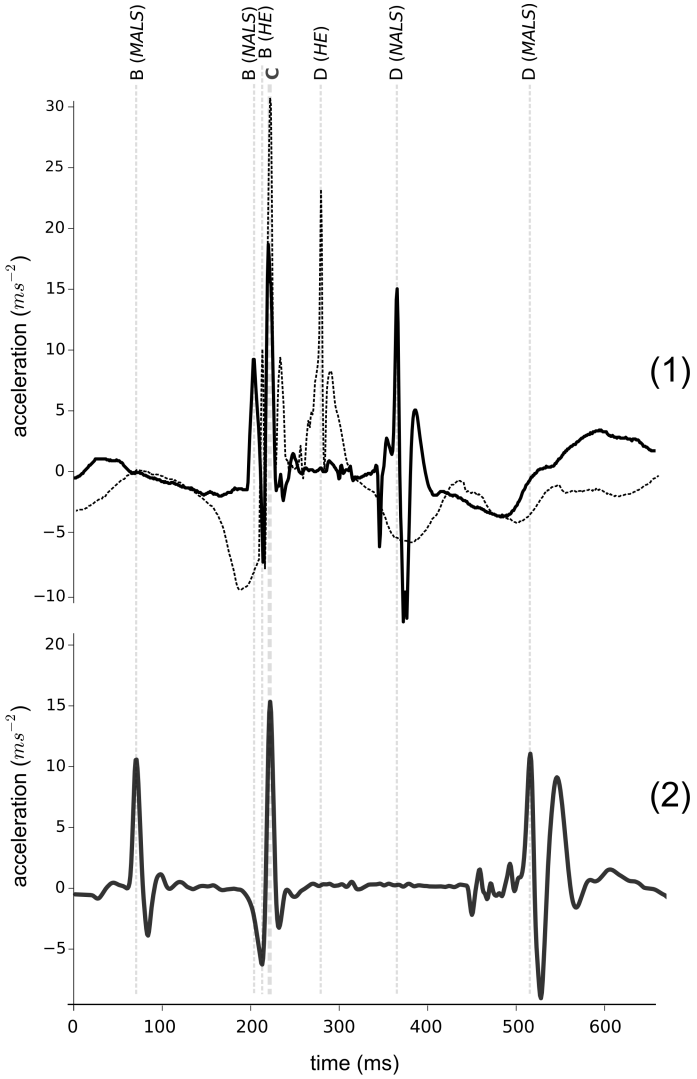

Figure 25 - Delay for pressing and releasing. Plots represent one keystroke in one healthy control (in dotted line) and two different assessments of the same ALS patient. There was an increasing delay in pressing the key (t_p) and for releasing it (t_hold) from the first assessment (1) to the last assessment recorded 9 months later (2). Acceleration also decreased from (1) to (2), either in key press and key release. Gray dotted lines indicate the events marked according to Figure 2 and the group of UL dysfunction. The three signals are aligned by the event of pressing down a key (C).

5.3.2.1 Formants (F1 and F2) and Vowel Triangle

Results for each recording were compared against the *ideal* vowel triangle. Percentage of formant span reduction (∆F1n and ∆F2n) normalized with respect to the control CF36 are given in Table 9.

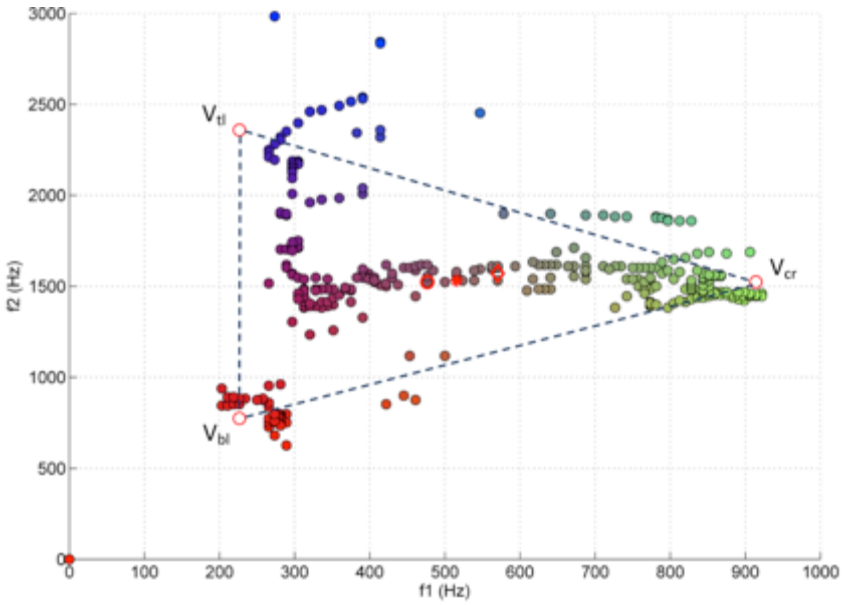

Figure 26 – Formant positions on the F1/F2 Vowel Triangle of CF36. Vertices of the idealized vowel triangle are defined by thin circles (V_{bl},V_{tl},V_{cr}).

The first recording (0) of PF1 shows a displaced and enlarged span for F1 (∆F1n=120%), and a much-compressed span for F2 (∆F2n=47%). Recordings (1) and (2) show a moderately compressed ∆F1n (84% and 68%) whereas the ∆F2n is also shrinking progressively (35% and 27%). These results would indicate, according to the biomechanical model of speech presented in Appendix A, a severe loss of activity in the stylo-glosus and genio-hyo-glosus muscles, whereas jaw control is moderately impaired.

Table 9. ∆F1/∆F2 in % relative to the control CF36, for each recording of the four ALS patients. The column under each patient (PF#) represents: (ALSFRS-R-B; Months after baseline evaluation) %∆F1/%∆F2.

	CF36	CF63	PF1	PF2	PF3	PF4
Age	36	63	38	64	77	79
Record.0	100/100	69/80	(6;0) 120/47	(9;0) 92/47	(8;0) 84/80	(11;0) 72/68
Record.1	-	-	(5;4) 84/35	(6;3) 61/46	(5;3) 66/62	(9;6) 67/88
Record.2	-	-	(3;6) 68/27	(6;5) 60/58	(5;7) 80/51	(6;10) 72/44
Record.3	-	-	-	(6;8) 54/28	(5;10) 55/37	-
Record.4	-	-	-	(6;11) 50/29	(2;13) 39/23	-

CF36: 36-year-old healthy control; CF63: 63-year-old healthy control; PF#: Patients (from 1 to 4)

The evolution of case PF2 has a larger number of recordings. It may be seen from the first recording (0) that the degree of affection of F1 is moderate (92%), its progression being apparently irreversible (61%-60%-54%-50%). On its turn the affection of the SG-GHG is already strong (47%) in the first recording (0) whereas progress is not steady in recordings (1)-(4), going through 46%-58%-28%-29%.

The third study case corresponds to an older patient (PF3, 77 years). The evolution for ∆F1n is 84%-56%-80%-35%-29%, which indicates a moderate initial affection, but a fast progression in the last recordings. The evolution of ∆F2n is 80%-62%-51%-37%-23% is indicating a progressive control loss of the stylo-glosus and genio-hyo-glosus muscles, and confirms the deterioration of jaw and tongue articulation functions in a similar way.

The last case corresponds to a 79-year old female (PF4). The progression for ∆F1n is 72%-67%-72%, which indicates an initial relative deterioration of the MS muscle, which was not progressing significantly during 11 months; on its turn the progression for ∆F2n is 68%-88%-44%, which indicates an irregular slow progression to articulation deterioration.

5.3.2.2 MNFS, VSA and FCR

The evolution of MNFS and VSA for the four cases studied, compared with the two controls CF36 and CF63 is described in Figure 27 and Figure 28. It may be seen that all patients show a progressive decrease in MNFS and VSA, from the first to the last recording. MNFS was positively correlated to VSA ($r=0.955$, $p<0.05$) and inversely correlated to FCR ($r=-0.913$, $p<0.05$), as FCR is increasing as illness progresses (Figure 28).

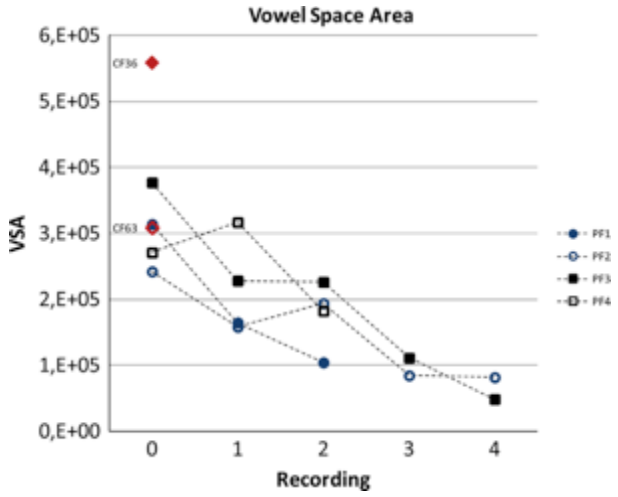

Figure 27 – Vowel space area for recordings from the four study cases presented compared to controls CF36 and CF63.

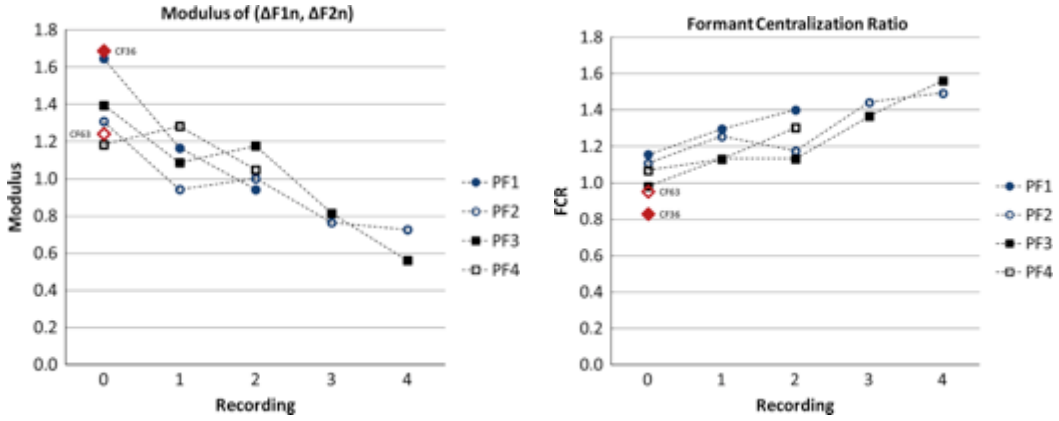

Figure 28 – (left) Modulus of the normalized formant span for recordings from the four study cases presented compared to controls CF36 and CF63. (right) Formant Centralized Ratio for recordings from the four study cases presented compared to controls CF36 and CF63.

5.4 Discussion

5.4.1 Markers of progression in typing activity

The main aim of this study was to quantify UL impairment in ALS patients by using a keyboard. In addition, we aimed to identify a sensitive marker that could be explored as a tool to monitor UL functional impairment over disease progression.

Inertial sensors were used for movement recording, with the advantages of being easy to place on the finger and without causing movement constraints. This kind of sensors has been proposed for motion tracking and quantitative assessment of UL function in many conditions (Uswatte et al., 2000; Lyons et al.,

2005; Zhou et al., 2008; Bai et al., 2014). For our purpose, we used a simple setup with one miniaturized accelerometer, for recording finger activity related to actions of tapping, pressing and releasing keys in a short typing task.

We observed that the mean delay between pressing and releasing keys (keyhold time – *t_hold*) increased in parallel with greater UL dysfunction. Moreover, in ALS patients with preserved UL function, this time was already increased. Possibly, this measurement could be a sensitive marker in early stages of ALS and a useful tool to monitor UL dysfunction over disease progression.

Delay to press (*t_p*) is apparently not sensitive to detect early changes in ALS patients. Progressive UL weakness causes a significant increase in *t_p* when UL impairment is marked. However, this increasing delay for pressing a desired key is particularly relevant for functional assessment, since lack of efficacy to press down a key or a button (e.g. bed alarm switch) is often the reason for initiating support with the use of special interfaces for control of assisted devices.

Mean acceleration of movements to release and press the keys were not sensitive to detect early changes in ALS patients with normal UL function, but did show significant decline over disease progression (UL dysfunction). Furuya & Altenmüller (2013) also found an association between duration of focal hand dystonia in pianists and slower and weaker tapping in piano keys.

For the aim of this work, inter-key rate and its variability were not considered, despite of interesting similarity of these variables with finger-tapping tests. Decline in finger tapping speed in ALS, as observed by Kwan et al. (2013), could not be tested with our method as we found considerable variations between patients. Time between two different keystrokes was much dependent on users experience with computers and would have to be tested in overlearned tasks (Austin et al., 2011).

Learning factors, as already described by Jobbágy et al. (2005) as a bias for finger-tapping test, must be considered in our study, since patients repeated the same typing task in more than one assessment. Nevertheless, results were robust to the influence of learning factors. We observed no differences due to previous user experience in using computers. Moreover, if a learning effect existed, it would be expected that users would improve performance in later assessments, due to increasing confidence on the task. On the contrary, patients tended to increase delays related to key press and release.

Although patients with clinical signs of dementia were excluded, we cannot exclude the influence of cognitive and behavioral factors. For example, we could identify some patients who often gesticulated with the hands during the task, especially those with severe dysarthria, as a way to communicate. Also, some patients were depressed or unconfident. However, other patients were enthusiastic in performing the tasks. Nevertheless, results from test-retest reliability, test of independence of user experience and longitudinal analysis of each ALS patient, raised confidence in our results.

5.4.2 Markers of disease progression in speech

Despite the low number of case studies (N=4) of this exploratory study, it is expected that the present methodology contributes to estimating ALS bulbar involvement, using quantitative and continuous evaluation techniques.

Both VSA and FCR are well-accepted parameters related with articulation degradation in Parkinson Disease (Sapir et al., 2011). The present cases show that these coefficients are well correlated with normalized formant spans, which are good indicators of neuromotor activity decay both in tongue and in jaw (Jürgens, 2002). In general, it may be said that the degree of affection observed in the stylo-glosus and genio-hyo-glosus muscles is always strong in the first recording (when bulbar dysfunction is already present), whereas the degree of involvement of the masseter muscle does not seem so significantly affected initially. These results are according with Yunusova et al. (2008) who found, in a study with 9 patients with ALS, impairment of articulatory vowels speed more consistently present in movements of the tongue and, occasionally, of the jaw. In agreement, it has been studied that F2 slope reflects changes in tongue function with disease progression and it is linked to speech intelligibility (Yunusova et al., 2012).

A clear explanation for cases where articulation affection seems to be reversed (recording 1 in PF1, recording 2 in PF2 and PF3) should be further investigated. In future studies it is important to determine if the apparent recovery is reliable enough or is due to artifacts. A possible cause could be due to the presence of artifacts in the estimation of the pair datasets {*F1(n)*, *F2(n)*}. Nevertheless this explanation does not seem consistent, as vowel triangles are estimated on large data distributions. For instance, as illness progresses longer

recordings are expected for the same sentence. Besides the expected decrease of speech rate, patients tend to speak slower to improve speech intelligibility, ranging in our sample from 3 s to 10 s, approximately, to say the same sentence. This means that at least from 1500 to 5000 formant pairs {*F1(n)*, *F2(n)*} were available to build quantile statistics. It does not seem plausible that quantile estimates would be affected by large artifacts, which are not apparent in vowel triangle plots, as these estimates are considered robust to outliers.

5.4.3 Age and gender

Age and gender are relevant factors in studies of motor control (Ashendorf et al., 2009). Aging leads to reduced motor performance, with a decrease in movements' speed (Bowden & McNulty, 2013; Campbell et al., 1973; Darling et al., 1989; Seidler et al., 2010). As a limitation of this work, due to specific characteristics of bulbar onset ALS patients, most patients were women above 60 years. Healthy participants were also mostly women in the same age group of ALS patients, but further investigation with a more heterogeneous group of ALS patients is necessary to validate results.

Concerning speech analysis based on biomechanical modeling, a ground reference is lacking, as patients were not evaluated prior to developing the disease. We chose a young control as reference for longitudinal comparisons in our study; however, the age of the controls is a controversial fact. Our choice was based on two arguments. Firstly, our elder control showed span reduction, which is also found in patients. We can speculate that this could be due to normal progressive voice aging processes or to unknown neurological abnormality under development. Secondly, young patients cannot be excluded from the analysis, no matter how seldom these cases may occur.

5.5 Conclusions

Considering ALS, the recording timeline is short, as the disease progression may be rapid and clinical assessments are limited to periodic appointments in the hospital settings.

Electronic assistive devices for communication are used by a large number of ALS patients. This fact can be further explored as a tool for in-home monitoring of disease progression, particularly for assessment of Communication. Functional

evaluation of the upper limbs, measure of key hold time can be implemented just with software applications in electronic assistive devices. These devices can also support recording tools to continuously monitor running speech, even prior to communication difficulties.

The methodology proposed in our study can be applied to the study of other progressive neurological conditions that affect speech or UL movements, such as Parkinson Disease. Using assistive devices as clinical monitoring tools has the advantage of collecting data remotely and non-invasively, in patients' natural environment, on a continuous assessment.

5.6 **New findings and their importance under research goals**

We explored novel methodologies to quantitatively monitor UL and speech dysfunction in ALS, out of the clinical settings. Results from this study broaden the classical perspective of ACD as technologies with the single purpose of improving communication related to speech dysfunction. Conversely, we introduced a novel perspective on the potential contribution of ACD to the quality of life in ALS: we demonstrated that, in complement to its importance in improving communication, these technologies can be further explored for in-home clinical support, as tools to continuously monitor progressive neurological conditions.

Published in:

Londral A, Pinto S, de Carvalho M. Markers for upper limb dysfunction in Amyotrophic Lateral Sclerosis using analysis of typing (2015). *Clinical Neurophysiology* (DOI: 10.1016/j.clinph.2015.06.017).

Gómez-Vilda P, Londral A. Rodellar-Biarge V, Ferrández-Vicente JM, de Carvalho M (2015). Monitoring amyotrophic lateral sclerosis by biomechanical modelling of speech production. *Neurocomputing 151*: 130-138.

Chapter 6 - Communication during stages of severe dysfunction: development of a new device to assess novel input signals

6.1 **Introduction**

In late stages of ALS progression, patients may experiment pervasive muscle weakness, with few functional body sites to access to communication devices. Patients may live at home or may have moved to palliative care settings, and spend most of the time lying in bed or in a comfort chair. In reference to severely disabled ALS-patients and on the use of BCIs, Birbaumer (2006) suggests "*a general underestimation of the positive attitudes in this group of patients*". In Chapter 4, we suggested that improvement of quality of life was associated to a better self-perceived communication effectiveness of the patients. Moreover, effective strategies that support patients in maintenance of their social network, even in later stages, are needed to cope with the disease (Lulé et al., 2009).

Even the most severely impaired patients can benefit from communication tools (using specific input devices) to extend their communication functions to receive information, participate in social networks and make decisions (Light & Gulens, 2000; Nijboer et al., 2010; Smith & Delargy, 2005; Hossler et al., 2011). As illustrated in Figure 29, when using ACD, patients can establish social contacts beyond very simple "yes/no" responses. Appendix C includes texts extracted from interactions made by patients using ACD, during our research, either for interaction with family or caregivers, as also with medical doctors.

Important factors for the success in assistive communication at these late stages should not be ignored: previous experience on using communication tools, easiness and robustness of assistive technologies, the motivation of the patient and the motivation of the caregiver to support the use of ACD (Ball et al., 2005; Beukelman et al., 2011; Londral et al., 2009; Brownlee & Bruening, 2012). However, when patients experiment general severe dysfunction, the most

important in supporting communication is to have input devices that can effectively capture input signals from the patient.

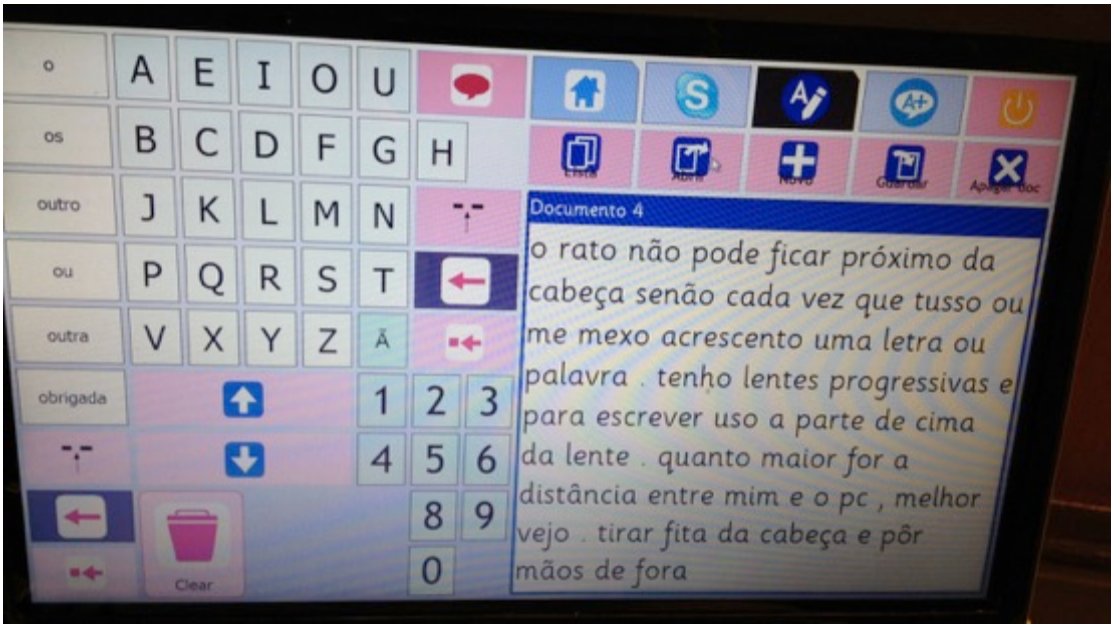

Figure 29 – One patient participating actively on decisions regarding technology adjustments. She is severely impaired (no speech and few residual movements in the head) and was using a head-switch as input device (scanning method).

Input devices that allow patients with severe physical dysfunction to access ACD are of utmost importance in this context. Finding the right input devices that fit to the physical conditions of the patient, and enabling him or her to efficiently generate input signals to access to an ACD, is sometimes a difficult task due to general muscle weakness. Input devices that can be used by patients in these conditions are described in section 2.3.2. Undoubtedly, recent development of eye-tracking technologies introduced important tools for patients in these conditions. However these must not be considered unique solutions. In fact, as already described in section 2.3.2.1, eye movements may be difficult to control in certain conditions.

Biosignals captured from sensors placed on the body have been explored in various ways to access to communication tools. These have the advantage of capturing data directly from the body, reducing patients' effort to control an external input device. Brain activity with EEG and other non-EEG signals have been extensively studied as input devices for ALS patients who are severely disabled, as is described in section 2.3.2.1. However, there are limitations in

existing input devices that are based on these biosignals: (i) Setup is complex and learning takes a long training process. Considering patients with severe neurological involvement, complexity may limit patients' motivation (Nijboer et al., 2010). Moreover, the use of ACD at these stages is closely dependent on caregivers' support, which is hard to achieve if the technology is difficult to setup and learn, as previously discussed in Chapter 4. (ii) Lack of flexibility to use different sources of input signals in the device. If there is more than one possible input signal, an assessment tool could study those input signals that maximize the flow of information with the minimal physical and cognitive workload for the user (Abascal, 2008). Especially in progressive conditions, as it is the case of ALS, input devices should dynamically adapt to physical and psychological stages of the patients, along the course of the disease (Londral et al., 2009; Beukelman et al., 2000). (iii) Many of the experimental results in the development of input devices for the disabled are obtained from non-disabled participants. Research where the target population participates can reveal usability factors that may be determinant for optimal design and effectiveness, when applying these technologies (Clarke et al., 2011).

The aim of this study was two-fold: (1) to develop a tool to assess new input signals for patients with very few residual movements, which can be used for communication; (2) to develop an input device based on the possibility to use various body sensors and underlying biosignals, avoiding the aforementioned limitations of other studies.

6.2 **Materials and Methods**

6.2.1 Design Requirements

Kintsch and Depaula (2002) have enumerated four important aspects to be considered in the development of any ACD: 1) it must be customizable; 2) it should be simple enough to set-up, customize and use; 3) it should be durable and robust; and 4) it must accommodate user's preferences, namely adapt to the users' environment and social context.

Considering these guidelines, we developed a new input device with the following design requirements:

a) It supports different sources of input signals (biosignals), to accommodate users' characteristics;
b) It must be simple to setup and use in the daily environment of the user;
c) It should be wireless and adaptable to different body sites, with reduced positioning constraints and flexible to follow progression of the disease symptoms;
d) It must be easy to learn (considering patients and caregivers) and have minimal additional setup.

6.2.2 System Description

6.2.2.1 General overview

We developed a platform that receives input signals from simple body-triggered activations. The input signal (voluntarily controlled by the user) is detected by the sensors (placed on the body) that collect the underlying biosignals, and transmit them via *Bluetooth*® to the computer. Signals from the sensors are then processed in real time to detect voluntary commands (i.e. voluntary body-triggered input signals). When any command is detected, the software emulates a keystroke (for example, to control a virtual keyboard using a scanning method) or an input command to assistive communication software. Figure 30 illustrates the block diagram of the proposed input device.

Figure 30 - Block diagram of the proposed system: (1) Data acquisition - user activates the sensor generating input signals; (2) Signal processing - input signal is sent via Bluetooth to the computer and processed to generate commands; (3) Switch-based control - when an event is detected, the system sends a command to an assistive communication software (e.g. a virtual keyboard)

6.2.2.2 Data Acquisition

For body signals acquisition we used a commercially available system (BiosignalsPlux™) with 4 analog channels. This system collects biosignals from different types of sensors and sends these signals via Bluetooth® wireless transmission to a base station (a computer). Its wireless transmission range of up to 100m is appropriate for the purpose of an input device. This system was setup for a sampling rate of 1000Hz and 12-bit resolution per channel.

6.2.2.3 Different sources of biosignals

For our input device, we focused on three different body sensors, namely: sEMG (gain:1000; CMRR: 110dB; passing band filter: 25-500Hz; input impedance >100MOhm), accelerometer (ACC) (3-axial MEMS; range: ±3G), and force sensitive resistor (FSR) (range: 0-10Kg; response time <5μS).

6.2.2.4 Signal Processing

After collecting the input signal (biosignal), this is processed through an algorithm to generate a *control signal*. Online detection of commands is based on a threshold value for the amplitude of the control signal, which is defined in the calibration procedure. Input signal, control signal and threshold can be visualized on the screen, as depicted in Figure 31.

Calibration. Before patient starts to control the system, there is a simple calibration procedure, where the user is asked to stay for 5 seconds at rest position. The power of the input signal is extracted from this "signal at rest" by calculation of the mean value of the input signal for the 5 seconds (5000 samples, f_s=1KHz*)* (Equation 2).

(Equation 2)

$$\overline{x} = \frac{1}{5000} \times \sum_{1}^{5000} x_i$$

x_i : magnitude of the signal in sample i

Treshold value (T_h) for the detection of *commands* is defined in Equation 3, as the power of the input signal (as defined in Equation 2) plus the standard deviation error of the signal multiplied by a scale factor N, which we defined depending on the type of input signal used. This value can then be manually adjusted by the user, after the calibration procedure.

(Equation 3)

$$T_h = power(signal_{rest}) - N \times stdev(signal_{rest})$$

Control signal: algorithm of variance. When a user makes a voluntary activation, the input signal (movement acceleration, muscle contraction, or force) shows a corresponding variation (increase) in amplitude. For example: if a user strongly contracts the muscle, sEMG will have increased amplitude. In our

approach, the variance of an input signal contains information about voluntary control of the signal. To process the control signal, we used the maximum-likelihood estimate of the local variance (Equation 4), computed for the windowed signal parts, in real time (Bonato et al., 1998). This function is analogous to a moving average window, except for a square term, which increases the difference between voluntary activation and *no activation* (Choi & Kim, 2007).

(Equation 4)

$$\sigma_x^2 = \frac{1}{n} \times \left[\sum_{i=1}^{n} {x_i}^2 - \frac{1}{n} \left(\sum_{i=1}^{n} x_i \right)^2 \right]$$

x_i : magnitude of the signal in sample i
n: number of samples defined for a data window

Detection of commands. The onset of a *command* is detected as the first point in the control signal that surpasses the predefined T_h for a minimum interval of 100ms. This interval was defined to filter sporadic (involuntary) activations. Figure 31 illustrates the detection of slight movements using an accelerometer.
Variance analysis is particularly effective to detect voluntary activations for sEMG signals (Choi & Kim, 2007b). Further we found that the variance algorithm can be generalized to detect voluntary activations with other input biosignals. This algorithm was then used in our system for all types of studied input signals (accelerometer, electromyography and force).

6.2.2.5 Visual Biofeedback

We developed software for online visualization of input signal and control signal. Users can then visualize both signals in real time, learn how to voluntarily activate the input signal and how to generate commands, using biofeedback strategies (Figure 31). When the control signal rises above the line of T_h, there is a visual feedback for the user, indicating the generation of a command.

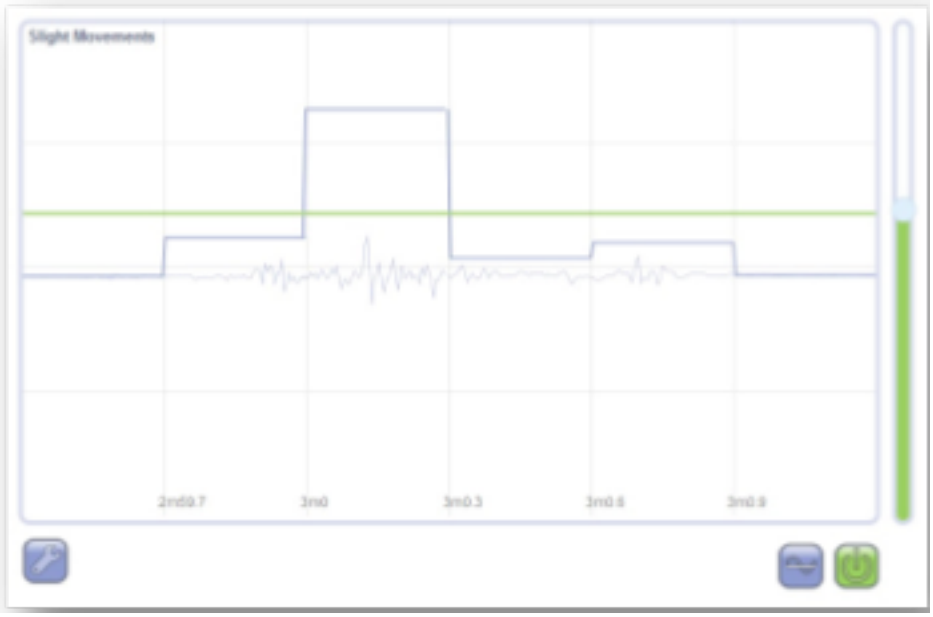

Figure 31 - Visual biofeedback window developed for the present study. Both body signal and control signal (from the variance algorithm) are visually presented to the user. User learns to control the body signal by watching it on the screen. The objective is to raise the signal above the horizontal green line, to be able to generate a command.

6.2.2.6 Commands and customization

The software platform includes a customization panel. Customization is an important factor to accommodate variability among users, particularly different tasks to perform. In this panel, the user can choose which type of body action (corresponding to a specific sensor) will be performed for control and which third-party application should receive the *command* events generated by the user. As an example, Figure 32 shows our system controlling an onscreen keyboard for a writing task. Threshold can also be manually adjusted, as aforementioned.

6.3 **Exploratory study**

6.3.1 Participants

With the objective of qualitatively evaluating our system, we performed an exploratory study including three of the participants in our research. All patients were between 50 and 65 years old. The selection criteria were: severe motor impairment in UL (few movements that patient could control) and strong dependence on others. Table 10 summarizes the clinical and social context of each participant.

Figure 32 - Example of the developed platform, controlling an onscreen keyboard to perform a writing task in a ©WordPad (from Microsoft) document. In this example, when detecting a control signal from EMG generated by the user, the key "Enter" is sent by the platform to the application of onscreen keyboard. This command performs a selection using the scanning method.

6.3.2 Procedure

Experiments were performed in a single session per participant, in their usual daily environment (*Residence* in Table 10). The purpose and procedures of the study were explained to patients and caregivers, before informed consent. Participants and caregivers were asked to give their opinion on the system, after the assessment. Patients were asked to show movements that they could perform; sensors were chosen according to the physical characteristics of those movements (Table 10).

Table 10. Selected patients included. For each participant, this table describes the place where they live, clinical condition, residual movements that were used for this study, speech preservation and the sensors tested.

Participant	*Residence*	*Clinical Condition*	*Residual Movement(s) in Upper Limbs*	*Speech*	*Sensors*
P1	Home	ALS	Right hand (closed)	No speech	ACC;FSR
P2	Elderly residence	ALS	Slight movements of the left hand fingers and muscle contractions in the arm	Moderate intelligibility	ACC;FSR sEMG
P3	Long term care clinic	ALS	Slight movements of right index finger	No speech	ACC, FSR

FRS: force resistance sensor; ACC: accelerometer; sEMG: surface electromyography

A computer screen was used to provide visual biofeedback of the input biosignal (both input signal and processed control signal) to the patient, in real-time. For each setup, participants tried to voluntarily activate the input signal by visualizing it (and its corresponding control signal) on the computer screen. Patients explored the system for approximately 2 minutes, watching the input

biosignal and practicing simple cause-effect activities. Then, participants were asked to perform two tasks: (Task1) to generate 5 to 10 onsets of the signal; and (Task 2) to generate an onset and hold it for 5 seconds (not considered for ACC sensors).

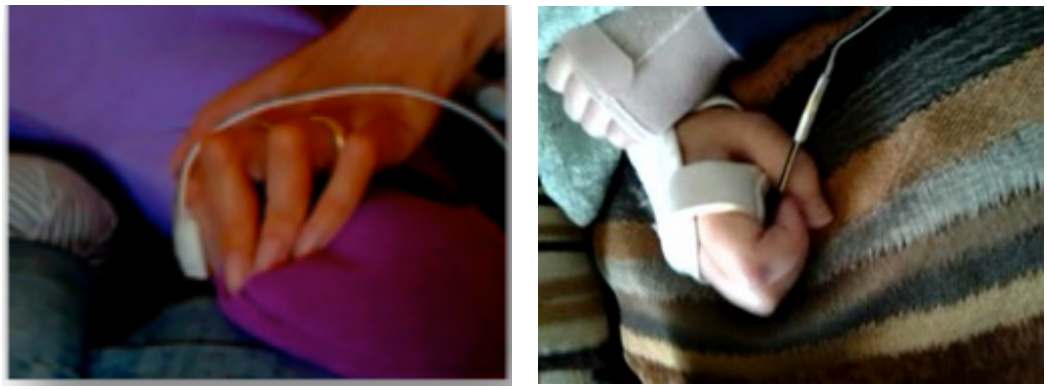

Figure 33 – (left) Accelerometer for detection of slight movements of index finger from the left hand; (right) a FSR sensor placed below the thumb finger from the right hand.

Qualitative outcomes were: sources (input biosignals) with which users could fulfill the proposed tasks, types of sensors that best fit to different residual movements and main difficulties observed in fulfilling the proposed tasks. Quantitative outcomes were: duration and number of onsets performed in each task.

6.3.3 Results

None of the patients had previous training sessions. We assessed voluntary control of movements in the body, with the feedback of patients, caregivers and therapists (in the case of P3), as depicted in Figure 33. After selecting the body sites and sensors to generate input biosignals, in each participant, we started the tests. Results are described in Table 11. Patients were able to fulfill the first task with one or more input biosignals. P2 was the only one who could voluntarily perform a long activation (Task 2) of the control signal (5025.2 ms) with the FSR sensor. P1 and P2 could control more than one input biosignal using ULs. P3 needed a longer time to *deactivate* the signal. Duration of activations in Task 1 is a measure for the ability to *activate and deactivate* a command in the control signal, equivalent to *press and release* a key or switch. Input biosignals corresponding to Task 1 are depicted in Figure 34, Figure 35 and Figure 36 for each patient tested in this study, respectively.

Table 11. Characteristics of the selected input biosignals for tasks T1 and T2

Part.[(a)]	*Sensor*	*Body placement*	*Task 1 onsets* [(b)]	*Task 1 Duration* [(c)] *(s)*	*Task 2 Duration* [(b)] *(s)*
P1	FSR	Right thumb pressure	5 / 5	2.5±1.1 (0.9 to 2.8)	No control
P1	ACC	Right thumb movement	5 / 6	1.1±0.1 (0.9 to 1.2)	n.a.
P2	ACC	Left index finger	10 / 10	0.4±0.1 (0.3 to 0.6)	n.a.
P2	FSR	Left index finger	10 / 10	0.4±1.0 (200 to 599)	5.0
P2	sEMG	Left arm *Biceps*	10 / 10	0.5±0.1 (0.3 to 0.6)	No control
P3	FSR	Right index finger	3/4	2.2±2.6 (0.4 to 5.8)	No control

(a) Participant
(b) Number of performed onsets / Detected activations
(c) Duration of each signal activation: Mean±Standard Deviation (Range)
FSR: force sensitive resistor; ACC: accelerometer; sEMG: superficial electromyography

6.4 **Discussion**

We developed a new input device for patients with severe functional impairments in upper and lower limbs. One of the main positive aspects of our proposed system was the flexibility to adapt to each user's characteristics. Due to the option for using different sensors and body sites, participants in this exploratory study did not have to change their environment or position to perform the proposed tasks. Moreover, we could observe that visual biofeedback is an important tool for assessment and training control of residual movements. In our tests, this tool was used, both by the patients, to learn to control the biosignal, and by the caregivers, to analyze and give feedback to the patients in the learning and motivation process before the tests.

Our input device showed to be a valid instrument to glean new sources of input biosignals captured on the body. In spite of the small number of patients and difficult physical conditions of our target population, results from experimental tests with these users are important to support further developments.

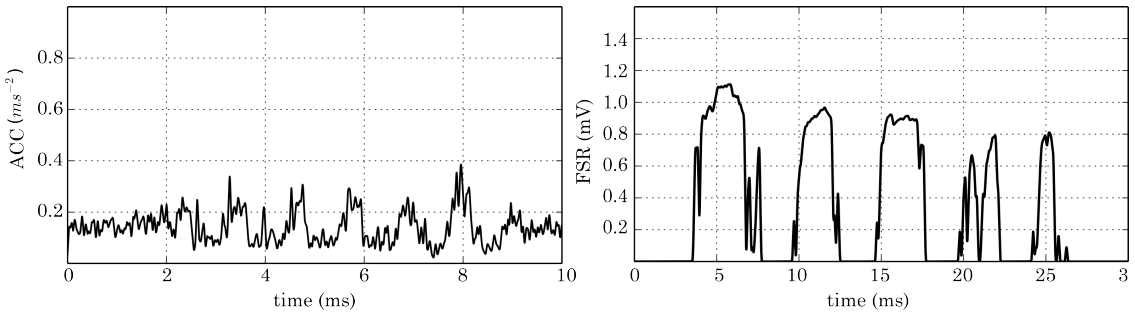

Figure 34 – Plots from two input biosignals for Task 1 performed by P1 (according to Table 11).

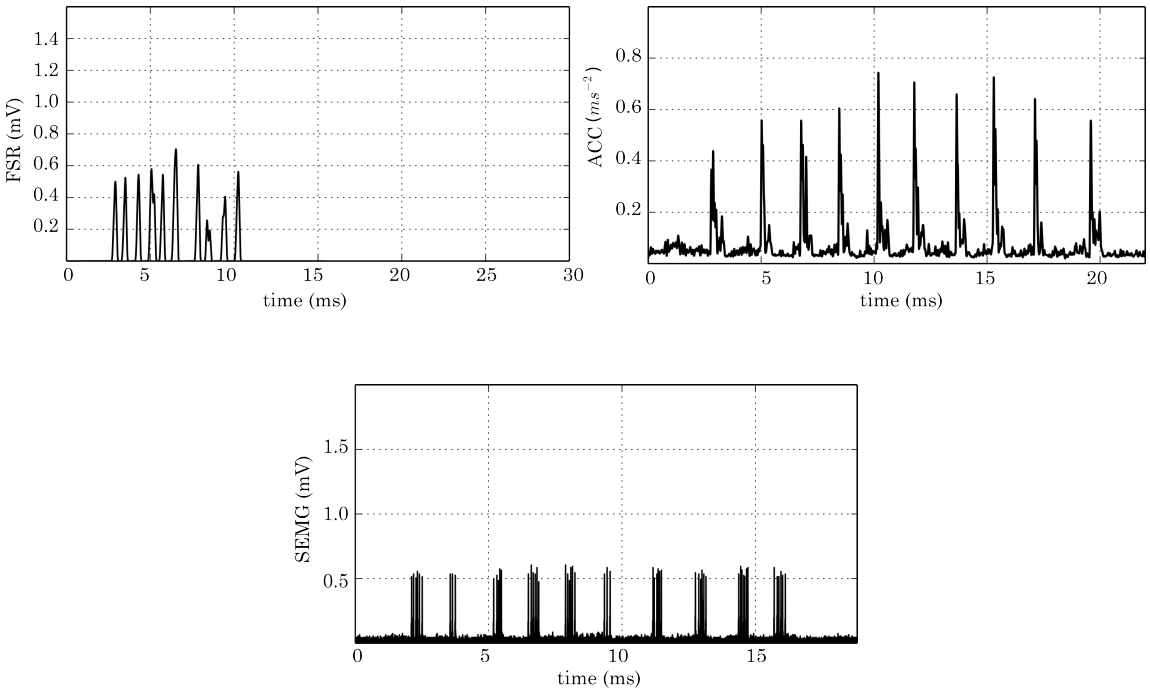

Figure 35 – Plots from three input biosignals for Task 1 performed by P2 (according to Table 11)

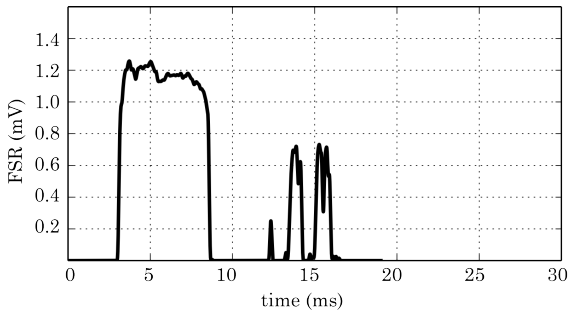

Figure 36 – Plots from one input biosignal for Task 1 performed by P3 (according to Table 11).

Functional evaluation of UL dysfunction in ALSFRS-R underestimate residual movements that patients can perform when muscle weakness is severe (Wicks et al., 2009). However, these residual movements can be important for support in communication. In this exploratory study, patients could use residual movements in fingers and arm to generate input signals. In particular, accelerometer should be further explored as a light sensor that can capture slight movements which cannot be used to press keys or switches. Input signals that are generated from those slight movements may be used with various purposes: to control an ACD with scanning method access, to perform a “select” command in eye-tracking devices, to activate a bed alarm or be connected to any other device.

The more input signals that a patient can generate, the more possibilities they have to communicate. Our system allows the assessment of function in performing residual movements that can be used for communication. In ALS or other neurodegenerative conditions, regular assessment of input signals is important to follow disease symptoms and enhance patients’ function in accessing to communication tools. For the rapid progression and patients’ dependence on caregivers, assessment tools and input devices that are easy to learn and control will have better acceptance from patients and caregivers.

As future work, tests must be performed on a broader range of users, exploring new algorithms for automatic detection of voluntary actions. More types of sensors to capture new biosignals on the body will also be tested with this input device.

6.5 **Conclusions**

We developed a novel input device for ALS-patients with general muscle weakness. The developed system allows the use of different sensors to detect residual movements that are not considered in clinical functional evaluation of UL (ALSFRS-R). We evaluated input biosignals from three different sensors (accelerometer, force and electromyography) on different body parts, in this exploratory study that included three ALS patients in their daily care context. From a qualitative analysis, we could observe that our system was easy to setup and learn; it was also flexible to robustly transduce residual movements from multiple sources in the body. Biofeedback is an important feature of this system: patients could explore residual movements, visualize them in real time on the computer

screen and learn how to control them. In particular, concerning neuromuscular degenerative conditions, our system is important for assessment of input signals that a patient can generate, during progression of disease symptoms.

6.6 **New findings and their importance under research goals**

We developed a new input device for the most severely impaired ALS-patients. Novelty of this new input device is the possibility of being used as an assessment tool to detect sources of input signals that are not considered in clinical functional evaluation. We propose *biofeedback* as a tool for assessing and learning new input signals that can be controlled by the patient to access to communication tools.

This work also contributes with design requirements that are necessary for the development of new input devices that are to be implemented in the context of ALS-patients in late stages, with no previous experience on using assistive communication tools.

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Chapter 7 - Discussion

7.1 General discussion of the overall work

This work tested the value of ACD on improving the QoL in ALS, from early to late stages. We hypothesized that early support for the use of ACD has a positive impact on the QoL of ALS-patients (and their caregivers) and we developed a methodology to quantitatively measure functional performance of written communication in early stages. We investigated markers of disease progression in communication tasks (typing and voice recording activities), considering that ACD can be used as tools for this purpose. A framework to explore novel monitoring tools based on typing and speech activities, in early stages of ALS, and novel functional input biosignals, in late stages, was an important contribution of this research.

7.1.1 On upper limbs functional performance for using assistive devices

Progression of UL dysfunction varies among ALS patients. It depends not only on the onset symptoms, but also on time of progression and the specific pattern of disease progression. Functional progression of UL symptoms may be evaluated with ALSFRS-R, as described in section 1.2, which assesses function in different activities of daily living. In this research, we studied methodologies to measure and characterize progression of UL function that is related to the use of ACD.

We found that handwriting performance is correlated to ALSFRS-R-ul, as it was expected since the function of handwriting is evaluated in this subscore of ALSFRS-R. It is interesting to note that our method to measure handwriting performance can be used as a quantitative method to evaluate handwriting, which is well correlated to a clinical tool that is broadly used in ALS (ALSFRS-R).

Concerning the use of the computer to write, typing performance is very dependent on patients' experience in using keyboards for writing. Performance of WPM relates to the number of keystrokes per minute, which depends on the memorization of the keyboard. For this reason, our results showed high variations of typing performance between patients. Still, we can conclude that typing performance is a measure of functional ability to use a keyboard and it can be a

quantitative measure of experience in use. Typing performance was not correlated to ALSFRS-R-ul, suggesting that ALSFRS-R may not be sensible to the function of using a keyboard or, more generally, an ACD. Results of this work are in agreement with the extension suggested by Wicks et al. (2009) for the ALSFRS-R, concerning control of assistive devices, as described in section 2.3.1.2. This extension should be used in the assessments for the use of ACD.

By evaluation of features of keystrokes extracted from the acceleration signal in a typing activity, we found that it is possible to monitor UL dysfunction that is relevant for the use of ACD. As the disease progresses, the increasing delay in performing keystrokes, as well as decreased acceleration of movements, are quantitative measures for the increasing difficulties of ALS patients in using a keyboard or pressing a switch. Analysis of typing can then be used as a quantitative method to mark UL dysfunction in ALS and contribute for the anticipation of the need for alternative input devices in support for communication.

7.1.2 On longitudinal data collection in ALS, involving patients' interaction

As ALS progresses, several factors, mainly related to the rapid aggravation of symptoms, difficult a long cooperation of the patient and their caregivers in longitudinal research studies that involve their active participation. We studied a group of ALS patients with bulbar onset. This group of patients represents 25% of all patients and has a more rapid functional decline, which raises a difficulty for longitudinal studies. Notwithstanding, rapid progression was also an advantage for the aims of the research, since it allowed faster observation of progression of symptoms and stages in ALS.

We followed a total of 30 patients with ALS, who were included in data collection of the different studies in this thesis. The cooperation of patients and caregivers was needed to monitor the use ACD, fill-in the questionnaires and perform the tasks related to speech, handwriting and typing recordings. Dropouts and variation in the number of assessments between different patients were mainly related to death or decreased motivation of some patients or caregivers to cooperate due to fast progression. As dysfunction increased and new complications (mainly related to feeding problems) demanded decisions on complex clinical intervention (sometimes hospital admission), collaboration for the evaluation tests was interrupted or depreciated, mainly by the caregivers. As

stated in Bedlack et al. (2014) "*studies of people with advanced ALS are possible, but subject retention and protocol adherence are challenging*".

7.1.3 On the methodology for data collection

The methodology developed to monitor disease progression is based on spoken and written material collection. Having hypothesized that ACD could be used for in-home monitoring, we developed techniques to extract features from data that was captured with simple tools: a simple laptop computer or tablet device. Despite the fact that most data from patients was collected at clinical settings, the methods that we developed can be used in the patients' home environment. Voice was captured with a voice recorder that is embedded in the computer; handwriting and typing performance were calculated from the time duration of each task's completion. Concerning data from the accelerometer, our procedure was simple and quick to set up. Furthermore, one of the features of the study with the accelerometer, the mean time while pressing down the keys of the keyboard, can be recorded using software tools (with no need to use the accelerometer or other additional equipment).

In ALS, the complexity and duration of the tests is critical to longitudinal studies that are dependent on the motivated involvement of patients. We used simple and short sentences, contrary to other clinical tests that require long collaboration of patients and controlled settings.

Simplicity of procedures and equipment used in our research methods contribute to asseverate further exploitation of the methodology of this research in studies for in-home monitoring with ACD.

7.1.4 A *patient* or a *user* of technologies

Assistive technologies are framed in the field of Rehabilitation. In this perspective, the emphasis on dysfunction, as focused in this research may raise controversy. In fact, assistive technologies were defined as services, products or strategies to *enhance function* (described in Section 2.1), which is in accordance to the International Classification of Functioning, Disability and Health (WHO, 2001). In our research work, some methodologies were focused on the evaluation of *dysfunction*. Also, the focus on the subject *patient* may be controversial to those who consider assistive technologies in the framework of modern holistic models

for Disability. The specific case of ALS and some other neurodegenerative diseases must then be considered.

In ALS, disease progression has no return. Vital support is needed from early stages in most of the bulbar onset patients. Symptoms manifest rapid changes in overall functionality, and demand close clinical support. For these facts, the user of assistive technologies in the context of ALS is always a *patient*. As so, decisions on support with ACD must not disregard clinical intervention in other areas than communication. On the contraire, ALS patients is a target group where the close work of the engineers with clinical professionals, patients and caregivers is absolutely necessary for the adequate and successful support with ACD.

7.1.5 Benefits of early support in assistive communication

As tablet devices and Internet tools became popular and accessible in the mass market, most patients are starting to use communication tools prior to clinical communication support. Many clinicians still consider handwriting as a preferable communication tool when patients claim decrease in speech intelligibility with no decreased function in ULs; or consider the use of ACD as an *ultimate resource,* when speech and ULs are no longer accessible. This arises particularly for patients with low school education or socio-economic levels. Despite the fact that there are various software applications that can be used as communication tools for ALS patients with severe dysarthria but high function in ULs, clinical intervention should intermediate the choice of these tools early, to help the patients to potentiate its use in further stages of the disease (Azevedo et al., 2009). If patients start being supported to use communication tools that can be further used in later stages, it is possible to raise motivation and economize patient's efforts to learn and adapt to new devices, as the disease progresses. As Miyasaka (2013, pp.165) remarks: "*every time an input device is changed, not only does the patient have to learn how to use it, but the caregivers also have to learn how to install each new device. Therefore, change a communication device can become a major hindrance for maintaining continuous communication in ALS support*".

Positive impact in early intervention of clinicians in assisting the use of ACD includes: (1) improved quality of life for patients and caregivers, (2) soft adaptation

to communication tools, since patients may start to use simple devices for learning how to use the software tools and adapt to new input devices as the disease progresses, with reduced effort for learning new communication tools (as discussed in Chapter 4); (3) decrease in the cost of equipment, since a planned strategy for communication reduces changes of devices as the disease progresses; and (4) the possibility of monitoring the disease progression continuously in daily living (as hypothesized in Chapter 5).

7.2 **Summary of Main Results**

This work focused on the use of assistive communication devices by patients with ALS, from early to later stages. We found that:

1) Early intervention with communication tools has a positive impact on QoL of both patients and caregivers. A trend for positive impact was found on psychological, well-being and support domains of quality of life (Chapter 4).
2) ALSFRS-R may not be sensitive to functional skills needed to assessment in the use of communication devices:
   a) Typing performance was not correlated to clinical functional assessment of UL (ALSFRS-R-ul); patients could perform typing for longer than handwriting, as ULs function decreased (Chapter 4).
   b) Main difficulties in using ULs for accessing to ACD are increasing delay for pressing and releasing buttons (or keys) and reduced acceleration of movements (Chapter 5).
   c) Despite decrease in functional scores of ALSFRS-R, patients with poor experience in using computer devices improved performance in typing, as a result of having learned how to use communication tools (Chapter 4).
3) Assistive Communication Devices can be used as tools to monitor progression of ALS.
   a) We defined a methodology to collect typing activity and speech with a simple and fast procedure that can be replicated out of the clinical setup, using ACDs (Chapter 5).
   b) Typing activity and speech recordings of running speech, carried out in ACs, can be used as tools to monitor progression of symptoms related to communication, on a continuous mode (Chapter 5).

4) We developed a new tool for the assessment and control of input signals based on various biosignals captured on the body, in particular for patients in late stages of ALS, that are severely disabled (Chapter 6).

7.3 **Limitations of the study**

Measuring the effect of the use of ACD on the quality of life of patients and caregivers was a main objective of this research. Due to the exploratory nature of our study, we analyzed multiple domains of quality of life. Despite the fact that we found a trend for a positive impact in some domains, we could not find statistical significance in results when considering correction for multi-comparisons. Nevertheless, results indicate that psychological, existential well-being and support domains should be investigated in further research on the impact of communication tools in ALS.

It is not possible to isolate the effect of a single variable in a disease that affects several physical functions in a progressive way. Quality of life may be affected by multiple other factors than communication. In the same way, the use of ACDs may be conditioned by physical dysfunction but also by multiple personal and social factors. Following these statements, the methodology based on 2 to 6 months intervals for evaluation of the use of ACD may be insufficient to reach rigorous results on aspects related to the use of assistive devices.

Another limitation of this study was that, in spite of the fact that all patients were a homogeneous group of ALS patients with bulbar onset, there was a considerable variability between patients. Main reasons were: different characteristics of progression, different disease stages and motivation, or difficulties in following patients due to their absence to scheduled clinical appointments (or for the fact that they moved from home to residential care units).

Chapter 8 - Perspectives and Future Work

8.1 **Impact of early support of ACD on longitudinal research for ALS**

Overall, studies performed in this thesis have exploratory characteristics due to multiple comparisons and reduced samples. Nevertheless, we developed methodologies and novel techniques that can be replicated in future projects on the use of communication tools in ALS. Further studies should include a larger sample of patients and controls are needed.

We studied the effects of early intervention in the use of assistive communication. From results of this research we hypothesize that early intervention with ACD will reduce the cognitive effort of later support in communication. Those patients that gain skills for using communication tools in early stages will be more motivated to use those tools during the course of the disease. Further investigation is needed to study the impact of early use of ACD on patients' motivation and acceptance of more complex technologies in later stages (e.g. the impact on the use of BCIs).

Concerning the study of the markers of disease progression using UL and speech functions, future research is needed to test the proposed methodologies in a larger population of patients with ALS, using remote data collection. Continuous data from a large group of patients would improve the characterization of UL and speech dysfunction towards a better clinical support for the use of ACD.

Most studies that involve the collaboration of patients are difficult to proceed when motor impairment is high. Methodologies that were developed in this research for the early use of ACD can be further explored for the development of new tools for assessing patients from home, from early to late stages. Evaluation instruments that can be accessed and filled-in by patients through communication tools can support novel longitudinal research, for example on cognitive screening or quality of life evaluation.

8.2 **Other populations that may benefit from the findings in this work**

Our results can be further explored in other progressive neurological conditions. While some aspects of the disease symptoms can be specifically

characteristic of ALS, methods and technologies used in this research work can be interesting in the study of disorders that limit communication but not language and consciousness (McCluskey, 2013). Methods that were developed during our research for using ACD as a tool to monitor speech and UL progression can be further explored for either progressive or potentially reversible disorders. Some examples are Parkinson's disease, Muscular Dystrophy, Multiple Sclerosis or some stroke conditions. Moreover, the developed platform for the use of different input biosignals, based on biofeedback training, was generally designed for those who are severely disabled. We have performed another study with two patients with brainstem stroke and one with traumatic brain injury for the assessment of input biosignals, which demonstrates application of this novel platform to other conditions than Amyotrophic Lateral Sclerosis.

8.3 **Modern paradigms for Assistive Communication Devices**

Research on how people interact with technology is leading a more comprehensive approach on the design of technologies that engage patients, their caregivers and health professionals. While traditionally, technologies developed for Healthcare were exclusively for the use of health professionals (for example, tools for diagnostic, monitoring or treatment purposes), presently, technologies that are also used by the patients and improve the flow of information and communication between all parts (patients, caregivers and the care team) are providing novel integrated experiences of Healthcare (Ball & Lillis, 2001; Urmimala et al., 2014).

In addition to the primary objective of ACD of compensating speech or UL dysfunction in ALS, we advocate that these devices are also valuable *instruments* to support the aforementioned novel integrated experiences in Healthcare. In fact, ACD are technologies to be used by the patients in their daily living environments to improve communication and social connections, enhance function in various or specific activities of daily living and preserve autonomy. Furthermore, in the frame of the neurological progressive diseases, modern ACD can give to ALS patients the access to a framework of new services, devices and strategies that is being developed with enormous impact in Europe: the *Ambient Assisted Living* (AAL)[3]

[3] AAL. The general objective of this new field of research (created in the context of European demographic changes) is to support mass research and development of information and communication technologies that enhance the

(Röcker & Ziefle, 2011). In line with the general objectives of AAL, assistive communication devices can be further explored as *personal health systems* (INTEL, 2008) playing a major role in connecting the patients to the health and social care professionals and services.

quality of life, extend the autonomy and social participation of the elderly population and thus, reduce the costs of health and social care (Rashidi & Mihailidis, 2013; van den Broek et al., 2009)

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Appendix A - Speech and phonation modelling

This appendix includes a description of the methodology used in estimating formant positions, spans, area and centralization, to derive the indices for jaw and tongue neuromotor affection, as extensively described in Gómez-Vilda et al. (2015).

Speech recordings were used to estimate a prototype of the vowel triangle (as in Figure 26) in the domain of the first two formants *F2* vs. *F1* corresponding to pairs {*F1(n)*, *F2(n)*}, where n is the discrete time index. Formant distributions used to estimate the distribution quantiles were:

$$q_i^{\theta} = \arg\left\{ \int_{\nu=q_i^{\theta}}^{\infty} \gamma_i(\nu)d\nu \Big/ \int_{-\infty}^{\infty} \gamma_i(\nu)d\nu = \theta \right\}$$

where $\gamma_i(\nu)$ is the probability density function of formant *i* in frequency ν, and θ is the specific quantile threshold (for instance θ*=0.03* would correspond to a 3% quantile). In the present study the following definitions apply: θ_1*=0.03*, θ_2*=0.5* and θ_3*=0.97*.

A.1 Ideal vowel triangle

An ideal vowel triangle enclosing most of the pair estimates {*F1(n)*, *F2(n)*} was defined (as illustrated in Figure 26) by the vertices given by

$$V_{tl} = \left\{ q_1^{\theta_1}, q_2^{\theta_3} \right\}$$
$$V_{bl} = \left\{ q_1^{\theta_1}, q_2^{\theta_1} \right\}$$
$$V_{cr} = \left\{ q_1^{\theta_3}, q_2^{\theta_2} \right\}$$

where V_{tl}, V_{bl} and V_{cr} are correspondingly the top left, bottom left and center right vertices, corresponding approximately to the positions tending to extreme vowels /i/, /u/ and /a/ on the standard vowel triangle.

Triangle geometrical centroid C_g (intersection of angle bisectors), formant span centroid C_f, and the statistical centroid C_s, were defined as:

$$C_g = \left\{ f_{1g}, f_{2g} \right\}$$

$$C_f = \left\{ \frac{q_1^{\theta_1} + q_1^{\theta_3}}{2}, \frac{q_2^{\theta_1} + q_2^{\theta_3}}{2} \right\}$$

$$C_s = \left\{ q_1^{\theta_2}, q_2^{\theta_2} \right\}$$

where the geometrical centroid coordinates f_{1g} and f_{2g} can be estimated as:

$$f_{1g} = \frac{q_2^{\theta_3} - q_2^{\theta_1}}{a_1 - b_1} + q_1^{\theta_1}$$

$$f_{2g} = a_1 \frac{q_2^{\theta_3} - q_2^{\theta_1}}{a_1 - b_1} + q_2^{\theta_1}$$

$$a_1 = \tan\left(\frac{\pi}{4} + \frac{\alpha}{2} \right)$$

$$b_1 = -\tan\left(\frac{\pi}{4} + \frac{\beta}{2} \right)$$

$$\alpha = \arctan\left(\frac{q_2^{\theta_2} - q_2^{\theta_1}}{q_1^{\theta_3} - q_1^{\theta_1}} \right)$$

$$\beta = \arctan\left(\frac{q_2^{\theta_3} - q_2^{\theta_2}}{q_1^{\theta_3} - q_1^{\theta_1}} \right)$$

A.2 Formant spans (∆F1 and ∆F2)

The formant spans ∆F1 and ∆F2 are defined as the range swept by both formants referred to the vertices in the ideal vowel triangle. Their normalized versions are evaluated in reference to the geometric centroid $\{ f_{1g}^{CF36}, f_{2g}^{CF36} \}$ of female control subject CF36 as:

$$\Delta\mathrm{F1n} = \frac{q_1^{\theta_3} - q_1^{\theta_1}}{f_{1g}^{CF36}}$$

$$\Delta\mathrm{F2n} = \frac{q_2^{\theta_3} - q_2^{\theta_1}}{f_{2g}^{CF36}}$$

A.3 Modulus of the normalized formant span (MNFS)

The formant span may be seen as a vector with the modulus and argument:

$$\left| \Delta\mathrm{Fn} \right| = \sqrt{\Delta\mathrm{F1n}^2 + \Delta\mathrm{F2n}^2}$$

$$\phi_{\Delta\mathrm{Fn}} = \arctan\left(\frac{\Delta\mathrm{F2n}}{\Delta\mathrm{F1n}} \right)$$

Appendix B – Questionnaires of Quality of Life and Communication

B.1 ALSFRS-R

1. ARTICULAÇÃO VERBAL

Discurso normal ☐
Perturbações detectáveis no discurso ☐
Inteligível com repetição ☐
Discurso combinado com comunicação não verbal ☐
Perda do discurso útil ☐

2. SALIVAÇÃO

Normal ☐
Ligeira, mas com excesso de saliva na boca, talvez se babe durante a noite ☐
Moderado excesso de saliva, um mínimo de baba ☐
Marcado excesso de saliva: com alguma baba ☐
Marcado excesso de baba: requer uso constante de lenço ☐

3. DEGLUTIÇÃO

Hábitos alimentares normais ☐
Problemas prematuros ao comer, com ocasional sufocamento ☐
Alterações na consistência da comida ☐
Necessita de sonda para alimentação suplementar ☐
Não se alimenta pela boca (alimentado exclusivamente por via parentérica ou entérica) ☐

4. ESCRITA

Normal ☐
Lenta e irregular, todas as palavras são legíveis ☐
Nem todas as palavras são legíveis ☐
Capaz de agarrar a caneta, mas incapaz de escrever ☐
Incapaz de segurar a caneta ☐

5.a. CORTAR A COMIDA E MANEJAR OBJECTOS (doentes sem gastrostomia)

Normal ☐
Algo lento e desajeitado mas não necessita de ajuda ☐
Pode cortar a maior parte da comida, embora lento e desajeitado, necessita de alguma ajuda ☐
A comida tem que ser cortada por alguém, mas ainda se consegue alimentar lentamente ☐
Necessita ser alimentado ☐

5.b. CORTAR A COMIDA E MANEJAR OBJECTOS (doentes com gastrostomia)

Normal ☐

Desajeitado, mas capaz de desempenhar todas as actividades independentemente ☐

Precisa de alguma ajuda para apertar e desapertar o botão da gastrostomia ☐

Dá ajuda mínima à pessoa que cuida dele/a ☐

Completamente dependente ☐

6. VESTIR E HIGIENE PESSOAL

Normal ☐

Independente apesar da tarefa requerer esforço e ter eficácia diminuída ☐

Ajuda intermitente ou substituição de métodos ☐

Necessita de auxilio para cuidado pessoal ☐

Total dependência ☐

7. VOLTAR NA CAMA E AJUSTAR A ROUPA DA CAMA

Normal ☐

Algo lento e desajeitado mas não necessita de ajuda ☐

Pode virar-se sozinho e ajustar os lençóis mas com muita dificuldade ☐

Pode iniciar mas não voltar-se ou ajustar os lençóis sozinho ☐

Incapaz ☐

8. ANDAR

Normal ☐

Prematuras dificuldades ambulatórias ☐

Caminha com ajuda ☐

Apenas movimento funcional não ambulatório ☐

Sem movimentos úteis dos membros inferiores ☐

9. SUBIR ESCADAS

Normal ☐

Lento ☐

Moderada instabilidade e fadiga ☐

Necessita assistência ☐

Impossível ☐

10. RESPIRAR

Normal ☐

Falta de ar para mínimo esforço (ex. andar, falar) ☐

Falta de ar em repouso ☐

Assistência ventilatória intermitente (ex. nocturna) ☐

Dependente do ventilador ☐

TOTAL: _____

B.2 MGill Quality of Life Questionnaire (in Portuguese)

QUESTIONÁRIO DE QUALIDADE DE VIDA MCGILL (MQOLQ - PT) ©

Data _____ Código_____

Instruções

As perguntas neste questionário começam com uma afirmação seguida de duas respostas opostas. As hipóteses de resposta são dadas em números que vão de um extremo ao outro da resposta (0 a 10). Por favor desenhe um círculo à volta do número entre 0 e 10 que seja o mais adequado a si. Não existem respostas correctas ou erradas. As respostas completamente honestas serão as mais úteis.

EXEMPLO:

Eu tenho fome.

nenhuma 0 1 2 3 4 5 6 7 8 9 10 **bastante**

- Se não tiver nem um pouco de fome desenharia o círculo à volta do 0.
- Se tivesse um pouco de fome (acabou agora mesmo de comer uma refeição mas ainda tem espaço para sobremesa), desenharia o círculo à volta do 1, 2 ou 3.
- Se estiver a sentir fome moderada (porque se está a aproximar a hora da refeição), desenharia o círculo à volta do 4, 5 ou 6.
- Se estiver com muita fome (por não ter comido durante todo o dia), desenharia o círculo à volta do 7, 8 ou 9.
- Se está com bastante fome, colocaria o círculo à volta do 10.

COMECE AQUI:

É MUITO IMPORTANTE QUE RESPONDA A TODAS AS QUESTÕES.
RESPONDA SEMPRE PENSANDO NO QUE TEM SENTIDO *NOS ÚLTIMOS DOIS (2) DIAS*.

PARTE A

Tendo em conta todos os aspectos da minha vida – física, emocional, social, espiritual e financeira – a minha qualidade de vida nos últimos dois (2) dias, tem sido:

muito má 0 1 2 3 4 5 6 7 8 9 10 **excelente**

Por favor continue na página seguinte...

PARTE B: Sintomas Físicos ou Problemas Físicos

(1) Nesta Parte "B", por favor liste os ***SINTOMAS OU PROBLEMAS FÍSICOS*** *que mais o tenham afectado nos últimos* ***dois (2)*** *dias. (Alguns exemplos são: dor, cansaço, fraqueza, náusea, vómitos, obstipação, diarreia, dificuldade em dormir, falta de ar, falta de apetite, suores, imobilidade. Pode referir-se a outros, se necessário).*

(2) Coloque um círculo à volta do número que melhor indica o grau do problema para si ***DURANTE OS ÚLTIMOS DOIS (2) DIAS****.*

(3) Se, nos últimos dois (2) dias, ***NÃO*** *teve sintomas ou problemas físicos, ou apenas tiver tido apenas um ou dois, responda a cada um dos que teve e escreva "nenhum" nas outra questão da Parte B, depois continue para a Parte C.*

1. Ao longo dos últimos dois (2) dias,
um problema / sintoma desagradável (incomodativo) tem sido: _____.
(escreva o sintoma)

Sem problema 0 1 2 3 4 5 6 7 8 9 10 **Problema tremendo**

2. Ao longo dos últimos dois (2) dias,
outro problema / sintoma desagradável (incomodativo) tem sido: _____.
(escreva o sintoma)

Sem problema 0 1 2 3 4 5 6 7 8 9 10 **Problema tremendo**

3. Ao longo dos últimos dois (2) dias,
um terceiro problema / sintoma desagradável (incomodativo) tem sido: _____.
(escreva o sintoma)

Sem problema 0 1 2 3 4 5 6 7 8 9 10 **Problema tremendo**

4. Ao longo dos últimos dois (2) dias tenho-me sentido, fisicamente:

Terrivelmente mal 0 1 2 3 4 5 6 7 8 9 10 **Completamente bem**

Por favor continue na página seguinte...

PARTE C *Por favor escolha o número que melhor descreve os seus sentimentos e pensamentos* ***DURANTE OS ÚLTIMOS DOIS (2) DIAS****.*

5. Durante os últimos dois (2) dias tenho-me sentido deprimido(a):

Absolutamente nada 0 1 2 3 4 5 6 7 8 9 10 **Extremamente**

6. Nos últimos dois (2) dias tenho estado nervoso(a) e preocupado(a):

Absolutamente nada 0 1 2 3 4 5 6 7 8 9 10 **Extremamente**

7. Nos últimos dois (2) dias durante quanto tempo se sentiu triste

Nunca 0 1 2 3 4 5 6 7 8 9 10 **Sempre**

8. Nos últimos dois (2) dias quando pensei sobre o futuro, senti-me:

Sem medo 0 1 2 3 4 5 6 7 8 9 10 **Completamente aterrorizado**

9. Nos últimos dois (2) dias a minha vida tem sido:

Totalmente sem sentido e sem objectivo 0 1 2 3 4 5 6 7 8 9 10 **Plena de sentido e significado**

10. Nos últimos dois (2) dias quando pensei sobre toda a minha vida, senti que em relação aos objectivos de vida eu:

Não consegui atingir nada 0 1 2 3 4 5 6 7 8 9 10 **Atingi plenamente o que queria**

Por favor continue na página seguinte...

11. Nos últimos dois (2) dias quando pensei sobre toda a minha vida, senti que até aqui a minha vida:

Tem sido completamente sem valor	0	1	2	3	4	5	6	7	8	9	10	**Valeu totalmente a pena**

12. Nos últimos dois (2) dias, quando olho para a minha vida tenho sentido que tenho:

Nenhum controlo sobre a minha vida	0	1	2	3	4	5	6	7	8	9	10	**Total controlo sobre a minha vida**

13. Nos últimos dois (2) dias tenho-me sentido bem enquanto pessoa.

Discordo completamente	0	1	2	3	4	5	6	7	8	9	10	**Concordo completamente**

14. Para mim, os últimos dois (2) dias foram:

Um fardo	0	1	2	3	4	5	6	7	8	9	10	**Um dom**

15. Nos últimos dois (2) dias o mundo tem sido:

Um lugar impessoal e sem sentimentos	0	1	2	3	4	5	6	7	8	9	10	**Onde me cuidam e respondem a todas as minhas necessidades**

16. Nos últimos dois (2) dias tenho-me sentido apoiado(a):

Absolutamente nada	0	1	2	3	4	5	6	7	8	9	10	**Completamente**

Por favor continue na página seguinte...

PARTE D

Por favor, faça uma lista ou descreva as coisas que mais afectaram a sua qualidade de vida nos últimos dois (2) dias. Diga, por favor, se cada uma das coisas que refere melhorou ou piorou a sua qualidade de vida durante este período. Se necessitar de mais espaço, por favor continue no verso desta folha.

Muito obrigada pela colaboração!...

B.3 WHOQOL-BREF (in Portuguese)

Instruções

Este questionário procura conhecer a sua qualidade de vida, saúde, e outras áreas da sua vida.

Por favor, responda a todas as perguntas. Se não tiver a certeza da resposta a dar a uma pergunta, escolha a que lhe parecer mais apropriada. Esta pode muitas vezes ser a resposta que lhe vier primeiro à cabeça.

Por favor, tenha presente os seus padrões, expectativas, alegrias e preocupações. Pedimos-lhe que tenha em conta a sua vida nas **duas últimas semanas**.

Por exemplo, se pensar nestas duas últimas semanas, pode ter que responder à seguinte pergunta:

	Nada	Pouco	Moderadamente	Bastante	Completamente
Recebe das outras pessoas o tipo de apoio que necessita?	1	2	3	4	5

Deve pôr um círculo à volta do número que melhor descreve o apoio que recebeu das outras pessoas nas duas últimas semanas. Assim, marcaria o número 4 se tivesse recebido bastante apoio, ou o número 1 se não tivesse tido nenhum apoio dos outros nas duas últimas semanas.

Por favor leia cada pergunta, veja como se sente a respeito dela, e ponha um círculo à volta do número da escala para cada pergunta que lhe parece que dá a melhor resposta.

		Muito Má	Má	Nem Boa Nem Má	Boa	Muito Boa
1 (G1)	Como avalia a sua qualidade de vida?	1	2	3	4	5

		Muito Insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito Satisfeito
2 (G4)	Até que ponto está satisfeito(a) com a sua saúde?	1	2	3	4	5

As perguntas seguintes são para ver até que ponto sentiu certas coisas nas duas últimas semanas.

		Nada	Pouco	Nem muito nem pouco	Muito	Muitíssimo
3 (F1.4)	Em que medida as suas dores (físicas) o(a) impedem de fazer o que precisa de fazer?	1	2	3	4	5
4 (F11.3)	Em que medida precisa de cuidados médicos para fazer a sua vida diária?	1	2	3	4	5
5 (F4.1)	Até que ponto gosta da vida?	1	2	3	4	5
6 (F24.2)	Em que medida sente que a sua vida tem sentido?	1	2	3	4	5
7 (F5.3)	Até que ponto se consegue concentrar?	1	2	3	4	5
8 (F16.1)	Em que medida se sente em segurança no seu dia-a-dia?	1	2	3	4	5
9 (F22.1)	Em que medida é saudável o seu ambiente físico?	1	2	3	4	5

As seguintes perguntas são para ver **até que ponto** experimentou ou foi capaz de fazer certas coisas nas duas últimas semanas.

		Nada	Pouco	Moderadamente	Bastante	Completamente
10 (F2.1)	Tem energia suficiente para a sua vida diária?	1	2	3	4	5
11 (F7.1)	É capaz de aceitar a sua aparência física?	1	2	3	4	5
12 (F18.1)	Tem dinheiro suficiente para satisfazer as suas necessidades?	1	2	3	4	5
13 (F20.1)	Até que ponto tem fácil acesso às informações necessárias para organizar a sua vida diária?	1	2	3	4	5
14 (F21.1)	Em que medida tem oportunidade para realizar actividades de lazer?	1	2	3	4	5

		Muito Má	Má	Nem boa nem má	Boa	Muito Boa
15 (F9.1)	Como avaliaria a sua mobilidade [capacidade para se movimentar e deslocar por si próprio(a)]?	1	2	3	4	5

As perguntas que se seguem destinam-se a avaliar se se sentiu **bem ou satisfeito(a)** em relação a vários aspectos da sua vida nas duas últimas semanas.

		Muito Insatisfeito	Insatisfeito	Nem satisfeito nem insatisfeito	Satisfeito	Muito Satisfeito
16 (F3.3)	Até que ponto está satisfeito(a) com o seu sono?	1	2	3	4	5
17 (F10.3)	Até que ponto está satisfeito(a) com a sua capacidade para desempenhar as actividades do seu dia-a-dia?	1	2	3	4	5
18 (F12.4)	Até que ponto está satisfeito(a) com a sua capacidade de trabalho?	1	2	3	4	5
19 (F6.3)	Até que ponto está satisfeito(a) consigo próprio(a)?	1	2	3	4	5
20 (F13.3)	Até que ponto está satisfeito(a) com as suas relações pessoais?	1	2	3	4	5
21 (F15.3)	Até que ponto está satisfeito(a) com a sua vida sexual?	1	2	3	4	5
22 (F14.4)	Até que ponto está satisfeito(a) com o apoio que recebe dos seus amigos?	1	2	3	4	5
23 (F17.3)	Até que ponto está satisfeito(a) com as condições do lugar em que vive?	1	2	3	4	5
24 (F19.3)	Até que ponto está satisfeito(a) com o acesso que tem aos serviços de saúde?	1	2	3	4	5
25 (F23.3)	Até que ponto está satisfeito(a) com os transportes que utiliza?	1	2	3	4	5

As perguntas que se seguem referem-se à **frequência** com que sentiu ou experimentou certas coisas nas duas últimas semanas.

		Nunca	Poucas vezes	Algumas vezes	Frequentemente	Sempre
26 (F8.1)	Com que frequência tem sentimentos negativos, tais como tristeza, desespero, ansiedade ou depressão?	1	2	3	4	5

B.4 Communication Effectiveness Index (adapted and translated from Beukelman et al. (2000)

Com que eficácia comunica quando...

1. conversa com pessoas familiares num ambiente calmo?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

2. conversa com estranhos num ambiente calmo?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

3. conversa ao telefone?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

4. conversa em ambiente ruidoso (ex: evento social, restaurante, centro comercial)?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

5. conversa com alguém a uma certa distância (entre divisões da casa)?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

6. fala para um grupo (ex: jantar familiar)?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

7. conversa com o seu médico?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

8. conversa com o seu cuidador?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

9. quer transmitir uma situação importante e urgente (p.ex., pedir ajuda)?

0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

10. transmite necessidades e opiniões acerca de decisões importantes para a sua vida?

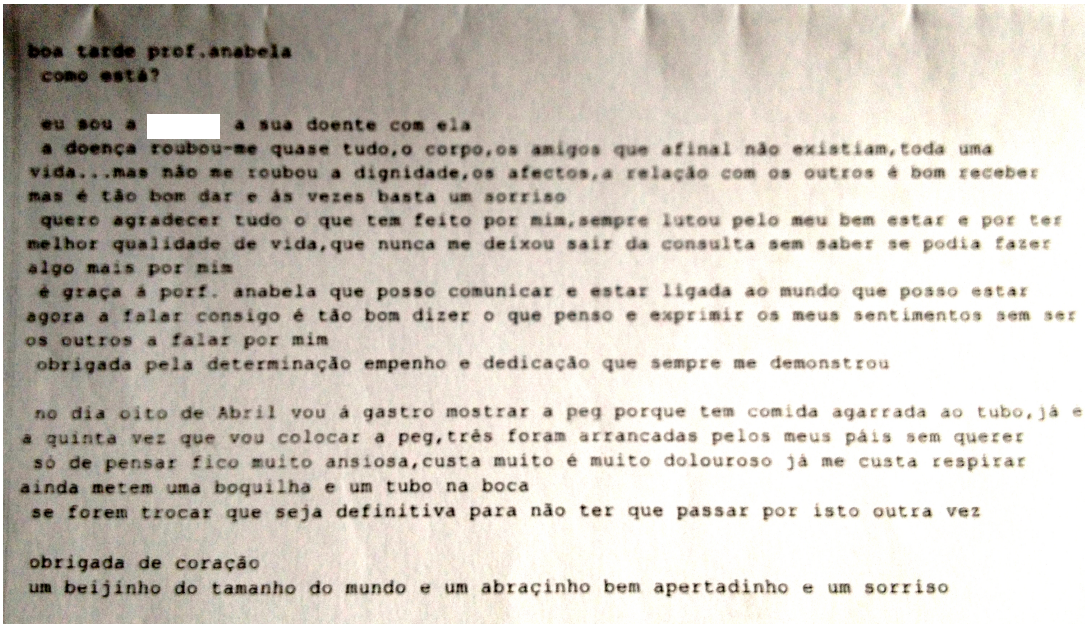
0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐

Não comunico — Faço-me entender muito bem

Appendix C – Transcription of communication from some patients and caregivers (in Portuguese)

Patient A

[An email from an ALS patient to the medical doctor, few weeks before she died]



boa tarde prof.anabela
como está?

eu sou a [redacted] a sua doente com ela
a doença roubou-me quase tudo,o corpo,os amigos que afinal não existiam,toda uma vida...mas não me roubou a dignidade,os afectos,a relação com os outros é bom receber mas é tão bom dar e ás vezes basta um sorriso
quero agradecer tudo o que tem feito por mim,sempre lutou pelo meu bem estar e por ter melhor qualidade de vida,que nunca me deixou sair da consulta sem saber se podia fazer algo mais por mim
é graça á porf. anabela que posso comunicar e estar ligada ao mundo que posso estar agora a falar consigo é tão bom dizer o que penso e exprimir os meus sentimentos sem ser os outros a falar por mim
obrigada pela determinação empenho e dedicação que sempre me demonstrou

no dia oito de Abril vou á gastro mostrar a peg porque tem comida agarrada ao tubo,já e a quinta vez que vou colocar a peg,três foram arrancadas pelos meus páis sem querer
só de pensar fico muito ansiosa,custa muito é muito dolouroso já me custa respirar ainda metem uma boquilha e um tubo na boca
se forem trocar que seja definitiva para não ter que passar por isto outra vez

obrigada de coração
um beijinho do tamanho do mundo e um abraçinho bem apertadinho e um sorriso

"a doença roubou-me quase tudo, o corpo, os amigos que afinal não existiam, toda uma vida... não me roubou a dignidade, os afectos, a relação com os outros é bom receber algo mais por mim.
(…) que posso comunicar e estar ligada ao mundo que posso estar agora a falar consigo é tão bom dizer o que penso e exprimir os meus sentimentos sem ser os outros a falar por mim.(…)"
"no dia oito de abril vou à gastro mostrar a peg porque tem comida agarrada ao tubo (…) já me custa respirar ainda metem uma boquilha e um tubo na boca…"

Patient B

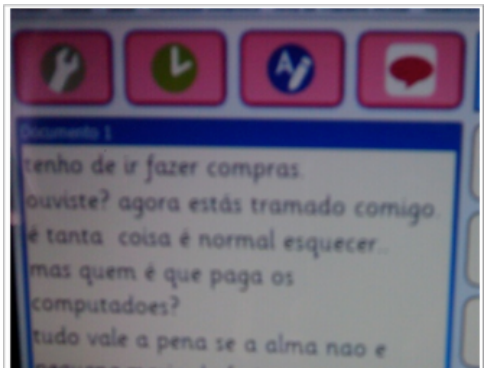
[Saved on a text file (in the ACD) to present in the clinical appointment]

"BOA TARDE PROFESSORA ANABELA. ESTOU A AGUARDAR NOVA CONSULTA ESTANDO NUMA SITUAÇÃo RAZOAVEL DE SAUDE COM OS LIMITES HABITUAIS ,MAS TENHO ULTIMAMENTE ALGUMAS DORES NO PESCOÇO TENDO ALGUMAS DIFICULDADES QUANDO ME MOVIMENTO PARA O LADO DIREITO. NA MOBILIZAÇÃO O LADO DIREITO ESTÁ MAIS FRACO, ESTANDO A FALA TAMBEM MAIS FRACA.APESAR DESTAS FRAQUEZAS MANTENHO-ME TRANQUILO NÃO SÓ PELO CONHECIMENTO DO

CONSUMISMO DA DOENÇA MAS TAMBEM PELA EQUIPA MEDICA QUE ME DÁ ASSISTENCIA (PROFESSOR MAMEDE E PROFESSORA ANABELA), PELO QUE JA FICAVA FELIZ SE O CONSUMISMO FICASSE COMO ESTOU E ASSIM VIVER AINDA MAIS TRANQUILO. PROFESSORA ANABELA ,FUI RECENTEMENTE SURPREENDIDO COM UMA CONSTIPAÇÃO COM MUITA ESPETURAÇÃO A JUNTAR-SE Á QUE JA EXISTIA E TOSSE QUE ME ATACA MUITO Á NOITE O QUE ME LEVOU A NÃO CONSEGUIR COLOCAR A MASCARA ,FELIZMENTE VOU ESTANDO MELHOR PELO QUE ESTOU CONVENCIDO QUE DENTRO DE DIAS JÁ A VOU CONSEGUIR COLOCAR,A QUAL,PARA ALEM DOS PROBLEMAS QUE NÃO TENHO CONSEGUIDO ULTRAPASSAR,ME DÁ QUANDO POSSIVEL ALGUMA TRANQUILIDADE DURANTE O SONO.ESSES PROBLEMAS QUE A PROFESSORA ANABELA JA CONHECE(FUGAS) QUE ME DÃO GRANDE TURBELENCIA E DESGASTE,COMPLICAM A NOITE.CONSULTEI O MEU DENTISTA O QUAL ME DISSE QUE NÃO É A PLACA DENTARIA QUANDO A TENHO COLOCADA ME PROVOCA ESSAS FUGAS E QUE ME ACONSELHA A NÃO DORMIR COM ELA COLOCADA. SUBLINHOU AINDA QUE ESSAS FUGAS PODEM TER ORIGEM DA FALTA DA PLACA MAS TAMBEM ESSA FALTA E A MAGREZA DA CARA SE JUNTAM NA ORIGEM DESSAS FUGAS,SENDO ATÉ POSSIVELMENTE A MAGREZA A UNICA CAUSA DESSAS FUGAS.JÁ SEI QUE A MINHA ESPOSA CONTATOU A PROFESSORA ANABELA E QUE VOU TER CONSULTA NA PROXIMA QUARTA- FEIRA."

Patient C

[Typing on a keyboard using upper limbs. Using a speech synthesizer for the first time. Communication with her husband and with me.]



"tenho de ir fazer compras. Ouviste? Agora estás tramado comigo.
É tanta coisa é normal esquecer.. mas quem é que paga os computadores?
tudo vale a pena se a alma nao e pequena"

[*Three months later, this patient is using a head switch for writing on a virtual keyboard, due to severe dysfunction of UL. She wrote:*]
"vamos ao decatlokn e ao oikea conpras roupa e almofadas que esta calor a maria qpodia fazer sopa de ervilhas com ovo a maria pode vir as 10 h mané podias ir com o joão amanhã as compras a maria faz lista do que falta nao temos"

[*Her son after her mothers' death*:]
"She wrote letters for everyone saying goodbye."

Patient D

[A patient was telling me what her son told her, after she started using the ACD with speech synthesizer:]

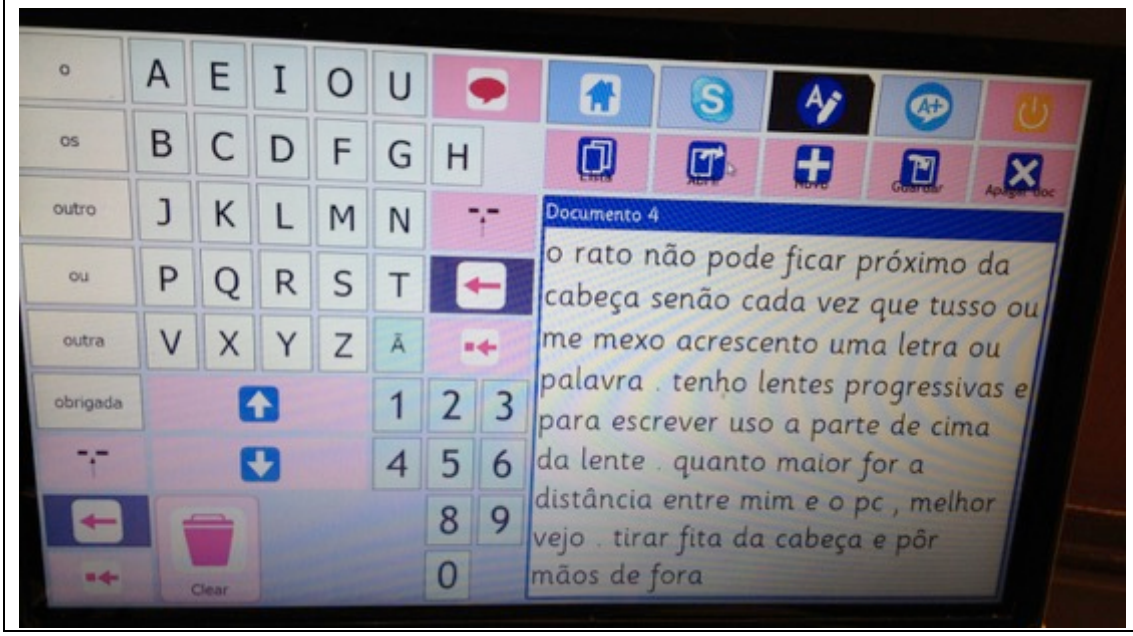
"don't exaggerate[referring to the use of the ACD]. Keep talking"
In the same session she expressed that the ACD was her "right arm".

Patient E

[*email that I received from a patient, about her computer:*]
"quarta-feira, 8 de Abril de 2015
Se tudo na vida tem uma razão de ser, eu continuo a procurar explicação para um sem número de provações a que fico sujeita ... ! Estive nove dias sem me poder comunicar ..... já é penitencia bastante estar prisioneira em meu próprio corpo e estar privada de falar sem o único meio de comunicar que é o computador, é sentir -me enterrada viva só com os olhos de fora !
Como são importantes as palavras faladas para a própria sanidade mental ... ! porque quando se tem de ouvir sem a capacidade de fugir, argumentar e responder, fica uma tarefa muito ardua para um simples mortal !!!
(…) que me ajuda a estar viva e conectada as palavras e ao Mundo !"

Patient F

[*a patient living in a palliative care unit, explaining to me how to adjust ACD to her context:*]



Appendix D - Published papers *facsimile*