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PhD in Clinical-Experimental Neuroscience and Psychiatry
XXXIII course

"BRADYKINESIA IN NON-PARKINSONIAN CONDITIONS: THE EMERGING CONCEPT OF A NETWORK DISORDER"

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Academic Year 2019/2020

SUMMARY:

Abbreviations: Alzheimer's disease (AD); abductor digiti minimi (ADM); amyotrophic lateral sclerosis (ALS); active motor threshold (AMT); atypical parkinsonisms (APs); abductor pollicis brevis (APB); Beck Depression Inventory (BDI); cervical dystonia (CD); coefficient of variation (CV); deep brain stimulation (DBS); dopamine transporter (DAT); elettromiography (EMG); Frontal Assessment Battery (FAB); first dorsal interosseous (FDI); focal hand dystonia (FHD); Fatigue Severity Scale (FSS); Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS); globus pallidus pars interna (GPi) and pars externa (GPe); Huntington's disease (HD); intracortical facilitation (ICF); input-output (I/O); inter-stimulus interval (ISI); intermittent theta-burst stimulation (iTBS); long term potentiation (LTP); Mild Congnitive Impairment (MCI); Movement Disorders Society (MDS); Mental State Examination (MMSE); Motor Evoked Potential (MEP); Montreal Cognitive Assessment (MoCA); Multiple Sclerosis (MS); paired associative stimulation (PAS); Parkinson's disease (PD); primary motor cortex (M1); progressive muscular atrophy (PMA); primary somatosensory cortex (S1); Progressive Supranuclear Palsy (PSP); pyramidal tract type neurons (PTNs); reaction time (RT); magnetic resonance imaging (MRI); resting motor threshold (RMT); short-latency afferent inhibition (SAI); short intracortical inhibition (SICI); somatosensory temporal discrimination threshold (STDT); SPECT scan without evidence of dopaminergic deficit (SWEEDs); substantia nigra pars reticulata (SNr); subthalamic nucleus (STN); Transcranial magnetic stimulation (TMS); Unified Parkinson's Disease Rating Scale (UPDRS).

1. ABSTRACT

Bradykinesia (movement slowness) is one of the cardinal motor symptoms of Parkinson's disease and atypical parkinsonism and it has hystorically been interpreted as a motor disorder due to basal ganglia dysfunction. Clinical and experimental studies, however, indicate that it may be also observed in the context of various neurological conditions not primarily characterized by parkinsonism. These conditions include hyperkinetic movement disorders, such as dystonia and chorea, as well conditions primarily characterized by tremor (e.g. essential tremor) or other nervous diseases characterized by the involvement of brain areas and network including not only the basal ganglia but also the cerebellum and upper motoneurons. Also, movement slowness may be observed in patients with neurodegenerative or inflammatory diseases of the central nervous system of various origin, like dementia or multiple sclerosis. From a pathophysiological standpoint, the observation of movement slowness in neurological conditions not primarily characterized by parkinsonism is possibly explained by a brain network dysfunction, as hypothesized in parkinsonism. In the present thesis, we will first provide an updated overview on bradykinesia in non-parkinsonian conditions and discuss major findings of clinical reports and experimental studies. In the experimental part of the present thesis, we will provide the results from three original studies, which investigated the presence of bradykinesia and its possible pathophysiological mechanisms in (i) patients with essential tremor, (ii) patients with Alzheimer's disease and (iii) patients with amyotrophic lateral sclerosis. Finally we will provide an unifying pathophysiological interpretation of bradykinesia in non-parkinsonian conditions from a network perspective and emphasize possible terminological implications.

2. INTRODUCTION

The term bradykinesia specifically refers to slowness of initiation or execution of voluntary movement and is considered one of the cardinal motor symptoms of Parkinsons' disease (PD) (Berardelli et al. 2001; Postuma et al. 2015; Berg et al. 2018) and atypical parkinsonisms (APs) (Gilman *et al.*, 2008; Armstrong *et al.*, 2013; Höglinger *et al.*, 2017; McKeith *et al.*, 2017). By clinical definition, in addition to movement slowness of single movements, the term bradykinesia in parkinsonisms also includes the progressive reduction in speed and amplitude (or progressive hesitations/halts) of repetitive or continued actions, also known as sequence effect (Espay *et al.*, 2009, 2011, Postuma *et al.*, 2015*a*, Bologna *et al.*, 2016*a*, 2018, 2019*b*).

Slowness of the initiation or execution of voluntary movement, sometimes called bradykinesia by the authors, has frequently been reported in neurological conditions other than PD and APs. Namely, slowness of movement has been reported in hyperkinetic movement disorders, historically been considered due to basal ganglia changes (Hefter et al. 1987; Thompson et al. 1988; van der Kamp et al. 1989; Agostino et al. 1992; Elble et al. 1994; Berardelli et al. 1996; Montgomery et al. 2000; Ozekmekçi et al. 2005; Duval et al. 2006; Costa et al. 2010; Jiménez-Jiménez et al. 2010; Stone et al. 2011; Thenganatt and Jankovic 2016a), and also in diseases primarily involving the cerebellum or the upper motor neurons, as well as in other neurological conditions, like Alzheimer's disease (AD) and multiple sclerosis (MS) and (Williams *et al.*, 1995*a*; Berardelli *et al.*, 1996; Qureshi *et al.*, 1996; Desai and Swash, 1999; Scarmeas *et al.*, 2004, 2005; D'Ascenzo *et al.*, 2012; Pupillo *et al.*, 2015; Oskarsson *et al.*, 2016; Shellikeri *et al.*, 2016; de Bie *et al.*, 2017; Kuruvilla-Dugdale and Chuquilin-Arista, 2017; Roalf *et al.*, 2018; Schirinzi *et al.*, 2018; Camarda *et al.*, 2019; Vöglein *et al.*, 2019).

From a pathophysiological point of view, bradykinesia in PD and APs is considered a movement abnormality primarily due to central dopaminergic loss and basal ganglia dysfunction (Bologna *et al.*, 2019*b*). The observation of movement slowness in conditions other than parkinsonisms supports the hypothesis that motor abnormalities in non parkinsonian conditions may result from a network dysfunction involving not only the basal ganglia but also other cortical and subcortical brain areas. In addition, whether the pathophysiological mechanisns underlying movement slowness in non parkinsonian conditions differ from those of bradykinesia in PD and APs has never been addressed before.

In the present thesis, we will first provide an overview of the clinical descriptions and of the experimental observations of movement slowness in non parkinsonian conditions, including hyperkinetic movement disorders and other conditions due to cerebellar, upper motor neuron or cortical and subcortical dysfunction. Namely, we will specifically refer to these motor abnormalities in various conditions and discuss the possible pathophysiological mechanisms. Notably, in each of the conditions here discussed we adopted the exact terminology used in each original article, reflecting the lack of consensus on the terminology for bradykinesia in non-parkinsonian conditions. In the second part of the present thesis, we will provide the results from three experimental studies, which investigated bradykinesia and its possible pathophysiological mechanisms in (i) patients with essential tremor (ET), (ii) patients with AD, (iii) patients with amyotrophic lateral sclerosis (ALS).

2.1.BRADYKINESIA IN HYPERKINETIC MOVEMENT DISORDERS

2.1.1. Dystonia

There are several examples on the coexistance between dystonia and bradykinesia as the major manifestation of parkinsonism. This is the case for example of specific genetic conditions, and among them the most representative is the rapid-onset dystonia-parkinsonism linked to mutations in the ATP1A3 gene (Balint and Bhatia, 2015). Another example is the frequent occurrence of dystonia in APs (Marsili *et al.*, 2019). Also, there may be situations where the clinical boundary between dystonia and parkinsonism are particulary uncertain despite the aid of molecular imaging. For example it is debated whether patients with dopamine transporter SPECT scan without evidence of dopaminergic deficit (SWEEDs) should be considered as dystonic, especially when they did not showed any decrement or fatigue during movement repetition (Schneider *et al.*, 2007). The results of DaTscan, however, are not necessarily conclusive and the examination can demonstrate a trend of uncertain significance toward a slight dopaminergic deficit in the striatum (Waln *et al.*, 2015). Moreover, a proportion of patients with a negative DaTscan may be still be diagnosed with parkinsonism on the basis of a levodopa response, clinical progression, and other data (Erro *et al.*, 2016). Parkinsonism has been also recently described in patients with cervical dystonia (CD) who had undergone to pallidal deep brain stimulation (DBS) to treat dystonia (Tisch *et al.*, 2007; Berman *et al.*, 2009; Wolf *et al.*, 2012; Huebl *et al.*, 2015; Mahlknecht *et al.*, 2018).

Earliest reference to bradykinesia (i.e. ‘bradykinesie spasmodique’) in a group of patients which we would now diagnosticate as affected by dystonia dates back to 1907 and it was specifically adopted to describe slowness of involuntary movements (Verger and Cruchet, 1907). Later clinical observation, which were summarized in a recent review (Haggstrom *et al.*, 2017), reported decreased arm swing, increased limb tone and facial hypomimia but no evidence of ‘true bradykinesia’ in 29 patients with focal hand dystonia (FHD) (Sheehy and Marsden, 1982), and in 10 patients with cervical, laryngeal or upper limbs dystonia

(Schneider *et al.*, 2007). Clumsy in foot tapping without 'true bradykinesia' was described in one patients with DYT1 dystonia (Stamelou *et al.*, 2013).

Neurophysiological investigation in task-specific dystonia, i.e. FHD, have shown that movement preparation can be abnormally prolonged, or normal, as evidenced by testing simple and choice reaction times (RTs) of self-initiated or externally-cued arm movements (Hallett, 2000; Murase *et al.*, 2000; Jankowski *et al.*, 2013; Kishore *et al.*, 2018). In both FHD and generalized dystonia, kinematic and electromyographic (EMG) recordings have demonstrated that patients performed single- and multi-joint arm movements with slower velocity and reduced amplitude in comparison to normal subjects (van der Kamp et al. 1989; Cohen and Hallett 1988; Buccolieri et al. 2004). More complex movements, like arm reaching in patients with idiopathic torsion dystonia were also found to be slow, mainly because of asymmetry of velocity profile and longer deceleration time (Inzelberg *et al.*, 1990, 1995). Movement slowness in FHD has also been observed during both externally triggered and self-initiated sequential arm movements, possibly due to longer pauses between movements (Currá *et al.*, 2000), i.e. slowness in switching from one movement to the next without a progressive increase in relation to the number of movement executed (Agostino *et al.*, 1992). Again, kinematic analyses of finger tapping showed movement slowness and rhythmic inconsistencies in task specific FHD (Jabusch *et al.*, 2004; Furuya and Altenmüller, 2013; Furuya *et al.*, 2018). Finally patients with CD consistently performed slowed pro-dystonic neck movements, i.e. toward the dystonic side, also characterized by reduced amplitude (Carboncini *et al.*, 2004; Gregori *et al.*, 2008; Shaikh *et al.*, 2015, Bologna *et al.*, 2016*b*).

Movement preparation and execution have been also investigated also in patients with focal dystonia in the unaffected body segments. Accordingly, an increase of RTs during upper limb movements was found in patients with spasmodic dysphonia (Simonyan *et al.*,

2013). Movement slowness of the upper limb was also observed in patients with CD performing single-joint arm extensions (Carboncini *et al.*, 2004) or reaching arm movement (Pelosin *et al.*, 2009) although the latter has not been confirmed in all studies (Katschnig-Winter *et al.*, 2014, Bologna *et al.*, 2016*b*). On the other hand, no velocity reduction was observed during finger movements in blepharospasm and spasmodic dysphonia (Conte *et al.*, 2018) and repetitive finger tapping (Simonyan *et al.*, 2013) or during neck movements in FHD (Bologna *et al.*, 2016*b*).

In summary, clinical and neurophysiological evidence showed that dystonic patients can be slower than normal, particularly when the voluntary movements are initiated or executed with the body part affected by dystonia. To date, however, there are no reports on the sequence effect in dystonia (Table 1).

2.1.2. Huntington's disease

Parkinsonism is a common clinical observation in patients with Huntington's disease (HD), for example in the Westphal variants of HD with early juvenile-onset, as well as in the latest stages of HD (Denny-Brown, 1960; Campbell *et al.*, 1961). Many physicians emphasized the presence of slowed voluntary movements in HD patients (Hamilton, 1908; Herz 1931; Bittenbender and Quadfasel, 1962). The most common alteration in HD was the difficulty of movement initiation as well as slowness and irregularity of movement execution (Hefter *et al.*, 1987).

Neurophysiological investigations showed that when HD patients performed wrist movements, they had prolonged simple RTs (Bradshaw *et al.*, 1992; Jahanshahi *et al.*, 1993; van Vugt *et al.*, 2004; Martínez Pueyo *et al.*, 2016) and were also slower than normal in performing fast wrist flexions (Thompson *et al.*, 1988). Movement slowness was also observed during single isometric contractions and alternating arm movements (Hefter

et al. 1987; Garcia Ruiz et al. 2000). Simultaneous and sequential arm movement were also slower and less accurate than normal and the pauses between repetitive movements were longer than normal (Thompson et al. 1988; Agostino et al., 1992, Johnson et al. 2000). The performance of sequential movements in HD worsened without external cues (Georgiou et al., 1995; Bradshaw et al. 1992; Currà et al. 2000) but not with movement repetition, i.e. no sequence effect was observed in HD (Agostino *et al.*, 1992). In addition, there was a reduction in the tapping rate (Andrich *et al.*, 2007) a slowness and a marked movement irregularity during repetitive finger tapping, other dexterity finger tasks (Garcia Ruiz et al. 2000; García Ruiz et al. 2002; Hinton et al. 2007; Bechtel et al. 2010; Rowe et al. 2010) and handwriting (Phillips *et al.*, 1994).

In summary, slowness in the initiation or execution of voluntary movement has frequently been reported in patients with HD during different motor tasks. Longer pauses and a marked irregularity, but no sequence effect, have been reported during repetitive movements (Table 2).

2.1.3. Essential tremor

The coexistence and overlapping featureas between essential tremor (ET) and bradykinesia, as the major manifestation of parkinsonism is another relevant issue, thus leading to the developement of the ET-PD concept (Fekete and Jankovic, 2011, Louis *et al.*, 2016*a*, *b*, Thenganatt and Jankovic, 2016*b*). When bradykinesia (a "soft neurological sign") is present, the new tremor classification suggest using the term ET-plus (Bhatia *et al.*, 2018).

There are several clinical reports on movement slowness in ET but the observations are still controversial (Hornabrook and Nagurney, 1976; Geraghty *et al.*, 1985; Cleeves *et al.*, 1988; Lou and Jankovic, 1991; Koller *et al.*, 1994; Tallón-Barranco *et al.*, 1997; Fekete

and Li, 2013; Espay *et al.*, 2017; Algarni and Fasano, 2018; Bhatia *et al.*, 2018; Haubenberger and Hallett, 2018; Hopfner and Deuschl, 2018).

In ET an objective assessment of movement slowness during voluntary movement has been performed only in a limited number of studies. The RT during fast wrist flexion and extension movements was normal or only marginally increased in patients (Elble *et al.*, 1994; Montgomery *et al.*, 2000). ET patients showed altered force variability during an isometric force task compared to PD, which instead showed abnormalities in the deceleration measures of ballistic movements and alterations of the torque rise time (Poon *et al.*, 2011). Grasping movements in ET were kinematically characterized by slowness of the total reach-to-grasp movement, particularly in patients with kinetic tremor (Deuschl *et al.*, 2000) In some studies, slowed velocity, irregular rhythm and impaired dexterity during rapid alternating movements of the upper limbs has been also described (Montgomery *et al.*, 2000; Duval *et al.*, 2006; Farkas *et al.*, 2006; Héroux *et al.*, 2006; Costa *et al.*, 2010; Goubault *et al.*, 2017). Ozekmekci et al., however, observed only a slight prolongation for movement time around the shoulder joint but no prolongation of upper limb movements at the level of the elbow and wrist joints or repetitive finger movement abnormalities (Ozekmekçi *et al.*, 2005). In ET, slowed alternating arm movements were not accompanied by reduced amplitude of movement, differently from what observed in PD performing the same task (Ghassemi *et al.*, 2006; Goubault *et al.*, 2017). Studies on repetitive finger movements in ET have objectively demonstrated movement slowness and irregular rhythm in this condition (Farkas *et al.*, 2006; Costa *et al.*, 2010; Jiménez-Jiménez *et al.*, 2010).

In summary, despite some controversial results, ET patients can be slower than normal in movement preparation or in performing rapid single and repetitive arm and finger movements. Other movement abnormalities can accompany slowness in ET, i.e.altered

movement rhythm, while there the sequence effect has not been investated in this condition (Table 3).

2.2. BRADYKINESIA IN CEREBELLAR DISORDERS

Clinical studies indicate that patients with cerebellar lesions may have slowness of movement in both the preparation and execution phases (Takiyama *et al.*, 1994; Manni and Petrosini, 1997; Holmes, 2007; Stoodley and Schmahmann, 2010; Bodranghien *et al.*, 2016).

Slowness of initiation of voluntary movement (prolonged RTs) has been demonstrated in patients with cerebellar diseases (Beppu *et al.*, 1984; Jahanshahi *et al.*, 1993; Bonnefoi-Kyriacou *et al.*, 1995; Day *et al.*, 1998). Slowness of voluntary movement execution in patients with cerebellar diseases has been demonstrated by neurophysiological investigations on simple upper limb movements (Avarello *et al.*, 1988; Mai *et al.*, 1988; Fujita and Nakamura, 1989; Brown *et al.*, 1990, Hallett *et al.*, 1991*a*, p. 199; Hore *et al.*, 1991) or more complex goal-directed arm movements (Beppu *et al.*, 1984; Becker *et al.*, 1990; Wild *et al.*, 1996; Day *et al.*, 1998). Patients with cerebellar atrophy also showed an impaired performance during a countermanding task, demonstrating an altered control of action inhibition (Olivito *et al.*, 2017). Kinematic analysis of patients with acute cerebellar stroke showed that nearly 70% of patients exhibited movement slowness during goal-directed arm movements (Konczak *et al.*, 2010). Movement slowness may also involve the lower limbs in cerebellar patients, e.g. rising on tiptoes, resulting in a longer time interval between the two phases (Diener *et al.*, 1992). It has been observed that cerebellar patients perform movements slower than healthy subjects since they made abnormally curved paths and tended to move one joint at a time (movement decomposition) (Bastian *et al.*, 1996) with dismetric movements to a target possibly due to generation of inappropriate levels of

muscular force (Topka *et al.*, 1998).

In summary, patients with various cerebellar disease are slower than normal. Cerebellar patients may, in some circumstances, implicitely choose to move more slowly than they are able to do in order to improve their accuracy (Table 4).

2.3. BRADYKINESIA IN MOTONEURON DISEASES AND STROKE

Slowness of movement, specifically referred to as bradykinesia, has been clinically reported in patients with motoneurons diseases, such as progressive muscular atrophy (PMA) (Williams *et al.*, 1995*b*) and amyotrophic lateral aclerosis (ALS) (Qureshi et al. 1996; Desai and Swash 1999; D'Ascenzo et al. 2012; Pupillo et al. 2015). In addition to the limited clinical observations, there are only a few neurophysiological studies on voluntary movement in patients with ALS, demonstrating abnormalities of upper limb movements (Hallett, 1979; Oskarsson *et al.*, 2016; de Bie *et al.*, 2017). Patients with ALS showed prolonged first agonist and antagonist bursts during ballistic elbow movements. The prolongation of the muscles bursts generates slowness of movements but at the same time permits the muscles to generate sufficient forces to accomplish the movements (Hallett, 1979). Other studies provided objective evidence of altered arm function in patients with ALS though not specifically investigating movement execution but considering the the reachable workspace, as a surrogate measure of arm function (Oskarsson *et al.*, 2016; de Bie *et al.*, 2017). Finally, there are only sporadic reports on quantitative assessment of lip and tongue movements during speech in ALS patients (Shellikeri *et al.*, 2016; Kuruvilla-Dugdale and Chuquilin-Arista, 2017) (Table 5).

In a patient with traumatic cerebral palsy (Angel, 1975) performing rapid abduction movements of the shoulder, the activity of the first agonist muscle had an abnormally long duration. Sahrmann and Norton observed the same abnormality during the execution of

rapid alternating movements in patients with various spastic conditions (Sahrmann and Norton, 1977).

In stroke patients, studies on motor preparation showed a delayed movement initiation more often in the right than in the left hemisphere strokes with a possible association with severe neglect (Mattingley *et al.*, 1994; Kim *et al.*, 2013). Similarly, motor execution of rapid elbow flexions and extensions in stroke patients were characterized by a reduced velocity (Fagioli et al. 1988; Canning et al. 1999). Kinematic analysis of goal-directed movements also showed movement execution abnormalties (Mattingley *et al.*, 1994). Loss of dexterity was observed during a tracking task performed by patients with stroke (Ada et al., 1996; Canning et al. 2000), and also in the limb ipsilateral to the brain lesion (Wetter *et al.*, 2005). Slowness of foot-tapping was also observed in stroke patients (Miller and Johnston, 2005). A reduced ankle dexterity and a reduced maximal movement velocity were observed in twelve stroke patients who presented a hemiparetic leg (Wirth *et al.*, 2008).

In summary, slowness in the execution of single movement has been reported in upper motor neurons syndromes of different origins, including ALS and stroke by a limited number of clinical and neurophysiological studies. The sequence effect has not been specifically investigated in upper motor neuron diseases.

2.4. BRADYKINESIA IN ALZHEIMER'S DISEASE

Recent clinical studies have emphasized the occurrence of bradykinesia in AD, ranging from 15% to 50% of the AD patients (Tsolaki *et al.*, 2001; Scarmeas *et al.*, 2004, 2005; Aggarwal *et al.*, 2006; Schirinzi *et al.*, 2018; Vöglein *et al.*, 2019). Again, it has been clinically demonstrated that bradykinesia may occur in both amnestic and non-

amnestic mild cognitive impairment (MCI) types (Louis *et al.*, 2005; Aggarwal *et al.*, 2006; Israeli-Korn *et al.*, 2010).

A number of neurophysiological studies have quantitatively assessed voluntary movement abnormalities in AD and MCI (Kluger *et al.*, 1997; Camarda *et al.*, 2007; Yan *et al.*, 2008; Rabinowitz and Lavner, 2014; Roalf *et al.*, 2018; Suzumura *et al.*, 2018). Kluger and colleagues studied six different motor function tests and found lower finger tapping speed in AD compared to MCI patients and to normal subjects, and impaired hand steadiness in AD and MCI (Kluger *et al.*, 1997). Camarda and colleagues studied the kinematics of directed movements in MCI and AD and found a slight, not significant, motor dysfunction in MCI subjects and the presence of a remarkable slowing down of pointing in AD subjects (Camarda *et al.*, 2007). Schröter kinematically investigated handwriting in AD and MCI, founding low accurancy and regularity in the AD group (Schröter *et al.*, 2003). Similarly, AD and MCI patients demonstrated slower, less smooth, less coordinated, and less consistent handwriting movements than their healthy counterparts in the study by Yan et al. 2008. Finger tapping analysis through a touchpad mounted on a pressure transducer showed increased length and variability of the finger-touch phase in participants with MCI or dementia compared to healthy participants (Rabinowitz and Lavner, 2014). Also Roalf et al. assessed finger tapping and found that AD and MCI performed fewer taps than healthy controls, with longer inter-tap interval and higher intra-individual variability (Roalf *et al.*, 2018). Suzumura et al. (2018) easured finger dexterity using a smart terminal device and found abnormal response time, rhythm, and contact duration in AD.

In summary, AD patients are slower than normal while performing repetitive finger movements (Table 6).

2.5. BRADYKINESIA IN MULTIPLE SCLEROSIS

Despite the relatively frequent involvement of the basal ganglia and subthalamic nucleus

MS inflammatory lesions, their relationship with movement disorders are uncertain (Folgar *et al.*, 2003). Notably, Kamphorst and Ravid reported no clinical parkinsonian signs in 3 patients with MS, although their brainstem autopsies showed the presence of Lewy body (Kamphorst and Ravid, 1997). A recent case control study reported the precence of very mild parkinsonian signs, including rigidity and hypomimia, in 5 of 22 patients with MS (23%) but it did not specifically describe the occurrence of bradykinesia in these patients (Drori *et al.*, 2018). The majority of MS cases with clinical bradykinesia had no evident anatomic/phenotypic correlates with brain magnetic resonance (MRI) imaging studies (Folgar *et al.*, 2003). This suggests that these manifestations are secondary to immune and neurodegenerative components. In this regard, Delgado and collegues found no lesions involving the basal ganglia or the midbrain but thay detected antibasal ganglionic antibodies in a patient with MS and parkinsonism (Delgado *et al.*, 2009). Clinical evidence of movement slowness in patients with MS mainly consists of isolated case reports (Vieregge *et al.*, 1992; Maranhão-Filho *et al.*, 1995; Burn and Cartlidge, 1996; Federlein *et al.*, 1997; Ozturk *et al.*, 2002; Folgar *et al.*, 2003; Barun *et al.*, 2008; Nociti *et al.*, 2008; Delgado *et al.*, 2009). These studies overall described a bilateral asymmetric bradykinesia, improving, in same cases, after corticosteroid treatment (Vieregge *et al.*, 1992; Federlein *et al.*, 1997; Folgar *et al.*, 2003).

Neurophysiological studies in MS indicate that patients has delayed movement initiation, as reflected in prolonged RTs in patients; the abnormality, however, has been ascribed to decreased alertness, fatigue, slowness of cognitive processing and abnormalities in sensorimotor integration (Kujala *et al.*, 1994, 1995; Kail, 1998; De Sonneville *et al.*, 2002; Godefroy *et al.*, 2002; Morgante *et al.*, 2011; Cabib *et al.*, 2015; Lubrini *et al.*, 2020). A recent study on motor execution showed an impaired movement accurancy during a dual-tasking performance in patients with MS but no changes of movement speed (Beste *et al.*,

2018). Another study, however, demonstrated that MS patients performed a low number of finger taps during a keyboard-tapping test and slowness correlated with their disability scores (Shribman *et al.*, 2018).

In summary, clinical and experimental data showed variable results on slowness of voluntary movement in MS. So far, there no study has specifically investigated the sequence effect in MS patints while executiong repetitive movements (Table 7).

2.6. PATHOPHYSIOLOGICAL MECHANISMS OF BRADYKINESIA IN NON PARKINSONIAN CONDITIONS

Although bradykinesia is classically considered the core motor symptom in patients with PD and APs, evidence of movement slowness, sometimes specifically referred to bradykinesia, has been provided in clinical and neurophysiological studies in dystonia, HD and ET as well as in patients with cerebellar diseases, upper motor neuron diseases or in those with MCI, AD or MS, all conditions not primarily characterized by parkinsonism. The main findings from these studies consisted in the evidence of altered movement preparation and execution, particularly slowness during upper limbs movements. Notably, no motor worsening of motor performance (sequence effect), when investigated, was observed with movement repetition in these conditions. It is worth noting that the clinical studies which provided the evidence of bradykinesia in non parkinsonian conditions mainly consisted of case reports or case serie. The neurophysiological studies also investigated bradykinesia in a relatively limited number of patients. Another controversial point concerns the methodology adopted for the clinical assessment. Most of the studies provided a clinical description of motor symtoms, and only few of them assessed bradykinesia using the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz *et al.*, 2008), i.e. the worldwide

used clinical scale to score bradykinesia in parkinsonism. Furthermore, in none of these studies were detailed the clinical features of bradykinesia or whether the sequence effect was clinically present. This heterogeneneity in the study methodology led to a broad heterogeneneity of terminology, with some authors reffering to the observed motor abnormalities with the general term of 'parkinsonism', others using the term of slowness, others 'bradykinesia' and/or 'hypokinesia. The appropriateness of the terminology of these clinical studies represents a debeated issue. In this regard, in the next part of the manuscript we will discuss the pathophysiological implication of these observations. We will first consider the effects of secondary factors, i.e. the presence of other major disturbances that characterize each specific condition. We will then focus on the pathophysiological role of the major brain areas known to be involved in each of the neurological condition considered. Finally we will provide a unifying pathophysiological view from a network perspective and emphasize possible terminological implications based on pathophysiological reasoning.

2.6.1. ROLE OF SECONDARY FACTORS

Increased muscle tone may have a detrimental effect in the execution of voluntary movement. For example, the EMG recordings in patients with FHD performing the task triggering the cramps showed a co-contraction of agonist and antagonist muscles (Cohen and Hallett, 1988). Accordingly, FHD patients had a specific triphasic EMG pattern during the execution of ballistic wrist movement, characterized by a prolonged first agonist burst, with little or no decrease in activity separating the second agonist burst, and a prolonged antagonist burst (MacKinnon *et al.*, 2004).

Movement slowness in dystonia, however, has also been demonstrated during upper limb movements where co-contraction activity between antagonist muscle groups cannot be

clearly identified (Prodoehl *et al.*, 2008), as well as in non-dystonic body segments, i.e. where there is no co-contraction activity (Pelosin *et al.*, 2009). All these findings indicate that co-contraction activity does not always explain movement slowness in dystonia. Increased muscle tone may also justify the presence of movement slowness in patienst with ALS, stroke or MS (Hallett, 1979; Fagioli *et al.*, 1988; Canning *et al.*, 2000). For example, rapid elbow flexion movements in patients with an upper motor neuron syndrome following a stroke were characterized by slowness and prolonged initial bursts in both the agonist and antagonist muscles (Fagioli *et al.*, 1988). In these type of patients, muscle weakness should be also considerd as a potential secondary factor of bradykinesia.

Action tremor is another factor that may potentially interfere with the execution of voluntary movement. In ET, a correlation between slowness in performing repetitive upper limb movements, such as repetitive forearm movements and severity of action tremor, has been described in some studies (Héroux *et al.*, 2006; Goubault *et al.*, 2017). In most cases, however, and particularly in the most recent studies, no relationship between slow movement and severity of tremor was found (Costa *et al.*, 2010). These data therefore suggest that action tremor in ET does not necessarily interfere with voluntary movement execution in this pathological condition. To date there is no specific study investigating the issue of action tremor interference on voluntary movement in conditions other than ET.

Cognitive deficit may also contribute in generating movement slowness, particularly interfering with the ability to perform rhythmic repetitive finger movements which requires higher levels of attention and other cognitive factors (Thomson *et al.*, 2008; Kuhn *et al.*, 2017). In this regard, there is evidence demonstrating that motor performance of finger movements negatively correlates with cognitive scores in AD (Suzumura *et al.*, 2018). Conversely, cognitive abnormalities likely play a less relevant role for single arm movements which require a relatively limited cognitive effort, and are strongly affected in

MS and AD. Finally, the role of cognitive dysfunction in conditionion like dystonia and ET is largely unexplored.

2.6.2. THE ROLE OF SPECIFIC BRAIN AREAS IN GENERATING MOVEMENT SLOWNESS IN NON PARKINSONIAN CONDITIONS

Basal ganglia

In dystonia and chorea, it is well known that the altered dopaminergic transmission and altered basal ganglia activity play a key pathophysiological role, as demonstrated by clinical observations and experimental studies (Berardelli *et al.*, 1998; Naumann *et al.*, 1998; Wolf *et al.*, 2012; Simonyan *et al.*, 2013; Reiner and Deng, 2018). In both conditions, according to traditional pathophysiological models, the dysfunction of the intrinsic basal ganglia circuit leads to the hyperactivation of the direct pathway and to an altered striato-thalamic drive. Consequently, reduced thalamic inhibition occurs which in turn leads to cortical hyper-activation (Albin *et al.*, 1989; DeLong, 1990). Consistent with these models, primary motor cortex (M1) abnormalities, including reduced intracortical inhibition and enhanced facilitation have been described in patients with dystonia and HD in transcranial magnetic stimulation studies (TMS) (Abbruzzese *et al.*, 1997; Priori *et al.*, 2000). The abnormal facilitation of the cortical areas in dystonia and HD could lead to an excess of movements. This hypothesis does not explain movement slowness in these patients, nor why pallidotomy and pallidal DBS relieve dyskinesias and dystonia, when they should make it worse. The most recent models of basal ganglia function overcame the paradoxes of the basal ganglia classical model (Marsden and Obeso, 1994; Eusebio and Brown, 2007) and suggested a co-activation, rather than an antagonistic effect, of the direct and indirect pathway in motor control (Cui *et al.*, 2013), thus explaining the presence of

movement slowness in hyperkinetic movement disorders. Finally, the role of basal ganglia in generating movement slowness in dystonia and chorea might be explained with other mechanisms. For example, it has been widely demonstrated the presence of altered oscillations and synchronous activity in the entire basal-ganglia network with anti-kinetic effect. Accordingly, pallidal DBS at same specific frequencies of stimulation can be complicated by the occurrence of slowness in finger tapping (Berman *et al.*, 2009; Huebl *et al.*, 2015).

Cerebellum

Neurophysiological observations consistently indicate that movement velocity and other kinematic parameter are widely and robustly encoded encoded in cerebellar neural activity (Ebner, 1998; Ebner *et al.*, 2011; Hewitt *et al.*, 2011). Hence it is possible that cerebellar dysfunction is involved in the pathophysiology of movement slowness in various conditions.

In ET, current pathophysiogical models emphasize the role of the cerebellum in the pathophysiology (Louis, 2018; Louis *et al.*, 2018), as demonstrated by clinical (Singer *et al.*, 1994; Bareš *et al.*, 2012), neuroimaging (Wills *et al.*, 1994; Pagan *et al.*, 2003; Quattrone *et al.*, 2008; Passamonti *et al.*, 2012), pathological observations (Louis *et al.*, 2007; Babij *et al.*, 2013) as well as several neurophysiologicall observations. Cerebellar lesions are known to generate movement slowness, which has been frequently reported in patients with cerebellar degenerative disease, tumors, and ischemic lesions (Hallett *et al.*, 1991*b*; Diener *et al.*, 1992; Berardelli *et al.*, 1996; Konczak *et al.*, 2010; Olivito *et al.*, 2017). Also more recent pathophysiological studies suggested a relationship between the cerebellum and bradykinesia in PD (Wu and Hallett, 2005, Bologna *et al.*, 2019*b*). Thus, it is likely that in ET cerebellar dysfunction causes an altered ability to efficiently modulate

the speed of movement to prevent dysmetria thus leading to excessive slowing than that expected for a given movement in healthy individuals (Markanday *et al.*, 2018). Again, there are several EMG studies suggesting an altered relationship between agonist-antagonist EMG bursts during movement execution in cerebellar patients, with abnormal prolongation of the first agonist and antagonist bursts or both (Hallett *et al.*, 1975, 1991*a*; Becker *et al.*, 1990). In this regard, it has been pointed out that different anatomical lesions of the cerebellum were associated with different agonist and antagonist EMG activities in cerebellar patients (Manto *et al.*, 1998, p. 19) Due to the well-established role of the cerebellum in movement timing, the hypothesis of cerebellar dysfunction in ET would also explain the movement rhythm abnormalities often combined to movement slowness in these patients (Buijink *et al.*, 2015). Finally, it is reasonable that abnormalities in other neural structures interconnected with the cerebellum may also contribute in generating movement slowness in ET (Muthuraman *et al.*, 2015; Haubenberger and Hallett, 2018), Recent studies suggest that cerebellum could play a role in the pathophysiology of dystonia (Bologna and Berardelli, 2018). This hypothesis is support by animal studies showing a cerebellar involvement in models of dystonia (Neychev *et al.*, 2011; Zhao *et al.*, 2011) as well as by studies in humans (Pearson 2016; Kuo et al. 2017; Schreglmann et al. 2018). To what extent this cerebellar dysfunction contribute to movement slowness in dystonia is still largely an unexplored issue.

Corticospinal tract

M1 is the principal source of corticospinal input to control voluntary movement. Thus, damage of the corticospinal tract is clearly the major pathophysiogically mechanism involved in generating movement slowness in patients with upper motor neuron syndromes. Damage of the corticospinal tract interferes with encoding of motor parameters

contributing to slowness of movement, and leads to agonist and antagonist muscle activity of longer duration, possibly reflecting a compensatory mechanism due to the reduction of motor neuronal recruitment (Hallett, 1979). Although not specificalky tested, in neurodenegerative conditions like ALS, it is likely that as the disease progresses the corticospinal tract deteriorates further, thus worsening the integrity of motor command encoding and as a consequiene, leading to movement slowness.

Consistent with the hypothesis of corticospinal tract involvement and movement slowness in upper motor neuron syndnromes, M1 'hypoactivation' during movement is also though to contribute to movement slowness in PD, as demonstrated by studies on animals and patients. For example, Pasquereau et al. (2016) tested hemiparkinsonian MPTP monkeys and found that the resting discharge of corticospinal neurons was lower than normal and that changes in discharge rate correlated with altered direction, force and acceleration during active movement (Pasquereau *et al.*, 2016). More recently, ita has been obserevd that changes of M1 excitability correlate with movement slowness during finger tapping in PD (Bologna *et al.*, 2018).

Sensorymotor integration

Several abnormalities of the sensory processing as well as of the sensorimotor integration have been specifically demonstrated by studies on patients with non-parkinsonian conditions, particularly dystonia (Tinazzi *et al.*, 2000; Scontrini *et al.*, 2009). These neural functions lilely depends on the connections between basal ganglia, cerebellum and corticospinal system (Abbruzzese and Berardelli, 2003; Conte *et al.*, 2018) further supporting the hypothesis of bradykinesia as a network disorder.

3. EXPERIMENTAL PART

3.1. STUDY 1: NEUROPHYSIOLOIGICAL ASSESSMENT OF BRADYKINESIA IN ESSENTIAL TREMOR

3.1.1 Abstract

ET is a movement disorder primarily characterized by upper limb postural and kinetic tremor. Although still under-investigated, bradykinesia may be part of the phenotypic spectrum of ET. We aimed to evaluate bradykinesia features in ET through clinical examination and kinematic analysis of repetitive finger movements. We compared data collected in ET patients with those recorded in PD patients and healthy controls. Overall, 258 subjects participated in the study (90 ET patients, 84 PD patients, and 84 healthy controls). Repetitive finger tapping was kinematically recorded using a motion analysis system. Movement velocity, amplitude, and decrement (sequence effect) were measured. We first compared the three groups by one-way analysis of variance. We also performed a cluster analysis to better address the data variability observed in ET patients. Possible relationships between kinematic and clinical data were assessed in ET patients. ET patients were slower than healthy controls. Movement slowness in ET did not correlate with postural or kinetic tremor severity. We also found that movement slowness in ET was not associated with sequence effect, which instead is a common feature in Parkinson's disease. Cluster analysis showed that a proportion of ET patients may have movement abnormalities similar to those observed in Parkinson's disease. Movement slowness without sequence effect is a common feature in ET patients. The present findings are relevant when interpreted in the context of the new tremor classification system and in the development of a more accurate bradykinesia definition.

3.1.2 Introduction

Bradykinesia is the cardinal motor symptom in PD and refers to movement slowness with a progressive reduction in speed and amplitude during repetitive movement (sequence effect) (Berardelli *et al.*, 2013; Postuma *et al.*, 2015; Bologna *et al.*, 2019, p. 20). Movement slowness has also been reported in ET, a movement disorder characterized by upper limb postural and kinetic tremor (Deuschl *et al.*, 2015; Espay *et al.*, 2017; Bhatia *et al.*, 2018; Haubenberger and Hallett, 2018; Hopfner and Deuschl, 2018). When movement slowness or other neurological signs (i.e., "soft neurological signs") are present, the new tremor classification suggests using the term ET-plus (Bhatia *et al.*, 2018).

In ET, movement slowness has objectively been demonstrated by kinematic analysis of repetitive movements (Montgomery *et al.*, 2000; Duval *et al.*, 2006; Farkas *et al.*, 2006; Costa *et al.*, 2010; Jiménez-Jiménez *et al.*, 2010; Goubault *et al.*, 2017). Importantly, none of these studies have assessed whether movement slowness in ET is associated with sequence effect (Algarni and Fasano, 2018), which is a feature of bradykinesia in PD (Berardelli *et al.*, 2001, Postuma *et al.*, 2015*b*, Bologna *et al.*, 2019*b*). The relationship between movement abnormalities and tremor severity in ET also needs clarification. While some authors indicate that movement slowness in ET is due to tremor (Goubault *et al.*, 2017), others favour the hypothesis that it is due to a distinct pathophysiology (Costa *et al.*, 2010).

In this study, we investigated voluntary movement abnormalities in ET using kinematic techniques. We specifically analysed repetitive finger movements, one of the most sensitive tests for bradykinesia assessment in PD clinical practice (Bologna *et al.*, 2019*b*). We measured various parameters, including movement velocity and amplitude and velocity reduction during movement repetition. To determine whether bradykinesia has specific features in ET patients, we compared data collected in ET patients with those

recorded in PD patients and healthy controls (HCs). We also performed a cluster analysis to better address the data variability observed in ET patients. Finally, we investigated possible relationships between movement abnormalities, postural and kinetic tremor severity, and other ET clinical features.

3.1.3 Materials and Methods

Participants

A total of 258 subjects participated in the study (90 patients with ET, 84 patients with PD, and 84 HCs). Patients were recruited at the Department of Human Neurosciences, Sapienza University of Rome. ET and PD diagnoses were based on clinical criteria (Berardelli *et al.*, 2013, Postuma *et al.*, 2015*a*). Patients with previous exposure to drugs acting on the central nervous system, including alcohol abuse or head trauma, were excluded from the study. Both ET and PD patients discontinued their medications at least 48 hours prior to the experiments. ET and PD patients were clinically assessed by a neurologist experienced in movement disorders. Cognitive evaluation in ET and PD patients was performed using the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005). Evaluation of ET patients was performed according to the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS) (Fahn S. Tolosa E. Concepcion M, 1993). Both ET and PD patients were assessed according to the motor section (part III) of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz *et al.*, 2008; Antonini *et al.*, 2013). Although a minor percentage of ET patients had rest tremor of the upper limbs (14/90 ET patients, 15%), as seen in other reports (Louis *et al.*, 2019), or slight movement slowness of the upper limbs (6/90 ET patients, 6.6%), rest tremor and movement slowness did not occur in combination in any of the ET patients we

tested. Thus, no ET patients enrolled in our study fit the current criteria for parkinsonism (Postuma *et al.*, 2015*a*), nor did any have overt signs of parkinsonism, including micrographia, hypomimia, hypophonia, reduced arm swing during walking, postural abnormalities, rigidity, or other features such as impaired tandem gait, dystonic posturing, or mild memory impairment. HCs were right-handed and none had a history of neurologic or psychiatric disorders or medication intake. The study was approved by the local institutional review board. All participants gave their written informed consent to participate in the study.

Kinematic recording and analysis

Repetitive finger tapping and tremor recordings were performed using a 3D optoelectronic system (SMART motion system, BTS, Milan, Italy). This system includes three infrared cameras (120 Hz frequency) that detect motion in the three-dimensional space of reflective markers taped at the level of the hand and on the distal phalanx of the index finger and the thumb of the dominant hand (Bologna *et al.*, 2016*a*, 2018).

Participants were asked to perform 15-s of repetitive finger movements, i.e. opening and closing the index finger and the thumb (finger tapping), as fast as possible and with the widest range of motion. Three 15-s recordings were performed in succession with a 60-s pause between recordings (Bologna *et al.*, 2016*a*, 2018). The choice to record 15-s of tapping was based on previous studies (Espay *et al.*, 2011; Ling *et al.*, 2012, Bologna *et al.*, 2016*a*, 2018). Kinematic data analysis was based on dominant hand performance in ET patients and HCs. In PD we tested the more affected side. Notably, we previously demonstrated no significant effect of handedness on motor performance in healthy controls and PD patients (Bologna *et al.*, 2016*a*, 2018). Movement analysis was performed offline with a dedicated software (SMART Analyzer, BTS Engineering, Italy) to determine the

total number of movements and movement rhythm, i.e. the coefficient of variation (CV) computed by the standard deviation/mean value of the inter-tap intervals (with higher values representing a lower regularity of repetitive movements). Linear regression techniques were then used to determine the intercept (which reflects the movement amplitude in degree and velocity in degree/s at the beginning of the motor sequence of 15 seconds) and the slope (representing amplitude and velocity decrement, i.e. sequence effect across the 15 sec trials) of the regression line across the scatter plot of the kinematic parameters (Y-axis) versus the movement number (X-axis) (Bologna *et al.,* 2016*a,* 2018). For postural tremor recordings, patients were asked to place their arms outstretched in front of their chest (three 30-s recordings each). For tremor analysis, power spectra were calculated by fast Fourier transformation using dedicated software (SMART Analyzer, BTS Engineering, Milan). Kinematic analysis was used to determine the dominant frequency peak (Hz) of the tremor spectrum. The tremor magnitude was measured and expressed in terms of GRMS^2 (Bologna *et al.,* 2015, 2019*a*; Paparella *et al.,* 2018). We measured the kinetic tremor of the upper limb, as determined by the curvature index (ratio of the arm endpoint average path length to that of a straight line joining the initial and final positions) during a pointing task (Paparella *et al.*, 2018).

Statistical analysis

Gender differences between ET and PD patients and HCs were evaluated using the Fisher exact test. The Kruskal-Wallis analysis of variance (ANOVA) was used to assess age differences between ET, PD and HCs. Comparison of finger tapping kinematics in ET, PD, and HCs was performed by one-way ANOVA using the intergroup factor 'GROUP'. Kinematic variables were assessed in separate ANOVAs. Fisher's least significant difference test was used for post-hoc analyses. We also performed a K-means clustering

analysis in order to distinguish possible subgroups of participants whose kinematic features differed. Linear relationship was determined using Pearson or Spearman correlations, and logistic regression analyses were performed to determine whether movement kinematics during finger tapping (dependent variables) depended on postural tremor severity (independent variable) as assessed by the FTMTRS and kinematic techniques, or on disease duration, or were influenced by other categorical demographic and clinical features, i.e. gender, familial history, age at onset > 60 years, presence of head tremor. All results are presented as mean values ± 1 standard error of the mean (SEM) unless otherwise specified. The significance level was set at $P<0.05$. Data were analysed using STATISTICA® (StatSoft, Inc) and implemented with R.

3.1.4 Results

Between-group analysis

No differences were found in the age and gender ratio between ET and PD patients and HCs (all Ps>0.05) (Table 8). All ET patients had a bilateral and symmetric tremor of the upper limbs, a positive family history was present in 50/90 cases (55.5%), 43 patients (38.7%) were > 60 years at disease onset, and 21 patients (23.3%) had tremor of the upper limbs plus head tremor (Table 8). None of the participants had significant cognitive abnormalities (MoCA score > 26 in all participants). The average FTMTRS score (± 1 SD) in the ET group was 19.10±11.33. The average UPDRS score (± 1 SD) in the ET group was 5.5±2.62 and was mainly due to postural and kinetic tremor (as assessed by items 3.14 and 3.15). We also found rest tremor of the upper limbs in 14/90 ET patients (15.6%) or slight movement slowness (item 3.4) of the upper limbs in 6/90 ET patients (6.6%). The average UPDRS score (±1 SD) in the PD group was 30.36±13.35.

We found no significant kinematic differences between the right and left side in a subgroup of 50 ET patients, and between the more and less affected hands performance for the entire sample of 84 PD patients (supplementary Table 1 and Table 2).

ANOVA disclosed a significant effect of the factor 'GROUP' on the number of movements ($F_{2, 255}=7.61$, $P<0.001$), CV ($F_{2, 255}=8.90$, $P<0.001$), amplitude ($F_{2, 255}=13.16$, $P<0.001$), velocity ($F_{2, 255}=23.37$, $P<0.001$), and slope amplitude ($F_{2, 255}=8.72$, $P<0.001$). The slope velocity did not differ between groups ($F_{2, 255}=0.43$, $P=0.65$). Post-hoc analysis revealed that the number of movements was lower in ET than in PD ($P=0.03$) and HCs ($P<0.01$), whereas no difference emerged between PD and HCs (Fig. 1). The CV was higher in PD than in ET ($P=0.002$) and HCs ($P<0.001$). Movement amplitude and velocity were lower in PD than in ET (amplitude: $P=0.002$; velocity: $P<0.001$) and HCs (amplitude: $P<0.001$; velocity: $P<0.001$). In addition, movement velocity was lower in ET patients than HCs ($P=0.04$). Finally, the amplitude decrement was more severe in PD than in ET and HCs (both $P<0.001$) (Fig. 1).

These data indicate that ET patients perform slower voluntary movements in comparison with HCs, as evidenced by the reduced number of performed movements and lower peak velocity during finger tapping. No other abnormalities or sequence effect were observed in ET patients. The observation that the number of performed movements was lower in ET than in PD patients may be explained by the fact that movement slowness in PD is accompanied by a significant reduction in movement amplitude, which does not occur in ET.

Finally, we found that ET-plus patients did not differ from ET patients in terms of movement slowness (movement velocity average ± standard error ET vs ET-plus: 956.2±27.2 vs 930.6 ± 50.9, $P=0.6$ by an unpaired t-test).

Cluster analysis

Since an inspection of the raw data revealed a significant variability in the data and a substantial overlap in the kinematic values between groups (Fig. 1), we applied a cluster analysis to determine whether combinations of kinematic parameters characterized the patterns of movement abnormalities without a priori categorization of subjects into groups. Cluster analysis identified two clusters. Movement velocity was the parameter with the greatest difference between the two clusters (cluster 1: 716.18 degrees/sec; cluster 2: 1157.16 degrees/sec; 38.10% difference). Movement amplitude (cluster 1: 38.01 degrees; cluster 2: 52.05 degrees; 26.97% difference) and CV (cluster 1: 0.128; cluster 2: 0.101; 26.73% difference) also differed between the two clusters. Amplitude decrement was slightly steeper in cluster 1 than in cluster 2 (cluster 1: -0.170 degrees/movement; cluster 2: -0.155 degrees/movement; 9.67% difference). Finally, the number of movements was the parameter with the lowest difference between the two clusters (cluster 1: 43.07; cluster 2: 46.39; 7.15% difference). Thus, cluster 1 included a combination of altered parameters, while cluster 2 was characterized by values within the normal range. Notably, between-cluster differences were mainly driven by changes in movement velocity, combined with altered amplitude and CV. Overall, the two clusters were distributed differently in ET patients, PD patients, and HCs ($P<0.001$; Fig. 2). There were more PD patients in cluster 1 (78.6% in cluster 1, 21.4% in cluster 2) and HCs in cluster 2 (66.7% in cluster 2, 33.3% in cluster 1). ET patients were almost equally distributed in the two clusters (47.8% in cluster 1, 52.2% in cluster 2; Fig. 2). The frequency of cluster 1 was highest in PD patients compared to ET patients and HCs (PD vs. ET and PD vs. HCs, P always <0.001), but it was also higher in ET patients than HCs ($P=0.05$). In summary, as compared to HCs (i.e. ~15% difference), a larger proportion of ET patients had a combination of movement

abnormalities categorized in cluster 1, which corresponded with those mainly observed in PD.

Regression analysis

We found no significant linear relationship between movement slowness in ET and postural or kinetic tremor, as assessed by the FTMTRS or kinematic techniques, or between movement slowness in ET and disease duration (all P values > 0.05). Additionally, logistic regression analysis showed no relationship between movement slowness and categorical demographic and clinical features, i.e. gender (OR: 2.25; 95% CI: 0.71–7.07; P=0.17), familial history (OR: 0.98; 95% CI: 0.37–2.60; P=0.97), age at onset > 60 years (OR: 2.33; 95% CI: 0.58–9.29; P=0.23), and presence of head tremor (OR: 0.30; 95% CI: 0.09–1.06; P=0.06).

3.1.5 Discussion

We investigated possible voluntary movement abnormalities in ET through kinematic analysis of repetitive finger tapping, one of the most commonly used tasks for bradykinesia evaluation in clinical practice (Bologna *et al.*, 2019*b*). As a group, ET patients had slower movement execution than HCs, but unlike PD patients they had no progressive reduction in speed or amplitude, i.e. sequence effect. No relationship between movement slowness and tremor severity or other clinical and demographic features in ET emerged from the analysis, indicating that movement slowness in ET cannot simply be explained as a secondary effect of tremor itself. Finally, cluster analysis showed that a significant proportion of ET patients displayed a combination of movement abnormalities that overlapped with those observed in PD.

When interpreting our findings, we can exclude that methodological aspects and other potential study limitations may have significantly influenced the results. First, patients with ET were consecutively recruited, therefore minimizing a possible selection bias. Since ET diagnosis is still currently based on clinical criteria (Bhatia *et al.*, 2018), there may be difficulties in some cases in the differential diagnosis with other conditions, including dystonia and PD. However, the ET patients were followed up in our outpatient clinic for a relatively long period, thus minimizing the risk of misdiagnosis. In this regard, all patients had bilateral postural and kinetic tremor of the upper limbs, while none had subtle dystonia signs or clinically detectable parkinsonian features (Pandey and Bhattad, 2019; Rajput *et al.*, 2019). All patients had discontinued all therapies at least 48 hours before the experimental evaluation, therefore reducing the possibility that medications affected our kinematic measurements. Finally, since demographic (age and gender) features were similar between groups it is unlikely that they significantly affected the results.

The novel finding that emerged from our kinematic analysis was that movement slowness in ET was not associated with sequence effect, which instead is a common feature in PD (Berardelli *et al.*, 1986, 2001, Bologna *et al.*, 2016*a*, 2018, 2019*b*). Since we found no significant correlations between slowed finger tapping and postural or kinetic tremor severity, as evaluated by clinical rating scores and kinematic techniques, we can exclude that movement slowness in ET patients represents a secondary and aspecific effect of tremor itself. Moreover, the lack of correlation between movement slowness and postural or kinetic tremor severity implies that the two movement abnormalities are due, at least in part, to distinct pathophysiological processes (Muthuraman *et al.*, 2015). The lack of a possible relationship between tremor severity and movement slowness in ET must be confirmed in further investigations comparing repetitive finger movement performance with and without treatment.

It is well known that cerebellar dysfunction plays a role in the pathophysiology of ET (Haubenberger and Hallett, 2018). Hence, it is possible that cerebellar dysfunction is also involved in the pathophysiology of movement slowness in ET. This hypothesis is supported by the observation that various kinematic parameters, particularly movement direction and velocity, are encoded in cerebellar neural activity. In particular, the spike firing of Purkinje cells, the main output of the cerebellar cortex, is thought to control movement velocity across multiple tasks, including hand kinematics (Ebner, 1998; Ebner *et al.*, 2011; Hewitt *et al.*, 2011). Furthermore, several studies have shown that degenerative cerebellar disease, cerebellar tumors, and ischemic lesions may be associated with movement slowness, which may be due to an inappropriate acceleration time for the first agonist burst. In patients in the acute stage of cerebellar stroke, it has been observed that voluntary arm movements are mainly characterized by slowness (bradykinesia) and not loss of movement coordination (ataxia). Interestingly, the movement slowness in patients with cerebellar stroke was associated with lesions in paravermal regions and the deep cerebellar nuclei (Hallett *et al.*, 1991*a*; Diener *et al.*, 1992; Berardelli *et al.*, 1996; Konczak *et al.*, 2010; Olivito *et al.*, 2017). One current hypothesis is that in healthy subjects the cerebellum is able to prevent dysmetria by adjusting movement duration to compensate for changes in movement velocity and that this ability is lost in cerebellar disease (Markanday *et al.*, 2018). Due to the well-established role of the cerebellum in movement timing, we would have expected movement rhythm abnormalities (as reflected by higher CV values) in ET patients as compared to HCs. The lack of significant movement rhythm differences between ET patients and HCs possibly indicates that additional mechanisms together with altered cerebellar output may be involved in the generation of movement slowness in ET. These mechanisms may involve altered

oscillating activity in the wider cerebral network, including not only the cerebellum, but also the thalamus and the M1 (Muthuraman *et al.*, 2015; Haubenberger and Hallett, 2018). In PD, basal ganglia-cortical loops are primarily involved in regulating different movement parameters, including speed. As in ET, the cerebellum is thought to be involved in the pathophysiology of bradykinesia in PD, which is now considered a network disorder (Berardelli *et al.*, 2001, Bologna *et al.*, 2019*b*). However, different movement abnormalities, particularly the lack of sequence effect during repetitive voluntary movement in ET as opposed to PD, point toward a different pathophysiological role of the cerebellum in the two conditions. Together with cortical motor areas, the cerebellum may be involved in the execution of continued and repetitive movements, which play a role in movement feedback and compensate for defective basal ganglia function (Bologna *et al.*, 2019*b*).

When performing cluster analysis, we found that almost half of ET patients were categorized with normal movement kinematics, similar to HCs. However, the remaining half of ET patients were categorized with abnormal movement kinematics, similar to most PD patients. Participant categorization into the two ET subgroups was mainly due to the presence of movement slowness and altered amplitude and rhythm, while sequence effect had less influence on participant categorization. Notably, the movement differences in the two ET subgroups could not be simply explained by clinical and demographic characteristics. The overlap in movement kinematics we found between a significant proportion of ET patients and most PD patients is consistent with previous clinical observations (Waln *et al.*, 2015; Espay *et al.*, 2017; Rajput *et al.*, 2019). It is worth noting, however, that none of the ET patients enrolled in our study had clinical parkinsonism according to current criteria (Postuma *et al.*, 2015*a*). In our study, patients did not undergo DaTscan examination, which would have helped clarify the possible presence of

dopaminergic alterations. However, it is impractical to perform DaTscan examinations in all patients and the results are not necessarily conclusive. In this regard, DaTscan examination can demonstrate a trend of uncertain significance toward a slight dopaminergic deficit in the striatum (Waln *et al.,* 2015). Moreover, there is a small proportion of patients with a negative DaTscan who may be diagnosed with PD on the basis of a positive levodopa response, clinical progression, and imaging and/or genetic evidence (Erro *et al.*, 2016).

It is important to note that the above observations on voluntary movement abnormalities are relevant when interpreted in the context of the new tremor classification system (Bhatia *et al.*, 2018). Accordingly, the term ET-plus defines tremor with ET characteristics and additional neurological signs of unknown significance, including voluntary movement abnormalities (Bhatia *et al.*, 2018). ET patients with movement abnormalities detected by kinematic analysis may therefore qualify for the definition of ET-plus (Bhatia *et al.*, 2018; Louis *et al.*, 2019). Since patients included in this study did not have parkinsonism, our findings thus indicate that quantitative measures and kinematic analysis of finger tapping allow a better categorization of ET patients. In this regard, kinematic analysis is likely to identify a higher proportion of ET-plus patients than clinical examination. Whether voluntary movement abnormalities in ET patients, as demonstrated by kinematic analysis, could be considered a motor prodrome of PD is an important issue that should be addressed in future studies. For example, longitudinal studies are needed to clarify whether voluntary movement objectively quantified by kinematic techniques may be an early marker predicting the future development of PD in patients with ET.

Finally, our results are relevant in the development of a more accurate definition of bradykinesia and the appropriate use of this term in patients with ET. The term bradykinesia has been used previously in a number of clinical and experimental studies in

ET patients. However, the use of this term in patients with ET can only be considered appropriate when strictly related to its simplest etymological meaning, i.e. movement slowness. In contrast, the use of this term may be inappropriate if reference is made to the definition of bradykinesia in the context of PD, since in this context the term implies the presence of sequence effect. Clarifying this issue goes beyond the purposes of this study. In conclusion, our study showed that ET patients as a group have significant movement slowness as compared to HCs, possibly due to abnormalities within the cerebello-thalamo-cortical network. Since no sequence effect was observed in ET, it is likely that the pathophysiological processes responsible for altered voluntary motor control in ET differ from those in PD. Our results also emphasize that a significant proportion of ET patients have movement abnormalities similar to those observed in PD patients. Our findings indicate that these patients could therefore be categorized as ET-plus, as supported by neurophysiological (though not clinical) evidence.

3.2 STUDY 2: BRADYKINESIA IN ALZHEIMER'S DISEASE AND ITS NEUROPHYSIOLOGICAL SUBSTRATES

3.2.1 Abstract

Alzheimer's disease is primarily characterized by cognitive decline; recent studies, however, emphasize the occurrence of motor impairment in this condition. Here, we investigate whether motor impairment, objectively evaluated with kinematic techniques, correlates with neurophysiological measures of the primary motor cortex in Alzheimer's disease.Twenty patients and 20 healthy subjects were enrolled. Repetitive finger tapping was assessed by means of a motion analysis system. Primary motor cortex excitability was assessed by recording the input/output curve of the motor-evoked potentials and using a conditioning-test paradigm for the assessment of short-interval intracortical inhibition and short-latency afferent inhibition. Plasticity-like mechanisms were indexed according to changes in motor-evoked potential amplitude induced by the intermittent theta-burst stimulation. Patients displayed slowness and altered rhythm during finger tapping. Movement slowness correlated with reduced short-latency afferent inhibition in patients, thus suggesting that degeneration of the cholinergic system may also be involved in motor impairment in Alzheimer's disease. Moreover, altered movement rhythm in patients correlated with worse scores in the Frontal Assessment Battery. This study provides new information on the pathophysiology of altered voluntary movements in Alzheimer's disease.The study results suggest that a cortical cholinergic deficit may underlie movement slowness in Alzheimer's disease.

3.2.2 Introduction

AD is a neurodegenerative condition mainly characterized by cognitive decline (Scheltens *et al.*, 2016). However, recent studies have emphasized the occurrence of motor impairment in this condition (Scarmeas *et al.*, 2005; Vöglein *et al.*, 2019). A range of motor symptoms and signs, including slowed voluntary movement (bradykinesia), have been reported in 15-50% of patients with AD (Tsolaki *et al.*, 2001; Scarmeas *et al.*, 2004, 2005). Motor signs predict cognitive and functional decline (Scarmeas *et al.*, 2005) and correlate with the deposition of amyloid-β in the basal ganglia and in other areas (Del Campo et al. 2016; Vöglein et al. 2019). It has also been suggested that amyloid-mediated degeneration of the cholinergic system may account for AD-related motor impairment (Schirinzi *et al.*, 2018). Despite clinical observations, only a limited number of studies have quantitatively assessed voluntary movement abnormalities in AD (Roalf *et al.*, 2018; Suzumura *et al.*, 2018). Roalf et al. evaluated motor performance by objectively analyzing finger tapping and observed a reduced number of taps, a longer inter-tap interval and higher intra-individual variability in AD patients than in healthy controls (Roalf *et al.*, 2018). Suzumura et al. also studied finger dexterity and confirmed abnormalities in movement rhythm in AD (Suzumura *et al.*, 2018).

Since corticospinal output from the M1 is a major pathway for the control of skilled movement, it is reasonable to assume that M1 dysfunction in AD contributes to movement abnormalities. Studies on animal models of AD have revealed structural and functional changes in M1 (Battaglia *et al.*, 2007; Iaccarino *et al.*, 2016). The hypothesis of M1 involvement in AD is supported by neurophysiological studies in patients based on TMS (Di Lazzaro *et al.*, 2002, 2004; Inghilleri *et al.*, 2006; Ferreri *et al.*, 2011, 2016; Guerra *et al.*, 2011; Wegrzyn *et al.*, 2013; Cantone *et al.*, 2014; Nardone *et al.*, 2014; Di Lorenzo *et al.*, 2016, 2019). Major neurophysiological abnormalities in M1 are decreased motor cortical inhibition, defective cholinergic neurotransmission, as detected by reduced

short-latency afferent inhibition (SAI), and reduced long-term potentiation (LTP)-like plasticity (Di Lazzaro *et al.*, 2002, 2004; Inghilleri *et al.*, 2006; Battaglia *et al.*, 2007; Ferreri *et al.*, 2011, 2016; Guerra *et al.*, 2011; Terranova *et al.*, 2013; Wegrzyn *et al.*, 2013; Cantone *et al.*, 2014; Nardone *et al.*, 2014; Di Lorenzo *et al.*, 2016, 2019; Schirinzi *et al.*, 2018). These abnormalities are present in the early disease stages and deteriorate as the disease progresses (Ferreri *et al.*, 2011; Trebbastoni *et al.*, 2015).

To our knowledge, data on possible correlations between voluntary movement abnormalities and neurophysiological abnormalities in M1 in AD are lacking. Gaining an insight into this issue might provide a better understanding of motor impairment in AD and its underlying pathophysiological mechanisms. In the present study, we specifically investigated possible relationships between movement kinematics and neurophysiological changes in M1 in AD patients. Voluntary movement was objectively assessed during repetitive finger tapping (Bologna *et al.*, 2016*a*, 2018). We evaluated movement amplitude, velocity and rhythm, as well as the amplitude and velocity decrement (sequence effect) during movement repetition (Bologna *et al.*, 2016*a*, 2018). We measured M1 excitability and plasticity at rest using various TMS techniques (Tokimura *et al.*, 2000; Huang *et al.*, 2005; Berardelli *et al.*, 2008, Bologna *et al.*, 2017*a*; Di Lorenzo *et al.*, 2019). AD patient data were compared with those from healthy subjects.

3.2.3 Materials and methods

Participants

We enrolled twenty patients with mild-to-moderate AD (9 females, mean age ± 1 standard deviation: 77.0 ± 8.0; Table 9) and 20 HCs with no overt cognitive or motor disturbances

(14 females, mean age ± 1 standard deviation: 71.0 ± 9.4). Current clinical criteria (McKhann *et al.*, 2011) were used for AD diagnosis. The patients underwent an accurate neurological examination, a complete battery of neuropsychological testing, laboratory screening, and brain MRI to rule out other causes of dementia, e.g. dementia with Lewy bodies (McKeith et al., 2017). The neuropsychological assessment included the Mini Mental State Examination (MMSE) (Folstein *et al.*, 1975), the Frontal Assessment Battery (FAB) (Dubois *et al.*, 2000) and the Beck Depression Inventory (BDI-II) (Beck *et al.*, 1961). In order to detect possible signs of parkinsonism, patients were also examined by using the motor section (part III) of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Goetz *et al.*, 2008; Antonini *et al.*, 2013). All the participants were right-handed, as evaluated by the Handedness Questionnaire. Any drugs that are known to affect corticospinal excitability or plasticity being taken by patients, including antipsychotics and cholinesterase inhibitors, were discontinued at least 72 h prior to the evaluation. Experimental procedures were carried out in accordance with the Declaration of Helsinki and international safety guidelines (Rossi *et al.*, 2009; Rossini *et al.*, 2015) and approved by the local ethics committee. Written informed consent to the study was provided by all participants.

Movement analysis

Subjects were seated on a chair and performed repetitive finger tapping with the right hand. Three trials consisting of 15 seconds of repetitive finger tapping were recorded. Participants were requested to start and stop tapping movements by verbal command. To avoid fatigue, a ~60-second rest was allowed between trials (Bologna *et al.*, 2016*a*, 2018). In addition, to ensure that participants understood the task, they were instructed to perform

one practice trial before the kinematic recordings. Kinematic recordings were made by using an optoelectronic system (SMART motion system, BTS Engineering, Italy). Three infrared cameras followed the 3D displacement of reflective markers of negligible weight with a 5-mm diameter, which were attached to the upper limb (sampling rate of 120 Hz). We placed two markers on the tips of the index finger and thumb. To define a reference plane and mathematically exclude contaminations of any unwanted hand movements that interfered with finger tapping we placed three additional markers were on the hand (Bologna *et al.*, 2016*a*, 2018). Movement analysis was carried out using special software (SMART Analyzer, BTS Engineering, Italy). For quantitative purposes, linear regression techniques were used to calculate the intercept, which reflects the movement amplitude (degree) and velocity (degree/s), and the slope, which reflects the amplitude and velocity decrement during movement repetition. The coefficient of variation (CV) of the inter-tap intervals (with higher values representing a lower regularity of repetitive movements) was also used to measure movement rhythm (Bologna *et al.*, 2016*a*, 2018).

TMS

To study cortical excitability, single- and paired-pulse TMS was delivered through a MagstimBiStim^2 and a standard figure-of-eight coil that delivered monophasic pulses (Magstim Company Limited, UK). The hotspot of the right first dorsal interosseous (FDI) muscle, defined as the optimal scalp position to elicit motor-evoked potentials (MEPs) in the muscle, was identified with the handle of the TMS coil positioned at a ~45° angle from the midline pointing backward. The resting motor threshold (RMT), active motor threshold (AMT), andintensity required to produce MEPs of ≈1 mV in size (1mV MEP) were established (Currà *et al.*, 2002). Then, the input-output (I/O) curve was measured by

delivering 10 single TMS pulses at six different stimulation intensities (60 pulses in total), ranging in 20% increments from 80% to 180% of the RMT. In order to avoid hysteresis effects the intensity order was randomized (Bologna *et al.*, 2017*a*, 2018). Moreover, short-interval intracortical inhibition (SICI) and SAI were assessed using standardized protocols (Tokimura *et al.*, 2000; Berardelli *et al.*, 2008). SICI was tested by delivering paired TMS pulses with a subthreshold conditioning stimulus at an intensity of 80% of the AMT, a supra-threshold test stimulus at 1mV MEP and an inter-stimulus interval (ISI) of 2 and 4 ms. For SAI, we performed median nerve stimulation at the wrist using a 0.1ms electrical rectangular pulse (Digitimer model DS7; Digitimer, UK) with a bipolar electrode and an intensity that induced a painless thumb twitch. The intensity of the TMS was set at 1mV MEP, and the ISIs (interval between the median nerve and the cortical stimulation) tested were 22 and 24 ms. SICI and SAI were tested in two separate blocks. Fifteen trials were acquired for each ISI for both SICI and SAI and randomized with 15 single-pulse stimuli delivered at an intensity of 1mV MEP (unconditioned MEPs). SICI and SAI were expressed as the ratio between the unconditioned and conditioned MEP.

We probed cortical plasticity by applying intermittent theta-burst stimulation (iTBS) (Huang *et al.*, 2005; Di Lorenzo *et al.*, 2016, Bologna *et al.*, 2017*a*; Di Lorenzo *et al.*, 2019). The iTBS protocol was delivered by using a high-frequency biphasic magnetic stimulator (Magstim Super Rapid; Magstim Company Limited, UK) connected to a figure-of-eight coil placed over the FDI hotspot. The stimulation intensity was set at 80% of the AMT. The protocol consisted of ten bursts of three pulses at 50 Hz, repeated at 200-ms intervals, delivered in short trains lasting 2 seconds, with an 8-second pause between consecutive trains (20 trains, 600 pulses in total). Given the limited duration of this protocol, we applied iTBS in order to minimize the time required for the experiments in patients.

MEPs were recorded by using surface electrodes taped in a belly-tendon montage. EMG signals were amplified and filtered (20 Hz-1 kHz) using Digitimer D360 (Digitimer, UK), stored on a computer (sampling rate of 5 kHz) through an analog-digital converter AD1401 plus (Cambridge Electronic Design, UK) and then analyzed off-line with a dedicated software (Signal version 5.08, Cambridge Electronic Design, UK). The MEP peak-to-peak amplitude was measured within a time window of 20-40 ms after the TMS artifact. Traces with background EMG activity exceeding 0.1mV in the 200-ms time window preceding the TMS artifact were rejected.

Experimental design

All subjects underwent a single experimental session. After having administered the various clinical and neuropsychological scales, kinematic recordings were performed. Then, TMS measures were collected: corticospinal (i.e., RMT, AMT and I/O curve) and intracortical (SICI and SAI) excitability paradigms were recorded before the iTBS protocol. In order to assess M1 plasticity, 15 MEPs evoked by single-pulse TMS at an intensity of 1mV MEP were recorded before (T0) and 5 (T1), 15 (T2) and 30 minutes (T3) after iTBS.

Statistical analysis

Differences in age and clinical scores between AD patients and HC were evaluated by using the Mann-Whitney U test. Gender differences between patients and HC were evaluated by using the Fisher-exact test.

Group comparisons on kinematic variables and motor thresholds between groups were performed using two-tailed unpaired t-tests. Possible differences in the I/O curve were assessed by means of a repeated-measures analysis of variance (rmANOVA) with the between-group factor 'GROUP' (2 levels: AD, HC) and the within-group factor 'STIMULUS INTENSITY' (6 levels: 80%, 100%, 120%, 140% 160% and 180% RMT). A rmANOVA with factors 'GROUP' and 'ISI' (2 levels: 2 and 4 ms) was used to evaluate SICI. The same analysis with factors 'GROUP' and 'ISI' (2 levels: 22 and 24 ms) was adopted to compare SAI in patients and HC. When evaluating the effects of iTBS, we used the factor 'TIME POINT' (4 levels: T0, T1, T2 and T3) on raw MEP data (peak-to-peak amplitude) in HC and AD to demonstrate the effectiveness of this intervention. A rmANOVA with factors 'GROUP' and 'TIME POINT' (3 levels: T1, T2 and T3) was conducted on data recorded at T1, T2 and T3, normalized to T0.

Pearson's coefficient was calculated to evaluate possible correlations between kinematic and TMS measures. For this purpose, we computed the steepness of the I/O MEP curve (i.e. the slope of the regression line across the scatter plot of the MEP amplitude – Y axis vs. the stimulation intensity - X axis) and the average SICI and SAI for the two ISIs tested as well as any changes in MEP amplitude after iTBS across the three measurement time points (T1, T2 and T3).The possible relationship between cognitive data (i.e. MMSE, FAB scores), UPDRS part III scores and neurophysiological measures (kinematic and TMS parameters) in AD patients were tested by using Spearman's rank correlation coefficient.

Unless otherwise stated, the results are indicated as mean values ± 1 standard error of the mean. Tukey's honestly significant difference was used for post-hoc analyses in ANOVAs. Greenhouse-Geisser corrections were applied whenever we found a violation of sphericity in Mauchly's tests. The level of significance was initially set at $P<0.05$. The results of

multiple correlations were Bonferroni corrected. The results that did not survive Bonferroni's correction were considered as a trend. Data were analyzed using STATISTICA® (StatSoft, Inc).

3.2.4 Results

All the study participants completed the experimental procedure, and none reported any adverse effects. No difference was found in age (P=0.12), gender distribution (P=0.10) or BDI-II scores (P=0.34) between AD patients and HC. As expected, the MMSE and FAB scores were significantly lower in AD patients than in HC (MMSE: 19.8 ± 3.6 vs. 28.4 ± 1.5, P<0.001; FAB: 10.3 ± 4.1 vs. 16.3 ± 2.0, P<0.001).

Finger tapping kinematics

Finger tapping kinematic parameters are shown in Fig. 3. The analysis revealed lower values for movement velocity (P=0.01) in patients than in HC, and higher values for CV in patients than in HC (P=0.03). No significant difference emerged between patients and HC in the number of movements (P=0.09), movement amplitude (P=0.13), amplitude slope (P=0.99) or velocity slope (P=0.52).

TMS measures

Corticospinal excitability: motor thresholds and I/O curve

Motor thresholds were comparable in patients and HC [RMT (AD: 48.6 ± 6.4 vs HC: 47.7 ± 7.3, P=0.69), AMT (AD: 38.5 ± 5.9vs HC: 38.7 ± 4.0, P=0.86), 1mV MEP (AD: 71.1 ± 14.9vs HC: 67.2 ± 17.2, P=0.45)]. The I/O curve was also similar in the two groups, as demonstrated by the non-significant effect of the main factor 'GROUP' ($F_{1,38}$=1.75, P=0.19) and the lack of any 'GROUP' x 'STIMULUS INTENSITY' interaction ($F_{5,190}$=1.17, P=0.33) in the rmANOVA. As expected, the main factor 'STIMULUS INTENSITY' was significant ($F_{5,190}$=70.58, P<0.001), which indicates that an increasing TMS stimulation intensity induces a larger MEP amplitude (Fig. 4, panel A).

Intracortical excitability: SICI and SAI

When SICI was analyzed, the rmANOVA revealed a significant effect of the main factors 'GROUP' ($F_{1,38}$=5.81, P=0.02), with less inhibition in AD than in HC, and 'ISI' ($F_{1,38}$=24.38, P<0.001), for which inhibition was more effective at 2 ms than at 4 ms. The 'GROUP' x 'ISI' interaction was not significant ($F_{1,38}$=0.27, P=0.60). When SAI was analyzed, the rmANOVA disclosed a significant effect of the main factor 'GROUP' ($F_{1,38}$=4.56, P=0.03), with higher values (i.e. less inhibition) being detected in patients than in HC. The effect of the main factor 'ISI' was not significant ($F_{1,38}$=3.28, P=0.08), suggesting comparable SAI values at ISIs of 22 and 24 ms, nor was any 'GROUP' x 'ISI' interaction detected ($F_{1,38}$=3.22, P=0.08). Differences in SICI and SAI between AD patients and HC are shown in Fig. 4, panel B.

M1 plasticity: iTBS after-effects

The analysis of the raw data indicated that MEP increased after iTBS in HC (factor 'TIME POINT': $F_{3,57}$=9.42, P<0.001) but not in AD (factor 'TIME POINT': $F_{3,57}$=1.70, P=0.17). The post-hoc analysis in HC suggested that MEP facilitation was present at T2 (T0 vs T2: P<0.001) and T3 (T0 vs T3: P=0.01), though not at T1 (T0 vs T1: P=0.13). When the effect of iTBS was compared in patients and HC, the rmANOVA disclosed a significant effect of the main factor 'GROUP' ($F_{1,38}$=5.60, P=0.02), with lower values being observed in AD patients than in HC. As expected, the factor 'TIME POINT' was significant ($F_{2,76}$=5.37, P=0.01), thereby confirming the presence of a peak of MEP facilitation at T2. There was no 'GROUP' x 'TIME POINT' interaction ($F_{2,76}$=2.97, P=0.06) (Fig. 4, panel C).

Correlation analysis

Neurophysiological (i.e. kinematic and TMS parameters) correlations demonstrated a negative relationship between movement velocity and SAI in patients with AD (r= -0.58, P=0.008; Fig. 5, panel A). The lower the velocity, the higher (i.e. the less effective) the SAI. When the clinical scores were considered, the analysis detected a negative correlation between the rhythm of movement (CV) and FAB scores (r= -0.59, P=0.006; Fig. 5, panel B). The relationships suggest that the higher the CV (i.e. less rhythmic movement), the lower the FAB scores (i.e. greater cognitive impairment). No other neurophysiological or clinical-neurophysiological correlations were observed (see Tables 10, 11 and 12). Finally, we found no significant correlations between kinematic parameters or neurophysiological measures and UPDRS part III scores (R values ranging from -0.02 to 0.29; Ps ranging from 0.21 to 0.97).

3.2.5 Discussion

Two novel aspects emerge from this study. First, we provide a neurophysiological characterization demonstrating that voluntary movement velocity and rhythm in AD are abnormal and that M1 excitability and plasticity are altered in this condition. Second, we performed a correlation analysis between altered movement kinematics, M1 neurophysiological abnormalities and clinical scores in AD. We found that movement slowness correlated with reduced SAI, thus supporting the hypothesis that AD-mediated cholinergic degeneration may account not only for cognitive disturbances but also for motor impairment in this condition. Finally, we found a correlation between altered rhythm and FAB scores.

Neurophysiological abnormalities

We found that the velocity of repetitive finger movements was lower in patients than in healthy subjects and that the movement rhythm was altered. By providing more objective results, our kinematic analysis of repetitive finger movements in AD extends previous clinical observations on movement impairment in these patients (Tsolaki *et al.*, 2001; Scarmeas *et al.*, 2004, 2005; Schirinzi *et al.*, 2018; Vöglein *et al.*, 2019).Our results are also broadly in line with those of other neurophysiological investigations in which a quantitative finger movement analysis was performed in AD patients (Roalf *et al.*, 2018; Suzumura *et al.*, 2018). Although a full kinematic analysis was not performed in these studies (Roalf *et al.*, 2018; Suzumura *et al.*, 2018), the authors did quantify the number and the variability of finger movements in patients with AD, observing a certain degree of motor dysfunction. Roalf et al. reported a reduced number of taps, a longer inter-tap

interval and higher intra-individual variability compared with healthy controls (Roalf *et al.*, 2018), while Suzumura et al. detected abnormalities in movement rhythm when they assessed finger dexterity (Suzumura *et al.*, 2018). The analysis we performed here of repetitive finger tapping, i.e. the most widely used maneuver to assess bradykinesia in the clinical setting, did not disclose any significant reduction in amplitude (hypokinesia) or any significant decrease in movement amplitude and velocity during finger tapping repetition (sequence effect). Notably, hypokinesia and the sequence effect are both prominent bradykinesia features in Parkinson's disease (PD) (Espay *et al.*, 2011, Postuma *et al.*, 2015*b*, Bologna *et al.*, 2016*a*, 2018). The conclusion that we may draw from these findings is that bradykinesia features in AD, and their underlying pathophysiological mechanisms, differ from those observed in PD.

When we assessed the TMS parameters of M1, we did not find any differences in motor thresholds or in the MEP I/O curve between AD and healthy subjects, which points to a similar level of excitability in these two groups. Previous observations in the literature have not reported changes in the overall M1 excitability in AD either (Di Lazzaro *et al.*, 2002; Inghilleri *et al.*, 2006; Nardone *et al.*, 2014). Here we observed that SICI, a neurophysiological measure reflecting GABA-A-ergic intracortical inhibition (Berardelli *et al.*, 2008; Ferreri *et al.*, 2011), was less effective in patients than in controls. A significant reduction in SICI has been often described in previous reports although other studies did not find any significant difference in SICI between patients with AD and healthy subjects (Nardone *et al.*, 2014). While these discrepancies in SICI may be due to the variable nature of this parameter, which may be significantly affected by methodological factors (Orth *et al.*, 2003), they may also reflect the considerable clinical heterogeneity of AD. As expected, we found a significant decrease in SAI in AD than in healthy controls (Di Lazzaro *et al.*, 2002, 2004; Cantone *et al.*, 2014; Nardone *et al.*, 2014; Di Lorenzo *et al.*,

2016; Benussi *et al.*, 2017). Because SAI is a well-known indicator of M1 cholinergic neurotransmission (Tokimura *et al.*, 2000; Di Lazzaro *et al.*, 2002; Ferreri *et al.*, 2012, p. 20), SAI reduction in AD is supportive of the hypothesis of cortical cholinergic dysfunction in this condition (Cantone *et al.*, 2014; Scheltens *et al.*, 2016; Schirinzi *et al.*, 2018). Finally, as previously demonstrated in neurophysiological studies in humans and animals (Battaglia *et al.*, 2007), we found the lack of M1 LTP-like plasticity in patients, which confirms the abnormal responses to rTMS (Inghilleri *et al.*, 2006; Nardone *et al.*, 2014; Di Lorenzo *et al.*, 2016, 2019) and to paired associative stimulation observed in previous studies (Battaglia *et al.*, 2007; Terranova *et al.*, 2013).Taken together, these findings support the hypothesis that the disruption of LTP-like plasticity may be considered a pathophysiological mechanism in AD.

Correlations between neurophysiological abnormalities as well as with clinical scores

To our knowledge, no prior study has investigated the relationship between movement kinematics and neurophysiological abnormalities, as assessed by TMS, in AD. Here we demonstrate a linear correlation between movement velocity and SAI in patients. That is, the slower the voluntary movements, the less effective the SAI. In keeping with previous studies (Terranova *et al.*, 2013; Di Lorenzo *et al.*, 2016), we did not observe any correlation between SAI abnormalities and cognitive scores assessed by MMSE and FAB. We may thus rule out that the association between movement velocity and SAI is an unspecific finding ascribable to cognitive impairment. Moreover, despite changes in their cognitive performance, all the patients were able to understand the instructions of the motor task. Thus, our observations indirectly indicate that changes in cholinergic interneurons excitability do alter the corticospinal encoding of a specific movement

parameter, i.e. movement velocity. In this case, as the cortical cholinergic tone decreases, movement slowness develops and gradually deteriorates. It has recently been demonstrated that parkinsonian signs, as quantified by UPDRS (part III), in patients with AD correlate directly with Aβ42 levels (but not with t-tau and p-tau) in cerebrospinal fluid as well as with a reduced SAI (Schirinzi *et al.*, 2018). Thus, together with previous clinical observations, our results support the hypothesis of a possible association between movement abnormalities and amyloid-mediated degeneration of the cholinergic system. The data observed in AD also support the hypothesis that the cholinergic system is one key factor involved in motor behavior (MacLaren *et al.*, 2014; Takakusaki *et al.*, 2016). Hence, the cholinergic deficit in AD may be associated with various motor disorders, including slowed movement of the upper limbs in either the early or intermediate disease stages. An alternative hypothesis is that bradykinesia in AD is related to dopaminergic pathway abnormalities. Several studies have reported dopaminergic alterations in this condition, including dopaminergic neuron loss and reduced levels of dopamine in the ventral tegmental area, which projects to various cortical regions, including the prefrontal cortices (Nobili *et al.*, 2017; Krashia *et al.*, 2019). Accordingly, movement slowness in AD may be due not only to a central cholinergic deficit but also to the coexisting dopaminergic deficit, as well as to the abnormal interplay between these two neurotransmitter systems. This hypothesis is supported by the well-known existence of relationships between cholinergic and dopaminergic systems in both AD and PD. For example, changes of SAI in PD parallel the degree of motor impairment, indirectly reflecting dopaminergic loss in this condition (Dubbioso *et al.*, 2019). Notably, however, the dopaminergic neurons of the substantia nigra pars-compacta are intact in AD (Nobili *et al.*, 2017). The lack of changes in the nigrostriatal pathway in the latter condition may explain the difference between bradykinesia features in AD and PD.

Another prominent movement abnormality we found in AD is altered rhythm. Interestingly, we found a negative correlation between altered movement rhythm and frontal dysfunction, as assessed by FAB. The higher the movement irregularity (i.e. higher CV values), the lower the clinical scores obtained in FAB. The ability to perform rhythmic voluntary movements involves an extensive network that includes both the cortical and subcortical motor systems. In this study, we tested internally triggered voluntary movements. These are generated by specific brain networks (Jahanshahi *et al.*, 1995; Gerloff *et al.*, 1998) involving frontal areas, particularly the anterior cingulate cortex, whose role in planning and executing motor sequences has previously been thoroughly investigated (Blanchard and Hayden, 2014). Thus, the relationship between altered movement rhythm and frontal impairment in AD may suggest that the dysfunction in these specific areas contributes to attentive and executive deficits, which, in turn, interfere with the ability to perform rhythmic voluntary movements. The hypothesis that movement rhythm abnormality is not only due to M1 dysfunction is further supported by the lack of correlation between CV and TMS measures of M1 excitability and plasticity in AD. Finally, in keeping with the findings of a previous study that reported an association between abnormal finger dexterity and cognitive scores (Suzumura *et al.*, 2018), we observed a trend for a negative correlation between MMSE scores and movement rhythm. Taken as a whole, these findings further suggest that objective movement analysis may be used as a surrogate marker for cognitive dysfunction in AD. This observation needs, however, further confirmation in longitudinal studies.

Study limitations

The present study has some limitations that warrant mentioning. Firstly, we did not use a neuro-navigation system for the TMS procedures. It should be also borne in mind that this study was performed on a sample of patients with a clinical diagnosis of AD without biomarker assessment, thus implying the risk of misdiagnosis with other neurodegenerative conditions characterized by dementia and parkinsonism (e.g. dementia with Lewy bodies). Since M1 excitability deteriorates as the disease progresses (Ferreri *et al.*, 2011; Trebbastoni *et al.*, 2015), we cannot assume that the relationships we observed also characterize the more advanced disease stages. Further studies on patients in different stages of AD, and longitudinal studies on patients with mild cognitive impairment, are needed to investigate intra-individual correlations. Moreover, numerous observations suggest that altered excitability and plasticity parameters may be a common pathophysiological findings in other dementias (Cantone *et al.*, 2014; Benussi *et al.*, 2017). Whether such abnormalities in other diseases affect voluntary movement as in AD is an area of research that needs to be investigated further. A final comment concerns the lack of correlations between kinematic parameters or neurophysiological measures and UPDRS part III score. This finding is likely explained by the fact that UPDRS part III scores is a proxy of motor impairment and moreover it includes items that are not solely related to upper limb bradykinesia.

In conclusion, the relationship between neurophysiological abnormalities suggests that a cortical cholinergic deficit may underlie movement slowness in AD. The correlation analysis between clinical and kinematic abnormalities points to a frontal dysfunction that is involved in altered movement rhythm in AD. Besides providing a neurophysiological insight into motor impairment in AD, the results of our study may help in a better understanding of bradykinesia in neurological conditions (Tsolaki *et al.*, 2001; Scarmeas *et al.*, 2004, 2005, Bologna *et al.*, 2017*b*; Vöglein *et al.*, 2019). Notably, in our study we

referred to bradykinesia considering its simplest etymological meaning, that is movement slowness (Bologna *et al.*, 2019*b*). According to the current clinical definition (Postuma *et al.*, 2015*b*), bradykinesia in PD refers to slowness of movement and decrement in amplitude or speed as movements are continued (sequence effect). The present study demonstrates that the features of bradykinesia in AD are different from those observed in PD and that these differences likely reflect specific pathophysiological mechanisms in each condition. The results of this study may be helpful in reaching a more accurate definition of bradykinesia in both parkinsonian and non-parkinsonian conditions.

3.3 STUDY 3: KINEMATIC ASSESSMENT OF BRADYKINESIA IN PATIENTS WITH AMYOTROPHICA LATERAL SCLEROSIS

3.3.1 Abstact

Amyotrophic lateral sclerosis is primarily characterized by a progressive degeneration of motor neurons, leading to muscle weakness and motor impairment. There are some clinical reports of bradykinesia in this condition, but no studies have objectively assessed the movement abnormalities in these patients. Moreover, the relationship between motor neurons involvement and movement abnormalities in this condition is largely unknown. Here, we aimed to kinematically assess abnormalities of repetitive upper limbs movements in patients with amyotrophic lateral sclerosis compared to healthy controls. We also investigate possible relationships between altered movement kinematics and neurophysiological measures of motor neurons involvement in patients with amyotrophic lateral sclerosis. Thirteen patients with a diagnosis of amyotrophic lateral sclerosis and thirteen healthy controls were enrolled. Repetitive finger tapping was assessed by means of a motion analysis system. Patients also underwent to a motor nerve conduction study, a needle electromyography and a central motor conduction time assessment. The kinematic variables from the two groups were compared by unpaired t-tests. Possible relationships between clinical, kinematic and neurophysiological data were assessed in patients with amyotrophic lateral sclerosis. Patients with amyotrophic lateral sclerosis performed less movements and they were slower than healthy controls. Patients also showed an altered movement rhythm. The number of movements correlated with the amplitude of the compound muscle action potential recorded from the first dorsal interosseus and the abductor pollicis brevis muscles in patients. Also, the number of movements as well as the

altered rhythm it negatively correlted with the denervation activity recorded form the first dorsal interosseus muscle. This study provides new information on the evidence of bradykinesia in amyotrophic lateral sclerosis, characterized by movement slowness and altered movement rhythm without decrement. In amyotrophic lateral sclerosis movement slowness likely depends on the lower motor neurons involvement.

3.3.2 Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurological disorder characterized by degeneration of both upper motor neurons (UMNs) and lower motor neurons (LMNs) leading to severe muscle weakness and progressive motor impairment (Brooks *et al.*, 2000; de Carvalho *et al.*, 2008; Inghilleri and Iacovelli, 2011). Several clinical reports have emphasised the presence of bradykinesia, rigidity and other parkinsonian signs associated with sporadic ALS (Williams *et al.*, 1995*b*; Qureshi *et al.*, 1996; Desai and Swash, 1999; D'Ascenzo *et al.*, 2012; Pupillo *et al.*, 2015), although the pathophysiological basis of parkinsonian signs in patients with ALS are still unclear. In this regard, D'Ascenzo et al. described mild to severe bradykinesia in 16 ALS patients but did not find any correlation between bradykinesia and the altered striatal (123)I-FP-CIT uptake, concluding that movement slowness and postural instability noted in these patients could be mostly attributed to spasticity and not to nigrostriatal impairment on DaTSCAN (D'Ascenzo *et al.*, 2012).

Differently form clinical observations, there are only a few neurophysiological studies on patients with ALS. Earlier observations demonstrated that ALS patients showed prolonged muscles bursts during ballistic elbow movements (Hallett, 1979). More recent studies

kinematically assessed the reachable workspace, as a surrogate measure of altered arm function in patients with ALS (Oskarsson *et al.*, 2016; de Bie *et al.*, 2017). Most of the other neurophysiological studies assessed lip and tongue movements during speech (Shellikeri *et al.*, 2016; Kuruvilla-Dugdale and Chuquilin-Arista, 2017) and none of these neurophysiological studies have systematically assessed the movement kinematics of the upper limbs in patients with ALS. Moreover, no study has yet clearly established a possible relationship between UMNs and LMNs involvement, assessed by means standard neurophysiological examination, and the motor impairment, including the possible occurrence of bradykinesia as objectively analyzed by means of kinematic techniques. Here we aim to objectively describe the abnormalities of repetitive movements in patients with ALS. We selected repetitive upper limbs movement because are the most useful task for detecting bradykinesia in parkinsonian syndromes (Berardelli *et al.*, 2001, Postuma *et al.*, 2015*a*, Bologna *et al.*, 2019*b*). We also investigated possible relationships between altered movement kinematics and clinical and neurophysiological measures of UMNs and LMNs involvement. The results of the present study may help in the understanding the pathophysiology of upper limbs motor abnormalities in patients with ALS. Finally, our results may be interpreted for a better definition of bradykinesia in non parkinsonian conditions.

3.3.3 Materials and Methods

Participants

Thirteen patients with ALS (7 males, mean age ± 1 standard deviation (SD): 66.3 ± 9.04 years) and thirteen healthy controls (HCs) (6 males, mean age: 62.07 ± 5.76 years) were enrolled in the study (Table 13). All participants were older than 18 years. All of them were right-handed, as evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971). Patients were diagnosed with definite, probable or probable- laboratory supported ALS according to the El Escorial (EE) diagnostic classification (Brooks *et al.*, 2000) and to the recent supplementary electrophysiological criteria (de Carvalho *et al.*, 2008). None of the patients presented a diagnosis of neuromuscular junction disorders, myopathies, neuropathies, primary lateral sclerosis, flail arm syndrome, spinal bulbar muscular atrophy and other neurological conditions. All patients underwent brain magnetic resonance imaging and laboratory screening to rule out any potential confounding factor. Treatment with drugs potentially influencing neural activity, including Riluzole, was discontinued at least 72 h prior to the evaluation. A structured questionnaire was administered to participants, including the date of birth, gender, years of education, family history of any neurodegenerative disease, site of disease onset (spinal or bulbar), disease duration, slow vital capacity (SVC). Patients were also evaluated using the ALS Functional Rating Scale-Revised (ALSFRS-R) (Cedarbaum *et al.*, 1999) and the Medical Research Council (MRC) scale for strenght. Their flexors digitorum strength were also evaluated through a dynamometer. Clinical evaluation in participants also included the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) (motor section) (Goetz *et al.*, 2008; Antonini *et al.*, 2013) to assess any possible clinical evidence of bradykinesia. Finally, participants were tested for cognitive impairment using the Montreal Cognitive Assessment (MoCA) (Nasreddine *et al.*, 2005) and the Frontal Assessment Battery (FAB) (Dubois *et al.*, 2000). The Beck Depression Inventory (BDI-II) was also administered (Beck *et al.*, 1961). Finally, the Fatigue Severity

Scale (FSS) was performed in participants (Krupp *et al.*, 1989). The study conformed to the Declaration of Helsinki and international safety guidelines and was approved by the local ethics committee. All subjects provided written informed consent for their participation in the study.

Neurophysiological evaluation

The neurophysiological assessment was performed by an experienced EMG technologist blinded to the results of the other measures of interest. It included a routine motor nerve conduction study of bilateral median and ulnar nerves (measurements of compound muscle action potential - CMAP recorded using pairs of surface electrodes, with recording electrode placing on the belly of muscles while reference electrode on the distal tendon). The peak-to-peak amplitudes of CMAPs were documented with supramaximal electric stimuli of ulnar (with registration both from abductor digiti minimi -ADM- and FDI) and median nerves (with registration from abductor pollicis brevis –APB). A needle EMG was performed from FDIs and the number of fibrillating points on ten were semi-quantitively assessed. The central motor conduction time (CMCT) was assessed wit transcranial magnetic stimulation (TMS) by subtracting the latency of the response after cervical stimulation from the total latency of the response elicited stimulating the motor cortex in the hotspot for FDIs with an eight-shaped coil. The magnetic coil for the root stimulation was placed over D1 (Groppa *et al.*, 2012).

Kinematic assessment of upper limbs movement

Finger tapping movements were kinematically recorded from both hand using an optoelectronic system (SMART motion system, BTS Technology, Italy). Subjects sat comfortably on a chair and were asked to tap their index finger repetitively on their thumb as widely and quickly as possible for 15 s (Bologna *et al.*, 2016*a*, 2018). Three finger-tapping trials were recorded (plus one practice trial before kinematic recording began in order to familiarize participants with the motor task). A 60-s rest interval was let between trials to avoid fatigue. Three infrared cameras (sampling rate of 120 Hz) followed the displacement of reflective markers of negligible weight and a 5-mm diameter taped to the participant's upper limb. Two markers were placed on the tips of the index finger and thumb. Three other markers attached to the hand (one on the head of the 2nd metacarpal bone, one on the base of the 2nd metacarpal bone, and one on the base of the 5th metacarpal bone) were used to define a reference plane and mathematically exclude possible interference of undesired hand movements during finger-tapping recordings (Bologna *et al.*, 2016*a*, 2018). Movement analysis was performed using specialized software (SMART Analyzer, BTS Engineering, Italy). The average of the three finger tapping trials were included in the analysis. Linear regression techniques to determine the intercept reflecting movement amplitude (degree) and velocity (degree/s) were used to quantify repetitive finger movement kinematics, as well as the slope representing amplitude and velocity decrement during movement repetition. We also used the coefficient of variation (CV), as calculated by SD/mean value of the intertap intervals, to measure movement rhythm, with higher values indicating lower repetitive movement regularity (the higher the CV value, the less rhythmic the movement performed) (Bologna *et al.*, 2016*a*, 2018). The average between the two sides (right and left) were considered for each kinematic value.

Statistical analysis

The Mann-Whitney U test was used to evaluate possible differences in age and MoCA, FAB, and UPDRS-III scores between ALS patients and HCs, while Fisher's exact test was applied to evaluate possible differences in gender distribution between groups. Unpaired t tests were used to compare kinematic variables between ALS and HCS. Pearson's coefficient was used to test possible correlations between kinematic and neurophysiological measures, whereas Spearman's rank correlation coefficient was adopted to verify possible relationships between patient clinical data and neurophysiological measures (kinematic and neurophysiological parameters). Unless otherwise stated, results are presented as mean values ± 1 standard error of the mean. The level of significance was set at $p<0.05$ with the false discovery rate (FDR) subsequently being applied to multiple comparisons (Curran-Everett, 2000). Data were analyzed using STATISTICA (TIBCO Software Inc., Palo Alto, California, US).

3.3.4 Results

Clinical and demographic data

All participants completed the study. Age ($p=0.1824$), gender distribution ($p=0.6949$) and FAB scores (0.5215) did not differ between ALS patients and HCs. MOCA scores were lower in patients than in HCs (mean ± SD in ALS: 25.28 ± 2.56; HCs: 27.58 ± 1.30, $p=0.011$). Conversely, BDI score were higher in ALS than in HCs (mean ± SD in ALS: 12.53 ± 9.92; HCs: 5.46 ± 4.82, $p=0.025$), as well as the scores obtained at the FSS (mean

± SD in ALS: 34.42 ± 9.73; HCs: 22.22 ± 10.01, p=0.003). The mean ± SD of UPDRS-III in ALS was: 19.53 ± 15.09 (Table 13). This was due to the presence of speech disturbances, slight movement slowness of the upper and/or limbs, gate disorders. Notably, none of the patients satisfied the criteria for parkinsonism (Postuma *et al.*, 2015*a*).

Neurophysiological data

The mean ± SD of flexors digitorum strength measured by the dynamometer was 15.18 ± 5.92 Kg in the right side and 17.18 ± 8.74 Kg in the left side. The CMAP amplitude recorded from the right FDI was 7.56 ± 5.52 mV; the CMAP amplitude recorded from the left FDI in patients was 9.75 ± 5.79 mV. The CMAP amplitude recorded from the right APB was 4.3 ± 5.42 mV; the CMAP amplitude recorded from the left APB in patients was 6.11 ± 6.31 mV. The CMCT was 8.19 ± 3.08 ms (with the right FDI as hot-spot) and 7.67 ± 3.17 ms (with the left FDI as hot-spot). The denervation at the EMG was 4.91 ± 2.27 in the right FDI and 4.54 ± 3.32 in the left FDI.

Movement kinematics

The analysis demonstrated altered movement features in patients with ALS patients compared to HCs. The number of movements performed by patients during the 15s tapping trials was significantly lower than HCs (ALS patients: 31.75 ± 15.05; HCs: 61.25± 10.18, $p<0.001$) as well as the velocity peak reached by patients (ALS patients: 650.43 ± 251.42 degrees/s, HCs: 1016.34 ± 212.84 degrees/s, $p<0.001$). Notably, higher CV values with respect to HCs were observed in patients (aMCI patients: 0.12 ± 0.048; HCs: 0.085 ±

0.022, p=0.036), representing an altered movement rhythm in ALS. In contrast, movement amplitude (ALS patients: 46.12 ± 15.01 degrees, HCs: 46.82 degrees ± 9.21, p=0.88), amplitude decrement (ALS patients: -0.43 ± 0.66 degrees/n mov; HCs: -0.12 ± 0.17 degrees/n mov, p=0.12) and velocity decrement (ALS patients: 4.11 ± 3.60 (degrees/s)/n mov, HCs: 4.76 ± 3.28 (degrees/s)/n mov, p=0.63) were all similar between ALS patients and HCs (Fig. 6).

Correlation analysis

The correlation analysis between clinical and neurophysiological data showed that the number of movements during the 15s finger tapping and the movement velocity significantly correlated with the MRC scale for the inch opposition (R= 0.61, p=0.038 for the number of movement; R= 0.78, p=0.02 for the velocity peak) (Fig. 7). The correlation analysis between kinematic and neurophysiological data showed that in patients the number of movements during the 15s finger tapping significantly correlated with the amplitude of the CMAP recorded form the FDI (R= 0.62, p=0.028) and with the amplitude of the CMAP recorded form the APB (R= 0.62, p=0.029). Conversely, an inverse correlation was found between the total number of movements and the grade of denervation from FDI (R= -0.64, p<0.024) (Fig. 8). Finally, the CV correlated to the grade of denervation in FDI (R= 0.77, p=0.003). Notably, no correlation were found between kinematic data and neurophysiological measures from the ADM, i.e. a muscle not specifically involved in the finger tapping task.

3.3.5 Discussion

In the present study, we investigated voluntary movement execution in patients with ALS through the kinematic analysis of repetitive finger tapping. We also tested whether movement abnormalities correlated with clinical and neurophysiological measures of UMNs and LMNs impairment. We found that finger tapping in ALS was characterized by slowness of movements and altered rhythm as compared to HCs. Movement slowness correlated with the amplitude of the CMAP recorded from the muscles involved in the task, and it also negatively correlated with the denervation in the FDI. Also, altered rhythm correlated with the denervation in the FDI. Our results provide novel evidence of bradykinesia in ALS and give an insight into its possible pathophysiological mechanisms, indicating that it is possibly related with the LMNs involvement. Our data may be interpreted in the context of the terminological controversies on the use of bradykinesia in non-parkinsonian conditions.

We exclude the possibility that the differences in kinematic features of finger tapping between patients and HCs were due to differences in the demographic features of the two groups because they were well matched in terms of age and gender ratio. All patients had a diagnosis of definite, probable or probable- laboratory supported ALS according to the current criteria (Brooks *et al.*, 2000), thus excluding a possible biases in the recruitment. Finally, we tested patients after the withdrawal of drugs potentially influencing the central nervous system activity, thus excluding this confounding factor.

The observation of bradykinesia, in addition to muscle weakness and motor impairment in ALS, is in line with previous studies. Clinical case reports and case series underlined the presence of parkinsonian signs in sporadic motor neuron disease patients, which some authors referred to as hypokinesia, meaning reduced movement (Desai and Swash, 1999), others as bradykinesia, thus indicating slowness of movement in ALS (Williams *et al.*, 1995*a*; Qureshi *et al.*, 1996; D'Ascenzo *et al.*, 2012; Pupillo *et al.*, 2015). A limited

number of studies, however, investigated bradykinesia in ALS trough neurophysiological techniques, providing an insight into bradykinesia features in ALS. The EMG recording of rapid elbow movements in ALS showed a prolongation in the first agonist and antagonist bursts (Hallett, 1979). Latest studies mainly focused on lip and tongue movements during speech (Shellikeri *et al.*, 2016; Kuruvilla-Dugdale and Chuquilin-Arista, 2017) and only few of them assessed the upper limb motor impairment through the evaluation of the reachable workspace (Oskarsson *et al.*, 2016; de Bie *et al.*, 2017). Notably, none of the previous studies investigated the bradykinesia features in ALS using the assessment of repetitive finger movements, which represent the most useful task for the evaluation of bradykinesia in parkinsonian conditions, nor of them investigated the correlation between bradykinesia and motoneurons involvement. Here we found specific kinematic abnormalities of finger tapping in ALS. These included movement slowness and altered rhythm and thus differ from the kinematic features previously observed in PD (Agostino *et al.*, 1992, 2003, Bologna *et al.*, 2016*a*, 2018), i.e. sequence effect, i.e. the progressive reduction in amplitude and speed during movement repetition. Interesting, the reduced velocity and altered rhythm observed in ALS patients likely resemble the kinematic features of bradykinesia in AD (See Study 2). In AD patients, however, the altered rhythm correlated with abnormal FAB scores, indicating a possible relationship between voluntary movement abnormalities and frontal lobe dysfunction (Dubois *et al.*, 2000; Kume *et al.*, 2011). In our ALS sample, FAB scores were normal and no correlations were found between them and kinematic data.

We here observed a correlation between movement slowness and altered rhythm (i.e. number of movement and CV) and measures of LMN functionality (i.e. amplitude of the CMAP recorded from the muscles involved in the task and denervation from the FDI). Conversely, there was not relationships between motor abnormalities and measures of

UMN involvement. i.e. CMCT, nor correlation between kinematic and neurophysiological data recorded from a control muscle, i.e. ADM.

Overall, our observations may help in the understanding of the pathophysiology of parkinsonian signs in patients with ALS, which is still unclear. Some authors stated that movement slowness may be a compensation to the muscle weakness able to generate sufficient forces to accomplish the movements (Hallett, 1979). Another hypothesis is that bradykinesia in ALS may depend on the involvement of M1. In this regard, several studies have demonstrated that one of the hypothesized pathogenetic mechanisms of ALS is glutamate-driven excitotoxicity in M1 (Zanette *et al.*, 2002). Moreover, sensory-motor networks are demonstrated to be impaired in SOD1 ALS mice, which exhibit specific delays in acquiring sensory-motor skills even during the first week after birth (Durand *et al.*, 2006), and also in humans (Ceccanti *et al.*, 2018). Finally, taking in consideration the role of basal ganglia in generating bradykinesia in PD (Berardelli *et al.*, 2001, Bologna *et al.*, 2019*b*), abnormalities in the basal ganglia motor loops may be considered as playing a key role in bradykinesia in ALS. Supporting the latter hypothesis, some genetic models of ALS share with parkinsonisms the same gene mutation. One example above all is the mutation of C9ORF72, the most frequent reason for familiar ALS, which presents expanded triplets also in some typical and atypical parkinsonisms (Bourinaris and Houlden, 2018; Cali *et al.*, 2019). Other examples are provided by TARDBP (Cannas *et al.*, 2013; Khani *et al.*, 2019), TBK1 (Van Mossevelde *et al.*, 2016; Oakes *et al.*, 2017), FUS (Wharton *et al.*, 2019). Also in the sporadic ALS patients, the involvement of basal ganglia at MRI images (Sharma *et al.*, 2019) and PET (Takahashi *et al.*, 1993) were demonstrated. Despite these evidence, however, D'Ascenzo et al. described mild to severe bradykinesia in 16 ALS patients but did not find any correlation between bradykinesia and the altered striatal (123)I-FP-CIT uptake, concluding that movement slowness and postural

instability noted in these patients could be mostly attributed to spasticity and not to nigrostriatal impairment on DaTSCAN (D'Ascenzo *et al.*, 2012). Accordingly, here we did not find the sequence effect in ALS, as opposed to PD, indicating that the defective basal ganglia function is not predominant in the genesis of voluntary movement abnormalities in ALS. Conversely, our results suggest that movement slowness in ALS is likely related to the involvement of the LMNs. Thus, the more the degeneration of the axonal fibers, the lower the number of movements and the velocity peak, and the higher the rhythm irregularity.

The differences in MOCA and BDI scores between ALS and HCs we observed in the present paper point out the possibility that that altered kinematics may be due to cognitive or psychiatric disturbances. The alterations of these function in ALS is in accordance to previous reports (Ohta *et al.*, 2017; Prell *et al.*, 2019; Zucchi *et al.*, 2019). Moreover, it is well known that the performance of the finger-tapping task as regularly and precisely as possible requires a high level of attention (Albert *et al.*, 2011; McLaughlin *et al.*, 2014; Kirova *et al.*, 2015) and that cognitive functions, e.g. memory (Rabinowitz and Lavner, 2014) may contribute to finger tapping alterations. In this regard, despite changes in their cognitive performance, all the patients were able to understand the instructions of the motor task. Moreover, the lack of correlation between cognitive and psychiatric scores and kinematic data makes unlikely that the finger tapping alterations were solely due to these cognitive/psychiatric factors.

Our study has some limitations that must be considered. First, the sample size is relatively small, although the objective techniques used to quantify finger tapping movements provided accurate and reproducible measurements of motor impairment (Heldman *et al.*, 2014). Secondly, we here did not investigate the nigrostriatal impairment through a

DaTSCAN in patients. In this regard, however, it should be noted that none of the patients satisfied the clinical criteria for parkinsonism (Postuma *et al.*, 2015*a*).

In conclusion, our study provides new information on fine voluntary movement impairment in ALS patients. We found movement slowness and altered movement rhythm in patients, possibly correlating with the LMNs denegeneration, and no sequence effect during the finger tapping. Future longitudinal studies combining kinematic methods with other neurophysiological measures should be assessed to confirm our results and to identify neurophysiological abnormalities possibly predicting the clinical course in ALS patients.

4. NETWORK PROSPECTIVE

The observation that movement slowness is present in neurological conditions markedly heterogeneous from a clinical and pathophysiological point of view, supports the hypothesis that movement slowness can be generated by the predominent pathophysiological involvement of different brain areas, although other specific mechanisms in each pathological condition may play a role. In this regard, it should be considered that there are close interconnections between the cortico-nucleobasal and cerebellum-thalamus-cortical systems as well as direct and reciprocal interconnections between the basal ganglia and the cerebellum. Again, basal ganglia, cerebellum and corticospinal system do not act independently of each other but on the contrary are closely interconnected. From a network perspective, it is possible that in each non-parkinsonian condition the pathophysiological involvement of a specific node, like basal ganglia, cerebellum or corticospinal system prevails, although others nodes in the network may still be relevant. The hypothesis of the network dynsfuntion in non-parkinsonian conditions is compatible with a similar model described for bradykinesia in PD and APs (Bologna *et al.*, 2019*b*). By assuming the hypothesis of a network dysfunction for bradykinesia in both parkinsonian and non-parkinsonian conditions it is therefore possible to hypothesize a unifying model. Accordingly, the differential kinematic features in a given condition likely depend on a different degree of involvement of each specific node of this same network. Consistently with this, for example, the sequence effect may lack in hyperkinetic movement disorders because the compensatory role played by the motor loops involving the M1 and the cerebellum is still effective (Bologna *et al.*, 2019*b*).

The network hypothesis would also explain why movement slowness is a common observation in patients with widespread disorders of the central nervous system. This is particularly the case in MS and AD, where delayed movement initiation and slowness of

voluntary movements execution may be due to various factors, i.e. impairment of specific central circuits resulting not only in the abnormalities of motor function, attentional and cognitive deficits as well as in delays in motor conduction time along the corticosopinal system. In this regard, movement slowness in patients with diffuse abnormalities of the central nervous system may be associated with white matter hyperintensities, lacunes, atrophy of the basal ganglia or global cerebral atrophy (Camarda *et al.*, 2019). Again, subtle extrapyramidal signs in AD correlated with amyloid-β 42 cerebrospinal fluid levels in this and basal ganglia amyloid-β deposition (Schirinzi *et al.*, 2018; Vöglein *et al.*, 2019). These findings also suggest an association between movement slowness and amyloid-mediated degeneration of the cholinergic system (Saunders *et al.*, 2015; Mori *et al.*, 2016). Also, the involvement of a complex network including frontal and prefrontal areas in MS and AD may explain abnormalities in performing internally generated movements, such us finger tapping, for which planning and execution these frontal areas are fundamental (Papa *et al.*, 1991; Jahanshahi *et al.*, 1995; Gerloff *et al.*, 1998).

5. TERMINOLOGICAL IMPLICATIONS

As previously mentioned, although movement slowness is a common movement abnormality in conditions not primarily characterized by parkinsonism, the phenomenon of the sequence effect has never been clinically or experimentally demonstrated in these studies. Through clinical interpretation, the term bradykinesia includes the progressive reduction (or gradual hesitations/halts) of repetitive and continuous movements (Postuma *et al.*, 2015*a*). The implication is that the term bradykinesia in conditions not primarily characterized by parkinsonism can only be considered appropriate when strictly related to its simplest etymological meaning, i.e. movement slowness. In contrast, the use of this term may be inappropriate if reference is made to the definition of bradykinesia in the

context of parkinsonism since in this context the term implies the presence of sequence effect. This issue requires further discussion in dedicated work.

6. GENERAL CONCLUSIONS

The present thesis demonstrates that movement slowness is a common motor abnormality in various neurological conditions not primarily characterized by parkinsonism. The most common feature described by clinical and neurophysiological studies is movement slowness without sequence effect during the repetition of movement. It should be acknowledged, however, that while the sequence effect has been broadly investigated in PD and parkinsonisms, but not in all the n-parkinsonian conditions. Moreover, there are some cases, for example in the latest staged of PD or in APs patients, where the sequence effect is also lacking (Ling *et al.*, 2012, Bologna *et al.*, 2016*a*). Following the clinical criteria, the term bradykinesia includes the progressive reduction (or gradual hesitations/halts) of repetitive and continuous movements. The implication is that the term bradykinesia in conditions not primarily characterized by parkinsonism can only be considered appropriate when strictly related to its simplest etymological meaning, i.e. movement slowness. In contrast, the use of this term may be inappropriate if reference is made to the definition of bradykinesia in the context of parkinsonism since in this context the term implies the presence of sequence effect.

The evidence of movement slowness in non parkinsonian conditions can be interpreted in different ways. On one hand, it may indicates that different brain areas, including the basal ganglia, cortical areas and the cerebellum, may in some way generate movement slowness. More likely, the observation of bradykinesia in non parkinsonian conditions supports the hypothesis that a brain network more than a single area is involved in generating bradykinesiain non-parkinsonian diseases and that the differential kinematic features

between conditions are a consequence of a different degree of involvement of specific nodes. Besides the pathophysiological implication, the present paper may help in drawing attention to important terminological issues and help to achieve a new, more accurate, and widely-shared definition of bradykinesia in the context of movement disorders and other neurological conditions. Notably, in none of the these non-parkinsonian conditions, whenever investigated, there is clinical evidence of the sequence effect, whih is instead an essential feature of bradykinesia in PD. Thus, there are two striking aspects resulting from the present review.The first striking aspect is that in the use of the term bradykinesia in non-parkinsonian conditions is questionable, since no reference is made to existing bradykinesia definitions. Another striking aspect of the present review is the occurrence of the same abnormality, i.e. slowness of voluntary movement, in markedly hetereogeneous conditions from clinical perspective with no common pathophysiological background, thus making it difficult the interpretation of the possible mechanisms underlying movement slowness.

7. REFERENCES

Abbruzzese G, Berardelli A. Sensorimotor integration in movement disorders. Mov Disord 2003; 18: 231–40.

Abbruzzese G, Buccolieri A, Marchese R, Trompetto C, Mandich P, Schieppati M. Intracortical inhibition and facilitation are abnormal in Huntington's disease: a paired magnetic stimulation study. Neurosci Lett 1997; 228: 87–90.

Aggarwal NT, Wilson RS, Beck TL, Bienias JL, Bennett DA. Motor Dysfunction in Mild Cognitive Impairment and the Risk of Incident Alzheimer Disease. Archives of Neurology 2006; 63: 1763.

Agostino R, Berardelli A, Formica A, Accornero N, Manfredi M. Sequential arm movements in patients with Parkinson's disease, Huntington's disease and dystonia. Brain 1992; 115 (Pt 5): 1481–95.

Agostino R, Currà A, Giovannelli M, Modugno N, Manfredi M, Berardelli A. Impairment of individual finger movements in Parkinson's disease. Mov Disord 2003; 18: 560–5.

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia 2011; 7: 270–9.

Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 1989; 12: 366–75.

Algarni M, Fasano A. The overlap between Essential tremor and Parkinson disease. Parkinsonism Relat Disord 2018; 46 Suppl 1: S101–4.

Andrich J, Saft C, Ostholt N, Müller T. Assessment of simple movements and progression of Huntington's disease. J Neurol Neurosurg Psychiatry 2007; 78: 405–7.

Angel RW. Electromyographic patterns during ballistic movement of normal and spastic limbs. Brain Res 1975; 99: 387–92.

Antonini A, Abbruzzese G, Ferini-Strambi L, Tilley B, Huang J, Stebbins GT, et al. Validation of the Italian version of the Movement Disorder Society--Unified Parkinson's Disease Rating Scale. Neurol Sci 2013; 34: 683–7.

Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, et al. Criteria for the diagnosis of corticobasal degeneration. Neurology 2013; 80: 496–503.

Avarello M, Bolsinger P, Mai N. Fast repetitive force changes in hemiparetic and cerebellar patients. Eur Arch Psychiatry Neurol Sci 1988; 237: 135–8.

Babij R, Lee M, Cortés E, Vonsattel J-PG, Faust PL, Louis ED. Purkinje cell axonal anatomy: quantifying morphometric changes in essential tremor versus control brains. Brain 2013; 136: 3051–61.

Balint B, Bhatia KP. Isolated and combined dystonia syndromes - an update on new genes and their phenotypes. Eur J Neurol 2015; 22: 610–7.

Barbey A, Aybek S. Functional movement disorders. Curr Opin Neurol 2017; 30: 427–34.

Bareš M, Husárová I, Lungu OV. Essential tremor, the cerebellum, and motor timing: towards integrating them into one complex entity. Tremor Other Hyperkinet Mov (N Y) 2012; 2

Barun B, Brinar VV, Zadro I, Lusić I, Radović D, Habek M. Parkinsonism and multiple sclerosis--is there association? Clin Neurol Neurosurg 2008; 110: 958–61.

Bastian AJ, Martin TA, Keating JG, Thach WT. Cerebellar ataxia: abnormal control of interaction torques across multiple joints. J Neurophysiol 1996; 76: 492–509.

Battaglia F, Wang H-Y, Ghilardi MF, Gashi E, Quartarone A, Friedman E, et al. Cortical Plasticity in Alzheimer's Disease in Humans and Rodents. Biological Psychiatry 2007; 62: 1405–12.

Bechtel N, Scahill RI, Rosas HD, Acharya T, van den Bogaard SJA, Jauffret C, et al. Tapping linked to function and structure in premanifest and symptomatic Huntington disease. Neurology 2010; 75: 2150–60.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961; 4: 561–71.

Becker WJ, Kunesch E, Freund HJ. Coordination of a multi-joint movement in normal humans and in patients with cerebellar dysfunction. Can J Neurol Sci 1990; 17: 264–74.

Benussi A, Di Lorenzo F, Dell'Era V, Cosseddu M, Alberici A, Caratozzolo S, et al. Transcranial magnetic stimulation distinguishes Alzheimer disease from frontotemporal dementia. Neurology 2017; 89: 665–72.

Beppu H, Suda M, Tanaka R. Analysis of cerebellar motor disorders by visually guided elbow tracking movement. Brain 1984; 107 (Pt 3): 787–809.

Berardelli A, Abbruzzese G, Chen R, Orth M, Ridding MC, Stinear C, et al. Consensus paper on short-interval intracortical inhibition and other transcranial magnetic stimulation intracortical paradigms in movement disorders. Brain Stimul 2008; 1: 183–91.

Berardelli A, Accornero N, Argenta M, Meco G, Manfredi M. Fast complex arm movements in Parkinson's disease. J Neurol Neurosurg Psychiatry 1986; 49: 1146–9.

Berardelli A, Hallett M, Rothwell JC, Agostino R, Manfredi M, Thompson PD, et al. Single-joint rapid arm movements in normal subjects and in patients with motor disorders. Brain 1996; 119 (Pt 2): 661–74.

Berardelli A, Rothwell JC, Hallett M, Thompson PD, Manfredi M, Marsden CD. The pathophysiology of primary dystonia. Brain 1998; 121 (Pt 7): 1195–212.

Berardelli A, Rothwell JC, Thompson PD, Hallett M. Pathophysiology of bradykinesia in Parkinson's disease. Brain 2001; 124: 2131–46.

Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, et al. EFNS/MDS-ES/ENS [corrected] recommendations for the diagnosis of Parkinson's disease. Eur J Neurol 2013; 20: 16–34.

Berg D, Adler CH, Bloem BR, Chan P, Gasser T, Goetz CG, et al. Movement disorder society criteria for clinically established early Parkinson's disease. Mov Disord 2018; 33: 1643–6.

Berman BD, Starr PA, Marks WJ, Ostrem JL. Induction of bradykinesia with pallidal deep brain stimulation in patients with cranial-cervical dystonia. Stereotact Funct Neurosurg 2009; 87: 37–44.

Beste C, Mückschel M, Paucke M, Ziemssen T. Dual-Tasking in Multiple Sclerosis - Implications for a Cognitive Screening Instrument. Front Hum Neurosci 2018; 12: 24.

Bhatia KP, Bain P, Bajaj N, Elble RJ, Hallett M, Louis ED, et al. Consensus Statement on the classification of tremors. from the task force on tremor of the International Parkinson and Movement Disorder Society: IPMDS Task Force on Tremor Consensus Statement. Movement Disorders 2018; 33: 75–87.

de Bie E, Oskarsson B, Joyce NC, Nicorici A, Kurillo G, Han JJ. Longitudinal evaluation of upper extremity reachable workspace in ALS by Kinect sensor. Amyotroph Lateral Scler Frontotemporal Degener 2017; 18: 17–23.

Bittenbender JB, Quadfasel FA. Rigid and akinetic forms of Huntington's chorea. Arch Neurol 1962; 7: 275–88.

Blanchard TC, Hayden BY. Neurons in dorsal anterior cingulate cortex signal postdecisional variables in a foraging task. J Neurosci 2014; 34: 646–55.

Bodranghien F, Bastian A, Casali C, Hallett M, Louis ED, Manto M, et al. Consensus Paper: Revisiting the Symptoms and Signs of Cerebellar Syndrome. Cerebellum 2016; 15: 369–91.

Bologna M, Berardelli A. The cerebellum and dystonia. In: Handbook of Clinical Neurology. Elsevier; 2018. p. 259–72

Bologna M, Berardelli I, Paparella G, Ferrazzano G, Angelini L, Giustini P, et al. Tremor Distribution and the Variable Clinical Presentation of Essential Tremor. Cerebellum 2019; 18: 866–72.

Bologna M, Bertram K, Paparella G, Papi C, Belvisi D, Conte A, et al. Reversal of long term potentiation-like plasticity in primary motor cortex in patients with progressive supranuclear palsy. Clin Neurophysiol 2017; 128: 1547–52.

Bologna M, Guerra A, Paparella G, Giordo L, Alunni Fegatelli D, Vestri AR, et al. Neurophysiological correlates of bradykinesia in Parkinson's disease. Brain 2018

Bologna M, Leodori G, Stirpe P, Paparella G, Colella D, Belvisi D, et al. Bradykinesia in early and advanced Parkinson's disease. J Neurol Sci 2016; 369: 286–91.

Bologna M, Paparella G, Fabbrini A, Leodori G, Rocchi L, Hallett M, et al. Effects of cerebellar theta-burst stimulation on arm and neck movement kinematics in patients with focal dystonia. Clin Neurophysiol 2016; 127: 3472–9.

Bologna M, Paparella G, Fasano A, Hallett M, Berardelli A. Evolving concepts on bradykinesia. Brain 2019

Bologna M, Rocchi L, Leodori G, Paparella G, Conte A, Kahn N, et al. Cerebellar Continuous Theta Burst Stimulation in Essential Tremor. The Cerebellum 2015; 14: 133–41.

Bologna M, Suppa A, Di Stasio F, Conte A, Fabbrini G, Berardelli A. Neurophysiological studies on atypical parkinsonian syndromes. Parkinsonism Relat Disord 2017; 42: 12–21.

Bonnefoi-Kyriacou B, Trouche E, Legallet E, Viallet F. Planning and execution of pointing movements in cerebellar patients. Mov Disord 1995; 10: 171–8.

Bourinaris T, Houlden H. C9orf72 and its Relevance in Parkinsonism and Movement Disorders: A Comprehensive Review of the Literature. Mov Disord Clin Pract 2018; 5: 575–85.

Bradshaw JL, Phillips JG, Dennis C, Mattingley JB, Andrewes D, Chiu E, et al. Initiation and execution of movement sequences in those suffering from and at-risk of developing Huntington's disease. J Clin Exp Neuropsychol 1992; 14: 179–92.

Brooks BR, Miller RG, Swash M, Munsat TL, World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 2000; 1: 293–9.

Brown SH, Hefter H, Mertens M, Freund HJ. Disturbances in human arm movement trajectory due to mild cerebellar dysfunction. J Neurol Neurosurg Psychiatry 1990; 53: 306–13.

Buccolieri A, Avanzino L, Marinelli L, Trompetto C, Marchese R, Abbruzzese G. Muscle relaxation is impaired in dystonia: a reaction time study. Mov Disord 2004; 19: 681–7.

Buijink AWG, Broersma M, van der Stouwe AMM, van Wingen GA, Groot PFC, Speelman JD, et al. Rhythmic finger tapping reveals cerebellar dysfunction in essential tremor. Parkinsonism Relat Disord 2015; 21: 383–8.

Burn DJ, Cartlidge NE. A case of parkinsonism associated with multiple sclerosis. Mov Disord 1996; 11: 460–1.

Cabib C, Llufriu S, Casanova-Molla J, Saiz A, Valls-Solé J. Defective sensorimotor integration in preparation for reaction time tasks in patients with multiple sclerosis. J Neurophysiol 2015; 113: 1462–9.

Cali CP, Patino M, Tai YK, Ho WY, McLean CA, Morris CM, et al. C9orf72 intermediate repeats are associated with corticobasal degeneration, increased C9orf72 expression and disruption of autophagy. Acta Neuropathol 2019; 138: 795–811.

Camarda C, Torelli P, Pipia C, Battaglini I, Azzarello D, Rosano R, et al. Mild Parkinsonian Signs in a Hospital-based Cohort of Mild Cognitive Impairment Types: A Cross-sectional Study. Curr Alzheimer Res 2019

Camarda R, Camarda C, Monastero R, Grimaldi S, Camarda LKC, Pipia C, et al. Movements Execution in Amnestic Mild Cognitive Impairment and Alzheimer's Disease. Behavioural Neurology 2007; 18: 135–42.

Campbell AM, Corner B, Norman RM, Urich H. The rigid form of Huntington's disease. J Neurol Neurosurg Psychiatry 1961; 24: 71–7.

Cannas A, Borghero G, Floris GL, Solla P, Chiò A, Traynor BJ, et al. The p.A382T TARDBP gene mutation in Sardinian patients affected by Parkinson's disease and other degenerative parkinsonisms. Neurogenetics 2013; 14: 161–6.

Canning CG, Ada L, O'Dwyer N. Slowness to develop force contributes to weakness after stroke. Arch Phys Med Rehabil 1999; 80: 66–70.

Canning CG, Ada L, O'Dwyer NJ. Abnormal muscle activation characteristics associated with loss of dexterity after stroke. J Neurol Sci 2000; 176: 45–56.

Cantone M, Di Pino G, Capone F, Piombo M, Chiarello D, Cheeran B, et al. The contribution of transcranial magnetic stimulation in the diagnosis and in the management of dementia. Clin Neurophysiol 2014; 125: 1509–32.

Carboncini MC, Manzoni D, Strambi S, Bonfiglio L, Andre P, Rossi B. Impaired agonists recruitment during voluntary arm movements in patients affected by spasmodic torticollis. Arch Ital Biol 2004; 142: 113–24.

de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol 2008; 119: 497–503.

Ceccanti M, Onesti E, Rubino A, Cambieri C, Tartaglia G, Miscioscia A, et al. Modulation of human corticospinal excitability by paired associative stimulation in patients with amyotrophic lateral sclerosis and effects of Riluzole. Brain Stimul 2018; 11: 775–81.

Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). J Neurol Sci 1999; 169: 13–21.

Cleeves L, Findley LJ, Koller W. Lack of association between essential tremor and Parkinson's disease. Ann Neurol 1988; 24: 23–6.

Cohen LG, Hallett M. Hand cramps: clinical features and electromyographic patterns in a focal dystonia. Neurology 1988; 38: 1005–12.

Conte A, Belvisi D, De Bartolo MI, Manzo N, Cortese FN, Tartaglia M, et al. Abnormal sensory gating in patients with different types of focal dystonias: Sensory Gating in Focal Dystonias. Movement Disorders 2018; 33: 1910–7.

Costa J, González HA, Valldeoriola F, Gaig C, Tolosa E, Valls-Solé J. Nonlinear dynamic analysis of oscillatory repetitive movements in Parkinson's disease and essential tremor. Mov Disord 2010; 25: 2577–86.

Cui G, Jun SB, Jin X, Pham MD, Vogel SS, Lovinger DM, et al. Concurrent activation of striatal direct and indirect pathways during action initiation. Nature 2013; 494: 238–42.

Currà A, Agostino R, Galizia P, Fittipaldi F, Manfredi M, Berardelli A. Sub-movement cueing and motor sequence execution in patients with Huntington's disease. Clin Neurophysiol 2000; 111: 1184–90.

Currá A, Berardelli A, Agostino R, Giovannelli M, Koch G, Manfredi M. Movement cueing and motor execution in patients with dystonia: a kinematic study. Mov Disord 2000; 15: 103–12.

Currà A, Modugno N, Inghilleri M, Manfredi M, Hallett M, Berardelli A. Transcranial magnetic stimulation techniques in clinical investigation. Neurology 2002; 59: 1851–9.

D'Ascenzo C, Cecchin D, Santelli L, Palmieri A, Gaiani A, Querin G, et al. Parkinson-like features in ALS with predominant upper motor neuron involvement. Amyotroph Lateral Scler 2012; 13: 137–43.

Day BL, Thompson PD, Harding AE, Marsden CD. Influence of vision on upper limb reaching movements in patients with cerebellar ataxia. Brain 1998; 121 (Pt 2): 357–72.

De Sonneville LMJ, Boringa JB, Reuling IEW, Lazeron RHC, Adèr HJ, Polman CH. Information processing characteristics in subtypes of multiple sclerosis. Neuropsychologia 2002; 40: 1751–65.

Delgado S, Baez S, Singer C, Sengun C, Sheremata WA, Papapetropoulos S. Parkinsonism/dystonia syndrome secondary to multiple sclerosis with anti-basal-ganglia antibodies. Mov Disord 2009; 24: 309–11.

DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990; 13: 281–5.

Denny-Brown D. Diseases of the basal ganglia. Their relation to disorders of movement. Lancet 1960; 2: 1155-1162 concl.

Desai J, Swash M. Extrapyramidal involvement in amyotrophic lateral sclerosis: backward falls and retropulsion. J Neurol Neurosurg Psychiatry 1999; 67: 214–6.

Deuschl G, Petersen I, Lorenz D, Christensen K. Tremor in the elderly: Essential and aging-related tremor. Mov Disord 2015; 30: 1327–34.

Deuschl G, Wenzelburger R, Löffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction clinical and kinematic analysis of intention tremor. Brain 2000; 123 (Pt 8): 1568–80.

Di Lazzaro V, Oliviero A, Pilato F, Saturno E, Dileone M, Marra C, et al. Motor cortex hyperexcitability to transcranial magnetic stimulation in Alzheimer's disease. J Neurol Neurosurg Psychiatry 2004; 75: 555–9.

Di Lazzaro V, Oliviero A, Tonali PA, Marra C, Daniele A, Profice P, et al. Noninvasive in vivo assessment of cholinergic cortical circuits in AD using transcranial magnetic stimulation. Neurology 2002; 59: 392–7.

Di Lorenzo F, Motta C, Bonnì S, Mercuri NB, Caltagirone C, Martorana A, et al. LTP-like cortical plasticity is associated with verbal memory impairment in Alzheimer's disease patients. Brain Stimul 2019; 12: 148–51.

Di Lorenzo F, Ponzo V, Bonnì S, Motta C, Negrão Serra PC, Bozzali M, et al. Long-term potentiation-like cortical plasticity is disrupted in Alzheimer's disease patients independently from age of onset. Ann Neurol 2016; 80: 202–10.

Diener HC, Dichgans J, Guschlbauer B, Bacher M, Rapp H, Klockgether T. The coordination of posture and voluntary movement in patients with cerebellar dysfunction. Mov Disord 1992; 7: 14–22.

Drori T, Givaty G, Chapman J, Lidar M, Langevitz P, Shoenfeld Y, et al. Extrapyramidal signs in neurosarcoidosis versus multiple sclerosis: Is TNF alpha the link? Immunobiology 2018; 223: 259–63.

Dubbioso R, Manganelli F, Siebner HR, Di Lazzaro V. Fast Intracortical Sensory-Motor Integration: A Window Into the Pathophysiology of Parkinson's Disease. Front Hum Neurosci 2019; 13: 111.

Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB: a Frontal Assessment Battery at bedside. Neurology 2000; 55: 1621–6.

Durand J, Amendola J, Bories C, Lamotte d'Incamps B. Early abnormalities in transgenic mouse models of amyotrophic lateral sclerosis. J Physiol Paris 2006; 99: 211–20.

Duval C, Sadikot AF, Panisset M. Bradykinesia in patients with essential tremor. Brain Res 2006; 1115: 213–6.

Ebner TJ. A role for the cerebellum in the control of limb movement velocity. Curr Opin Neurobiol 1998; 8: 762–9.

Ebner TJ, Hewitt AL, Popa LS. What features of limb movements are encoded in the discharge of cerebellar neurons? Cerebellum 2011; 10: 683–93.

Elble RJ, Higgins C, Hughes L. Essential tremor entrains rapid voluntary movements. Exp Neurol 1994; 126: 138–43.

Erro R, Schneider SA, Stamelou M, Quinn NP, Bhatia KP. What do patients with scans without evidence of dopaminergic deficit (SWEDD) have? New evidence and continuing controversies. J Neurol Neurosurg Psychiatry 2016; 87: 319–23.

Espay AJ, Beaton DE, Morgante F, Gunraj CA, Lang AE, Chen R. Impairments of speed and amplitude of movement in Parkinson's disease: a pilot study. Mov Disord 2009; 24: 1001–8.

Espay AJ, Giuffrida JP, Chen R, Payne M, Mazzella F, Dunn E, et al. Differential response of speed, amplitude, and rhythm to dopaminergic medications in Parkinson's disease. Mov Disord 2011; 26: 2504–8.

Espay AJ, Lang AE, Erro R, Merola A, Fasano A, Berardelli A, et al. Essential pitfalls in 'essential' tremor. Mov Disord 2017; 32: 325–31.

Eusebio A, Brown P. Oscillatory activity in the basal ganglia. Parkinsonism Relat Disord 2007; 13 Suppl 3: S434-436.

Fagioli S, Berardelli A, Hallett M, Accornero N, Manfredi M. The first agonist and antagonist burst in patients with an upper motor neuron syndrome. Mov Disord 1988; 3: 126–32.

Fahn S. Tolosa E. Concepcion M. Clinical Rating Scale for Tremor. In: Parkinson's disease and movement disorders. Baltimore: Williams and Wilkins; 1993. p. 271–80

Farkas Z, Szirmai I, Kamondi A. Impaired rhythm generation in essential tremor. Mov Disord 2006; 21: 1196–9.

Federlein J, Postert T, Allgeier A, Hoffmann V, Pöhlau D, Przuntek H. Remitting parkinsonism as a symptom of multiple sclerosis and the associated magnetic resonance imaging findings. Mov Disord 1997; 12: 1090–1.

Fekete R, Jankovic J. Revisiting the relationship between essential tremor and Parkinson's disease. Mov Disord 2011; 26: 391–8.

Fekete R, Li J. Clinical Differentiation of Essential Tremor and Parkinson's Disease. Clinical Medicine Insights: Case Reports 2013; 6: CCRep.S11903.

Ferreri F, Pasqualetti P, Määttä S, Ponzo D, Guerra A, Bressi F, et al. Motor cortex excitability in Alzheimer's disease: a transcranial magnetic stimulation follow-up study. Neurosci Lett 2011; 492: 94–8.

Ferreri F, Ponzo D, Hukkanen T, Mervaala E, Könönen M, Pasqualetti P, et al. Human brain cortical correlates of short-latency afferent inhibition: a combined EEG–TMS study. Journal of Neurophysiology 2012; 108: 314–23.

Ferreri F, Vecchio F, Vollero L, Guerra A, Petrichella S, Ponzo D, et al. Sensorimotor cortex excitability and connectivity in Alzheimer's disease: A TMS-EEG Co-registration study. Hum Brain Mapp 2016; 37: 2083–96.

Folgar S, Gatto EM, Raina G, Micheli F. Parkinsonism as a manifestation of multiple sclerosis. Mov Disord 2003; 18: 108–10.

Folstein MF, Folstein SE, McHugh PR. 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Fujita M, Nakamura R. Characteristics of the fastest isometric knee extension in patients with spinocerebellar degenerations. Tohoku J Exp Med 1989; 157: 13–7.

Furuya S, Altenmüller E. Finger-specific loss of independent control of movements in musicians with focal dystonia. Neuroscience 2013; 247: 152–63.

Furuya S, Uehara K, Sakamoto T, Hanakawa T. Aberrant cortical excitability reflects the loss of hand dexterity in musician's dystonia. J Physiol (Lond) 2018; 596: 2397–411.

Geraghty JJ, Jankovic J, Zetusky WJ. Association between essential tremor and Parkinson's disease. Ann Neurol 1985; 17: 329–33.

Gerloff C, Richard J, Hadley J, Schulman AE, Honda M, Hallett M. Functional coupling and regional activation of human cortical motor areas during simple, internally paced and externally paced finger movements. Brain 1998; 121 (Pt 8): 1513–31.

Ghassemi M, Lemieux S, Jog M, Edwards R, Duval C. Bradykinesia in patients with Parkinson's disease having levodopa-induced dyskinesias. Brain Res Bull 2006; 69: 512–8.

Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, et al. Second consensus statement on the diagnosis of multiple system atrophy. Neurology 2008; 71: 670–6.

Godefroy O, Lhullier-Lamy C, Rousseaux M. SRT lengthening: role of an alertness deficit in frontal damaged patients. Neuropsychologia 2002; 40: 2234–41.

Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008; 23: 2129–70.

Goubault E, Nguyen HP, Ayachi FS, Bogard S, Duval C. Do Bradykinesia and Tremor Interfere in Voluntary Movement of Essential Tremor Patients? Preliminary Findings. Tremor Other Hyperkinet Mov (N Y) 2017; 7: 459.

Gregori B, Agostino R, Bologna M, Dinapoli L, Colosimo C, Accornero N, et al. Fast voluntary neck movements in patients with cervical dystonia: a kinematic study before and after therapy with botulinum toxin type A. Clin Neurophysiol 2008; 119: 273–80.

Groppa S, Oliviero A, Eisen A, Quartarone A, Cohen LG, Mall V, et al. A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol 2012; 123: 858–82.

Guerra A, Assenza F, Bressi F, Scrascia F, Del Duca M, Ursini F, et al. Transcranial magnetic stimulation studies in Alzheimer's disease. Int J Alzheimers Dis 2011; 2011: 263817.

Haggstrom L, Darveniza P, Tisch S. Mild parkinsonian features in dystonia: Literature review, mechanisms and clinical perspectives. Parkinsonism Relat Disord 2017; 35: 1–7.

Hallett M. Ballistic elbow flexion movements in patients with amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 1979; 42: 232–7.

Hallett M. Disorder of movement preparation in dystonia. Brain 2000; 123 (Pt 9): 1765–6.

Hallett M, Berardelli A, Matheson J, Rothwell J, Marsden CD. Physiological analysis of simple rapid movements in patients with cerebellar deficits. J Neurol Neurosurg Psychiatry 1991; 54: 124–33.

Hallett M, Berardelli A, Matheson J, Rothwell J, Marsden CD. Physiological analysis of simple rapid movements in patients with cerebellar deficits. J Neurol Neurosurg Psychiatry 1991; 54: 124–33.

Hallett M, Shahani BT, Young RR. EMG analysis of patients with cerebellar deficits. J Neurol Neurosurg Psychiatry 1975; 38: 1163–9.

Haubenberger D, Hallett M. Essential Tremor. N Engl J Med 2018; 379: 596–7.

Hefter H, Hömberg V, Lange HW, Freund HJ. Impairment of rapid movement in Huntington's disease. Brain 1987; 110 (Pt 3): 585–612.

Heldman DA, Espay AJ, LeWitt PA, Giuffrida JP. Clinician versus machine: reliability and responsiveness of motor endpoints in Parkinson's disease. Parkinsonism Relat Disord 2014; 20: 590–5.

Héroux ME, Parisi SL, Larocerie-Salgado J, Norman KE. Upper-extremity disability in essential tremor. Arch Phys Med Rehabil 2006; 87: 661–70.

Hewitt AL, Popa LS, Pasalar S, Hendrix CM, Ebner TJ. Representation of limb kinematics in Purkinje cell simple spike discharge is conserved across multiple tasks. J Neurophysiol 2011; 106: 2232–47.

Hinton SC, Paulsen JS, Hoffmann RG, Reynolds NC, Zimbelman JL, Rao SM. Motor timing variability increases in preclinical Huntington's disease patients as estimated onset of motor symptoms approaches. J Int Neuropsychol Soc 2007; 13: 539–43.

Höglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, Lang AE, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. Mov Disord 2017; 32: 853–64.

Holmes G. The Croonian Lectures on the clinical symptoms of cerebellar disease and their interpretation. Lecture II. 1922. Cerebellum 2007; 6: 148–53; discussion 141.

Hopfner F, Deuschl G. Is essential tremor a single entity? Eur J Neurol 2018; 25: 71–82.

Hophing L, Bologna M, Berardelli A, Fasano A. Functional eyelid opening apraxia: a kinematic study. Eur J Neurol 2018; 25: e95–7.

Hore J, Wild B, Diener HC. Cerebellar dysmetria at the elbow, wrist, and fingers. J Neurophysiol 1991; 65: 563–71.

Hornabrook RW, Nagurney JT. Essential tremor in Papua, New Guinea. Brain 1976; 99: 659–72.

Huang Y-Z, Edwards MJ, Rounis E, Bhatia KP, Rothwell JC. Theta burst stimulation of the human motor cortex. Neuron 2005; 45: 201–6.

Huebl J, Brücke C, Schneider G-H, Blahak C, Krauss JK, Kühn AA. Bradykinesia induced by frequency-specific pallidal stimulation in patients with cervical and segmental dystonia. Parkinsonism Relat Disord 2015; 21: 800–3.

Iaccarino HF, Singer AC, Martorell AJ, Rudenko A, Gao F, Gillingham TZ, et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. Nature 2016; 540: 230–5.

Inghilleri M, Conte A, Frasca V, Scaldaferri N, Gilio F, Santini M, et al. Altered response to rTMS in patients with Alzheimer's disease. Clin Neurophysiol 2006; 117: 103–9.

Inghilleri M, Iacovelli E. Clinical neurophysiology in ALS. Arch Ital Biol 2011; 149: 57–63.

Inzelberg R, Flash T, Korczyn AD. Kinematic properties of upper-limb trajectories in Parkinson's disease and idiopathic torsion dystonia. Adv Neurol 1990; 53: 183–9.

Inzelberg R, Flash T, Schechtman E, Korczyn AD. Kinematic properties of upper limb trajectories in idiopathic torsion dystonia. J Neurol Neurosurg Psychiatry 1995; 58: 312–9.

Israeli-Korn SD, Massarwa M, Schechtman E, Strugatsky R, Avni S, Farrer LA, et al. Mild cognitive impairment is associated with mild parkinsonian signs in a door-to-door study. J Alzheimers Dis 2010; 22: 1005–13.

Jabusch H-C, Vauth H, Altenmüller E. Quantification of focal dystonia in pianists using scale analysis. Mov Disord 2004; 19: 171–80.

Jahanshahi M, Brown RG, Marsden CD. A comparative study of simple and choice reaction time in Parkinson's, Huntington's and cerebellar disease. J Neurol Neurosurg Psychiatry 1993; 56: 1169–77.

Jahanshahi M, Jenkins IH, Brown RG, Marsden CD, Passingham RE, Brooks DJ. Self-initiated versus externally triggered movements. I. An investigation using measurement of regional cerebral blood flow with PET and movement-related potentials in normal and Parkinson's disease subjects. Brain 1995; 118 (Pt 4): 913–33.

Jankowski J, Paus S, Scheef L, Bewersdorff M, Schild HH, Klockgether T, et al. Abnormal movement preparation in task-specific focal hand dystonia. PLoS ONE 2013; 8: e78234.

Jiménez-Jiménez FJ, Rubio L, Alonso-Navarro H, Calleja M, Pilo-de-la-Fuente B, Plaza-Nieto JF, et al. Impairment of rapid repetitive finger movements and visual reaction time in patients with essential tremor. Eur J Neurol 2010; 17: 152–9.

Johnson KA, Bennett JE, Georgiou N, Bradshaw JL, Chiu E, Cunnington R, et al. Bimanual co-ordination in Huntington's disease. Exp Brain Res 2000; 134: 483–9.

Kail R. Speed of information processing in patients with multiple sclerosis. J Clin Exp Neuropsychol 1998; 20: 98–106.

van der Kamp W, Berardelli A, Rothwell JC, Thompson PD, Day BL, Marsden CD. Rapid elbow movements in patients with torsion dystonia. J Neurol Neurosurg Psychiatry 1989; 52: 1043–9.

Kamphorst W, Ravid R. Movement disorders with multiple sclerosis. Mov Disord 1997; 12: 818.

Katschnig-Winter P, Schwingenschuh P, Davare M, Sadnicka A, Schmidt R, Rothwell JC, et al. Motor sequence learning and motor adaptation in primary cervical dystonia. J Clin Neurosci 2014; 21: 934–8.

Khani M, Alavi A, Shamshiri H, Zamani B, Hassanpour H, Kazemi MH, et al. Mutation screening of SLC52A3, C19orf12, and TARDBP in Iranian ALS patients. Neurobiol Aging 2019; 75: 225.e9-225.e14.

Kim E-J, Lee B, Jo M-K, Jung K, You H, Lee BH, et al. Directional and spatial motor intentional disorders in patients with right versus left hemisphere strokes. Neuropsychology 2013; 27: 428–37.

Kirova A-M, Bays RB, Lagalwar S. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. Biomed Res Int 2015; 2015: 748212.

Kishore A, Popa T, James P, Krishnan S, Robert S, Meunier S. Severity of Writer's Cramp is Related to Faulty Motor Preparation. Cereb Cortex 2018; 28: 3564–77.

Kluger A, Gianutsos JG, Golomb J, Ferris SH, George AE, Franssen E, et al. Patterns of Motor Impairment in Normal Aging, Mild Cognitive Decline, and Early Alzheimer' Disease. The Journals of Gerontology Series B: Psychological Sciences and Social Sciences 1997; 52B: P28–39.

Koller WC, Busenbark K, Miner K. The relationship of essential tremor to other movement disorders: report on 678 patients. Essential Tremor Study Group. Ann Neurol 1994; 35: 717–23.

Konczak J, Pierscianek D, Hirsiger S, Bultmann U, Schoch B, Gizewski ER, et al. Recovery of upper limb function after cerebellar stroke: lesion symptom mapping and arm kinematics. Stroke 2010; 41: 2191–200.

Krashia P, Nobili A, D'Amelio M. Unifying Hypothesis of Dopamine Neuron Loss in Neurodegenerative Diseases: Focusing on Alzheimer's Disease. Front Mol Neurosci 2019; 12: 123.

Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46: 1121–3.

Kuhn Y-A, Keller M, Ruffieux J, Taube W. Adopting an external focus of attention alters intracortical inhibition within the primary motor cortex. Acta Physiol (Oxf) 2017; 220: 289–99.

Kujala P, Portin R, Revonsuo A, Ruutiainen J. Automatic and controlled information processing in multiple sclerosis. Brain 1994; 117 (Pt 5): 1115–26.

Kujala P, Portin R, Revonsuo A, Ruutiainen J. Attention related performance in two cognitively different subgroups of patients with multiple sclerosis. J Neurol Neurosurg Psychiatry 1995; 59: 77–82.

Kume K, Hanyu H, Murakami M, Sato T, Hirao K, Kanetaka H, et al. Frontal Assessment Battery and brain perfusion images in amnestic mild cognitive impairment: Frontal Assessment Battery and brain perfusion. Geriatrics & Gerontology International 2011; 11: 77–82.

Kuo P-H, Gan S-R, Wang J, Lo RY, Figueroa KP, Tomishon D, et al. Dystonia and ataxia progression in spinocerebellar ataxias. Parkinsonism Relat Disord 2017; 45: 75–80.

Kuruvilla-Dugdale M, Chuquilin-Arista M. An investigation of clear speech effects on articulatory kinematics in talkers with ALS. Clin Linguist Phon 2017; 31: 725–42.

Ling H, Massey LA, Lees AJ, Brown P, Day BL. Hypokinesia without decrement distinguishes progressive supranuclear palsy from Parkinson's disease. Brain 2012; 135: 1141–53.

Lou JS, Jankovic J. Essential tremor: clinical correlates in 350 patients. Neurology 1991; 41: 234–8.

Louis ED. Essential tremor and the cerebellum. Handb Clin Neurol 2018; 155: 245–58.

Louis ED, Bares M, Benito-Leon J, Fahn S, Frucht SJ, Jankovic J, et al. Essential tremor-plus: a controversial new concept. Lancet Neurol 2019

Louis ED, Clark L, Ottman R. Familial Aggregation and Co-Aggregation of Essential Tremor and Parkinson's Disease. Neuroepidemiology 2016; 46: 31–6.

Louis ED, Diaz DT, Kuo S-H, Gan S-R, Cortes EP, Vonsattel JPG, et al. Inferior Olivary nucleus degeneration does not lessen tremor in essential tremor. Cerebellum Ataxias 2018; 5: 1.

Louis ED, Faust PL, Vonsattel J-PG, Honig LS, Rajput A, Robinson CA, et al. Neuropathological changes in essential tremor: 33 cases compared with 21 controls. Brain 2007; 130: 3297–307.

Louis ED, Schupf N, Manly J, Marder K, Tang MX, Mayeux R. Association between mild parkinsonian signs and mild cognitive impairment in a community. Neurology 2005; 64: 1157–61.

Louis ED, Wise A, Alcalay RN, Rao AK, Factor-Litvak P. Essential tremor-Parkinson's disease: A double whammy. J Neurol Sci 2016; 366: 47–51.

Lubrini G, Periáñez JA, Fernández-Fournier M, Tallón Barranco A, Díez-Tejedor E, Frank García A, et al. Identifying Perceptual, Motor, and Cognitive Components Contributing to Slowness of Information Processing in Multiple Sclerosis with and without Depressive Symptoms. Span J Psychol 2020; 23: e21.

MacKinnon CD, Velickovic M, Drafta C, Hesquijarosa A, Brin MF. Corticospinal excitability accompanying ballistic wrist movements in primary dystonia. Mov Disord 2004; 19: 273–84.

MacLaren DAA, Santini JA, Russell AL, Markovic T, Clark SD. Deficits in motor performance after pedunculopontine lesions in rats--impairment depends on demands of task. Eur J Neurosci 2014; 40: 3224–36.

Mahlknecht P, Georgiev D, Akram H, Brugger F, Vinke S, Zrinzo L, et al. Parkinsonian signs in patients with cervical dystonia treated with pallidal deep brain stimulation. Brain 2018; 141: 3023–34.

Mai N, Bolsinger P, Avarello M, Diener HC, Dichgans J. Control of isometric finger force in patients with cerebellar disease. Brain 1988; 111 (Pt 5): 973–98.

Manni E, Petrosini L. Luciani's work on the cerebellum a century later. Trends Neurosci 1997; 20: 112–6.

Manto MU, Setta F, Jacquy J, Godaux E, Hildebrand J, Roland H, et al. Different types of cerebellar hypometria associated with a distinct topography of the lesion in cerebellum. J Neurol Sci 1998; 158: 88–95.

Maranhão-Filho PA, Moraes Filho L, Camara LS, Salema CC. Fulminant form of multiple sclerosis simulating brain tumor: a case with parkinsonian features and pathologic study. Arq Neuropsiquiatr 1995; 53: 503–8.

Markanday A, Messner J, Thier P. A loss of a velocity-duration trade-off impairs movement precision in patients with cerebellar degeneration. Eur J Neurosci 2018; 48: 1976–89.

Marsden CD, Obeso JA. The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. Brain 1994; 117 (Pt 4): 877–97.

Marsili L, Bologna M, Kojovic M, Berardelli A, Espay AJ, Colosimo C. Dystonia in atypical parkinsonian disorders. Parkinsonism Relat Disord 2019; 66: 25–33.

Martínez Pueyo A, García-Ruiz PJ, Feliz CE, Garcia Caldentey J, Del Val J, Herranz A. Reaction time and rhythm of movement in Huntington's disease. J Neurol Sci 2016; 362: 115–7.

Mattingley JB, Phillips JG, Bradshaw JL. Impairments of movement execution in unilateral neglect: a kinematic analysis of directional bradykinesia. Neuropsychologia 1994; 32: 1111–34.

McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor J-P, Weintraub D, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 2017; 89: 88–100.

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 263–9.

McLaughlin PM, Anderson ND, Rich JB, Chertkow H, Murtha SJE. Visual selective attention in amnestic mild cognitive impairment. J Gerontol B Psychol Sci Soc Sci 2014; 69: 881–91.

Miller TM, Johnston SC. Should the Babinski sign be part of the routine neurologic examination? Neurology 2005; 65: 1165–8.

Montgomery EB, Baker KB, Lyons K, Koller WC. Motor initiation and execution in essential tremor and Parkinson's disease. Mov Disord 2000; 15: 511–5.

Morgante F, Dattola V, Crupi D, Russo M, Rizzo V, Ghilardi MF, et al. Is central fatigue in multiple sclerosis a disorder of movement preparation? J Neurol 2011; 258: 263–72.

Mori F, Nisticò R, Nicoletti CG, Zagaglia S, Mandolesi G, Piccinin S, et al. RANTES correlates with inflammatory activity and synaptic excitability in multiple sclerosis. Mult Scler 2016; 22: 1405–12.

Murase N, Kaji R, Shimazu H, Katayama-Hirota M, Ikeda A, Kohara N, et al. Abnormal premovement gating of somatosensory input in writer's cramp. Brain 2000; 123 (Pt 9): 1813–29.

Muthuraman M, Deuschl G, Anwar AR, Mideksa KG, von Helmolt F, Schneider SA. Essential and aging-related tremor: Differences of central control. Mov Disord 2015; 30: 1673–80.

Nardone R, Tezzon F, Höller Y, Golaszewski S, Trinka E, Brigo F. Transcranial magnetic stimulation (TMS)/repetitive TMS in mild cognitive impairment and Alzheimer's disease. Acta Neurol Scand 2014; 129: 351–66.

Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53: 695–9.

Naumann M, Pirker W, Reiners K, Lange KW, Becker G, Brücke T. Imaging the pre- and postsynaptic side of striatal dopaminergic synapses in idiopathic cervical dystonia: a SPECT study using [123I] epidepride and [123I] beta-CIT. Mov Disord 1998; 13: 319–23.

Neychev VK, Gross RE, Lehéricy S, Hess EJ, Jinnah HA. The functional neuroanatomy of dystonia. Neurobiology of Disease 2011; 42: 185–201.

Nobili A, Latagliata EC, Viscomi MT, Cavallucci V, Cutuli D, Giacovazzo G, et al. Dopamine neuronal loss contributes to memory and reward dysfunction in a model of Alzheimer's disease. Nat Commun 2017; 8: 14727.

Nociti V, Bentivoglio AR, Frisullo G, Fasano A, Soleti F, Iorio R, et al. Movement disorders in multiple sclerosis: Causal or coincidental association? Mult Scler 2008; 14: 1284–7.

Oakes JA, Davies MC, Collins MO. TBK1: a new player in ALS linking autophagy and neuroinflammation. Mol Brain 2017; 10: 5.

Ohta Y, Sato K, Takemoto M, Takahashi Y, Morihara R, Nakano Y, et al. Behavioral and affective features of amyotrophic lateral sclerosis patients. J Neurol Sci 2017; 381: 119–25.

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971; 9: 97–113.

Olivito G, Brunamonti E, Clausi S, Pani P, Chiricozzi FR, Giamundo M, et al. Atrophic degeneration of cerebellum impairs both the reactive and the proactive control of movement in the stop signal paradigm. Exp Brain Res 2017; 235: 2971–81.

Orth M, Snijders AH, Rothwell JC. The variability of intracortical inhibition and facilitation. Clin Neurophysiol 2003; 114: 2362–9.

Oskarsson B, Joyce NC, De Bie E, Nicorici A, Bajcsy R, Kurillo G, et al. Upper extremity 3-dimensional reachable workspace assessment in amyotrophic lateral sclerosis by Kinect sensor. Muscle Nerve 2016; 53: 234–41.

Ozekmekçi S, Kiziltan G, Vural M, Ertan S, Apaydin H, Erginöz E. Assessment of movement time in patients with essential tremor. J Neurol 2005; 252: 964–7.

Ozturk V, Idiman E, Sengun IS, Yuksel Z. Multiple sclerosis and parkinsonism: a case report. Funct Neurol 2002; 17: 145–7.

Pagan FL, Butman JA, Dambrosia JM, Hallett M. Evaluation of essential tremor with multi-voxel magnetic resonance spectroscopy. Neurology 2003; 60: 1344–7.

Pandey S, Bhattad S. Questionable Dystonia in Essential Tremor Plus: A Video-Based Assessment of 19 Patients. Mov Disord Clin Pract 2019; 6: 722–3.

Papa SM, Artieda J, Obeso JA. Cortical activity preceding self-initiated and externally triggered voluntary movement. Mov Disord 1991; 6: 217–24.

Paparella G, Ferrazzano G, Cannavacciuolo A, Cogliati Dezza F, Fabbrini G, Bologna M, et al. Differential effects of propranolol on head and upper limb tremor in patients with essential tremor and dystonia. J Neurol 2018

Pasquereau B, DeLong MR, Turner RS. Primary motor cortex of the parkinsonian monkey: altered encoding of active movement. Brain 2016; 139: 127–43.

Passamonti L, Cerasa A, Quattrone A. Neuroimaging of Essential Tremor: What is the Evidence for Cerebellar Involvement? Tremor Other Hyperkinet Mov (N Y) 2012; 2

Pearson TS. More Than Ataxia: Hyperkinetic Movement Disorders in Childhood Autosomal Recessive Ataxia Syndromes. Tremor Other Hyperkinet Mov (N Y) 2016; 6: 368.

Pelosin E, Bove M, Marinelli L, Abbruzzese G, Ghilardi MF. Cervical dystonia affects aimed movements of nondystonic segments. Mov Disord 2009; 24: 1955–61.

Phillips JG, Bradshaw JL, Chiu E, Bradshaw JA. Characteristics of handwriting of patients with Huntington's disease. Mov Disord 1994; 9: 521–30.

Poon C, Robichaud JA, Corcos DM, Goldman JG, Vaillancourt DE. Combined measures of movement and force variability distinguish Parkinson's disease from essential tremor. Clin Neurophysiol 2011; 122: 2268–75.

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015; 30: 1591–601.

Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015; 30: 1591–601.

Prell T, Witte OW, Gunkel A, Grosskreutz J. Cognitive deficits have only limited influence on health-related quality of life in amyotrophic lateral sclerosis. Aging Ment Health 2019: 1–5.

Priori A, Polidori L, Rona S, Manfredi M, Berardelli A. Spinal and cortical inhibition in Huntington's chorea. Mov Disord 2000; 15: 938–46.

Prodoehl J, Corcos DM, Leurgans S, Comella CL, Weis-McNulty A, MacKinnon CD. Changes in the relationship between movement velocity and movement distance in primary focal hand dystonia. J Mot Behav 2008; 40: 301–13.

Pupillo E, Bianchi E, Messina P, Chiveri L, Lunetta C, Corbo M, et al. Extrapyramidal and cognitive signs in amyotrophic lateral sclerosis: A population based cross-sectional study. Amyotroph Lateral Scler Frontotemporal Degener 2015; 16: 324–30.

Quattrone A, Cerasa A, Messina D, Nicoletti G, Hagberg GE, Lemieux L, et al. Essential head tremor is associated with cerebellar vermis atrophy: a volumetric and voxel-based morphometry MR imaging study. AJNR Am J Neuroradiol 2008; 29: 1692–7.

Qureshi AI, Wilmot G, Dihenia B, Schneider JA, Krendel DA. Motor neuron disease with parkinsonism. Arch Neurol 1996; 53: 987–91.

Rabinowitz I, Lavner Y. Association between Finger Tapping, Attention, Memory, and Cognitive Diagnosis in Elderly Patients. Percept Mot Skills 2014; 119: 259–78.

Rajput AH, Rajput EF, Bocking SM, Auer RN, Rajput A. Parkinsonism in essential tremor cases: A clinicopathological study. Mov Disord 2019; 34: 1031–40.

Reiner A, Deng Y-P. Disrupted striatal neuron inputs and outputs in Huntington's disease. CNS Neurosci Ther 2018; 24: 250–80.

Roalf DR, Rupert P, Mechanic-Hamilton D, Brennan L, Duda JE, Weintraub D, et al. Quantitative assessment of finger tapping characteristics in mild cognitive impairment, Alzheimer's disease, and Parkinson's disease. J Neurol 2018; 265: 1365–75.

Rossi S, Hallett M, Rossini PM, Pascual-Leone A, Safety of TMS Consensus Group. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. Clin Neurophysiol 2009; 120: 2008–39.

Rossini PM, Burke D, Chen R, Cohen LG, Daskalakis Z, Di Iorio R, et al. Non-invasive electrical and magnetic stimulation of the brain, spinal cord, roots and peripheral nerves: Basic principles and procedures for routine clinical and research application. An updated report from an I.F.C.N. Committee. Clin Neurophysiol 2015; 126: 1071–107.

Rowe KC, Paulsen JS, Langbehn DR, Duff K, Beglinger LJ, Wang C, et al. Self-paced timing detects and tracks change in prodromal Huntington disease. Neuropsychology 2010; 24: 435–42.

Sahrmann SA, Norton BJ. The relationship of voluntary movement to spasticity in the upper motor neuron syndrome. Ann Neurol 1977; 2: 460–5.

Saunders A, Oldenburg IA, Berezovskii VK, Johnson CA, Kingery ND, Elliott HL, et al. A direct GABAergic output from the basal ganglia to frontal cortex. Nature 2015; 521: 85–9.

Scarmeas N, Albert M, Brandt J, Blacker D, Hadjigeorgiou G, Papadimitriou A, et al. Motor signs predict poor outcomes in Alzheimer disease. Neurology 2005; 64: 1696–703.

Scarmeas N, Hadjigeorgiou GM, Papadimitriou A, Dubois B, Sarazin M, Brandt J, et al. Motor signs during the course of Alzheimer disease. Neurology 2004; 63: 975–82.

Scheltens P, Blennow K, Breteler MMB, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. Lancet 2016; 388: 505–17.

Schirinzi T, Di Lorenzo F, Sancesario GM, Di Lazzaro G, Ponzo V, Pisani A, et al. Amyloid-Mediated Cholinergic Dysfunction in Motor Impairment Related to Alzheimer's Disease. J Alzheimers Dis 2018; 64: 525–32.

Schneider SA, Edwards MJ, Mir P, Cordivari C, Hooker J, Dickson J, et al. Patients with adult-onset dystonic tremor resembling parkinsonian tremor have scans without evidence of dopaminergic deficit (SWEDDs). Mov Disord 2007; 22: 2210–5.

Schreglmann SR, Riederer F, Galovic M, Ganos C, Kägi G, Waldvogel D, et al. Movement disorders in genetically confirmed mitochondrial disease and the putative role of the cerebellum. Mov Disord 2018; 33: 146–55.

Schröter A, Mergl R, Bürger K, Hampel H, Möller H-J, Hegerl U. Kinematic Analysis of Handwriting Movements in Patients with Alzheimer's Disease, Mild Cognitive Impairment, Depression and Healthy Subjects. Dement Geriatr Cogn Disord 2003; 15: 132–42.

Scontrini A, Conte A, Defazio G, Fiorio M, Fabbrini G, Suppa A, et al. Somatosensory temporal discrimination in patients with primary focal dystonia. Journal of Neurology, Neurosurgery & Psychiatry 2009; 80: 1315–9.

Shaikh AG, Wong A, Zee DS, Jinnah HA. Why are voluntary head movements in cervical dystonia slow? Parkinsonism Relat Disord 2015; 21: 561–6.

Sharma VD, Lyons KE, Nazzaro JM, Pahwa R. Deep brain stimulation of the subthalamic nucleus in Parkinson's disease patients over 75 years of age. J Neurol Sci 2019; 399: 57–60.

Sheehy MP, Marsden CD. Writers' cramp-a focal dystonia. Brain 1982; 105 (Pt 3): 461–80.

Shellikeri S, Green JR, Kulkarni M, Rong P, Martino R, Zinman L, et al. Speech Movement Measures as Markers of Bulbar Disease in Amyotrophic Lateral Sclerosis. J Speech Lang Hear Res 2016; 59: 887–99.

Shribman S, Hasan H, Hadavi S, Giovannoni G, Noyce AJ. The BRAIN test: a keyboard-tapping test to assess disability and clinical features of multiple sclerosis. J Neurol 2018; 265: 285–90.

Simonyan K, Berman BD, Herscovitch P, Hallett M. Abnormal striatal dopaminergic neurotransmission during rest and task production in spasmodic dysphonia. J Neurosci 2013; 33: 14705–14.

Singer C, Sanchez-Ramos J, Weiner WJ. Gait abnormality in essential tremor. Mov Disord 1994; 9: 193–6.

Stamelou M, Edwards MJ, Bhatia KP. Late onset rest-tremor in DYT1 dystonia. Parkinsonism Relat Disord 2013; 19: 136–7.

Stone J, LaFrance WC, Brown R, Spiegel D, Levenson JL, Sharpe M. Conversion disorder: current problems and potential solutions for DSM-5. J Psychosom Res 2011; 71: 369–76.

Stoodley CJ, Schmahmann JD. Evidence for topographic organization in the cerebellum of motor control versus cognitive and affective processing. Cortex 2010; 46: 831–44.

Suzumura S, Osawa A, Maeda N, Sano Y, Kandori A, Mizuguchi T, et al. Differences among patients with Alzheimer's disease, older adults with mild cognitive impairment and healthy older adults in finger dexterity. Geriatr Gerontol Int 2018; 18: 907–14.

Takahashi H, Snow BJ, Bhatt MH, Peppard R, Eisen A, Calne DB. Evidence for a dopaminergic deficit in sporadic amyotrophic lateral sclerosis on positron emission scanning. Lancet 1993; 342: 1016–8.

Takakusaki K, Chiba R, Nozu T, Okumura T. Brainstem control of locomotion and muscle tone with special reference to the role of the mesopontine tegmentum and medullary reticulospinal systems. J Neural Transm (Vienna) 2016; 123: 695–729.

Takiyama Y, Oyanagi S, Kawashima S, Sakamoto H, Saito K, Yoshida M, et al. A clinical and pathologic study of a large Japanese family with Machado-Joseph disease tightly linked to the DNA markers on chromosome 14q. Neurology 1994; 44: 1302–8.

Tallón-Barranco A, Vázquez A, Javier Jiménez-Jiménez F, Ortí-Pareja M, Gasalla T, Cabrera-Valdivia F, et al. Clinical features of essential tremor seen in neurology practice: a study of 357 patients. Parkinsonism Relat Disord 1997; 3: 187–90.

Terranova C, Sant'Angelo A, Morgante F, Rizzo V, Allegra R, Arena MG, et al. Impairment of sensory-motor plasticity in mild Alzheimer's disease. Brain Stimulation 2013; 6: 62–6.

Thenganatt MA, Jankovic J. Psychogenic (functional) parkinsonism. Handb Clin Neurol 2016; 139: 259–62.

Thenganatt MA, Jankovic J. The relationship between essential tremor and Parkinson's disease. Parkinsonism Relat Disord 2016; 22 Suppl 1: S162-165.

Thompson PD, Berardelli A, Rothwell JC, Day BL, Dick JP, Benecke R, et al. The coexistence of bradykinesia and chorea in Huntington's disease and its implications for theories of basal ganglia control of movement. Brain 1988; 111 (Pt 2): 223–44.

Thomson RHS, Garry MI, Summers JJ. Attentional influences on short-interval intracortical inhibition. Clin Neurophysiol 2008; 119: 52–62.

Tinazzi M, Priori A, Bertolasi L, Frasson E, Mauguière F, Fiaschi A. Abnormal central integration of a dual somatosensory input in dystonia. Evidence for sensory overflow. Brain 2000; 123 (Pt 1): 42–50.

Tisch S, Zrinzo L, Limousin P, Bhatia KP, Quinn N, Ashkan K, et al. Effect of electrode contact location on clinical efficacy of pallidal deep brain stimulation in primary generalised dystonia. J Neurol Neurosurg Psychiatry 2007; 78: 1314–9.

Tokimura H, Di Lazzaro V, Tokimura Y, Oliviero A, Profice P, Insola A, et al. Short latency inhibition of human hand motor cortex by somatosensory input from the hand. J Physiol (Lond) 2000; 523 Pt 2: 503–13.

Topka H, Konczak J, Schneider K, Boose A, Dichgans J. Multijoint arm movements in cerebellar ataxia: abnormal control of movement dynamics. Exp Brain Res 1998; 119: 493–503.

Trebbastoni A, Pichiorri F, D'Antonio F, Campanelli A, Onesti E, Ceccanti M, et al. Altered Cortical Synaptic Plasticity in Response to 5-Hz Repetitive Transcranial Magnetic Stimulation as a New Electrophysiological Finding in Amnestic Mild Cognitive Impairment Converting to Alzheimer's Disease: Results from a 4-year Prospective Cohort Study. Front Aging Neurosci 2015; 7: 253.

Tsolaki M, Kokarida K, Iakovidou V, Stilopoulos E, Meimaris J, Kazis A. Extrapyramidal symptoms and signs in Alzheimer's disease: prevalence and correlation with the first symptom. Am J Alzheimers Dis Other Demen 2001; 16: 268–78.

Van Mossevelde S, van der Zee J, Gijselinck I, Engelborghs S, Sieben A, Van Langenhove T, et al. Clinical features of TBK1 carriers compared with C9orf72, GRN and non-mutation carriers in a Belgian cohort. Brain 2016; 139: 452–67.

Vieregge P, Klostermann W, Brückmann H. Parkinsonism in multiple sclerosis. Mov Disord 1992; 7: 380–2.

Vöglein J, Paumier K, Jucker M, Preische O, McDade E, Hassenstab J, et al. Clinical, pathophysiological and genetic features of motor symptoms in autosomal dominant Alzheimer's disease. Brain 2019; 142: 1429–40.

van Vugt JPP, Piet KKE, Vink LJ, Siesling S, Zwinderman AH, Middelkoop HAM, et al. Objective assessment of motor slowness in Huntington's disease: clinical correlates and 2-year follow-up. Mov Disord 2004; 19: 285–97.

Waln O, Wu Y, Perlman R, Wendt J, Van AK, Jankovic J. Dopamine transporter imaging in essential tremor with and without parkinsonian features. J Neural Transm (Vienna) 2015; 122: 1515–21.

Wegrzyn M, Teipel SJ, Oltmann I, Bauer A, Thome J, Großmann A, et al. Structural and functional cortical disconnection in Alzheimer's disease: a combined study using diffusion tensor imaging and transcranial magnetic stimulation. Psychiatry Res 2013; 212: 192–200.

Wetter S, Poole JL, Haaland KY. Functional implications of ipsilesional motor deficits after unilateral stroke. Arch Phys Med Rehabil 2005; 86: 776–81.

Wharton SB, Verber NS, Wagner BE, Highley JR, Fillingham DJ, Waller R, et al. Combined fused in sarcoma-positive (FUS+) basophilic inclusion body disease and atypical tauopathy presenting with an amyotrophic lateral sclerosis/motor neurone disease (ALS/MND)-plus phenotype. Neuropathol Appl Neurobiol 2019; 45: 586–96.

Wild B, Klockgether T, Dichgans J. Acceleration deficit in patients with cerebellar lesions. A study of kinematic and EMG-parameters in fast wrist movements. Brain Res 1996; 713: 186–91.

Williams DT, Ford B, Fahn S. Phenomenology and psychopathology related to psychogenic movement disorders. Adv Neurol 1995; 65: 231–57.

Williams TL, Shaw PJ, Lowe J, Bates D, Ince PG. Parkinsonism in motor neuron disease: case report and literature review. Acta Neuropathol 1995; 89: 275–83.

Wills AJ, Jenkins IH, Thompson PD, Findley LJ, Brooks DJ. Red nuclear and cerebellar but no olivary activation associated with essential tremor: a positron emission tomographic study. Ann Neurol 1994; 36: 636–42.

Wirth B, van Hedel HJA, Curt A. Ankle dexterity remains intact in patients with incomplete spinal cord injury in contrast to stroke patients. Exp Brain Res 2008; 191: 353–61.

Wolf RC, Grön G, Sambataro F, Vasic N, Wolf ND, Thomann PA, et al. Brain activation and functional connectivity in premanifest Huntington's disease during states of intrinsic and phasic alertness. Hum Brain Mapp 2012; 33: 2161–73.

Wu T, Hallett M. A functional MRI study of automatic movements in patients with Parkinson's disease. Brain 2005; 128: 2250–9.

Yan JH, Rountree S, Massman P, Doody RS, Li H. Alzheimer's disease and mild cognitive impairment deteriorate fine movement control. Journal of Psychiatric Research 2008; 42: 1203–12.

Zanette G, Tamburin S, Manganotti P, Refatti N, Forgione A, Rizzuto N. Different mechanisms contribute to motor cortex hyperexcitability in amyotrophic lateral sclerosis. Clin Neurophysiol 2002; 113: 1688–97.

Zhao Y, Sharma N, LeDoux MS. The DYT1 carrier state increases energy demand in the olivocerebellar network. Neuroscience 2011; 177: 183–94.

Zucchi E, Ticozzi N, Mandrioli J. Psychiatric Symptoms in Amyotrophic Lateral Sclerosis: Beyond a Motor Neuron Disorder. Front Neurosci 2019; 13: 175.

8. TABLES

Study	Year	Patients	Methodology	Major Findings/ Terminology adopted
Clinical studies				
Verger and Cruchet	1907	CD	Clinical description	"Bradykinesie spasmodique " was used to describe the slow involuntary movements in patients
Sheehy and Marsden	1982	29 FHD	Clinical description	Decreased arm swing and increased limb tone. No bradykinesia
Schneider et al.	2007	10 dystonic (UL, cervical or laryngeal)	Clinical description	Facial hypomimia, decreased arm swing. No akinesia with fatiguing and decrement
Stamelou et al.	2013	2 DYT1 dystonia	Clinical description	Clumsy in foot tapping without true bradykinesia in 1 patient
Neurophysiological studies				
Cohen and Hallett	1988	19 FHD	EMG recordings of UL movements triggering the cramps	Co-contraction of agonist and antagonist muscles
Van der Kamp et al.	1989	10 FHD	EMG recordings of UL movements	Slower and more variable elbow flexions, smaller amplitude and longer duration of the first agonist burst, cocontraction of agonists and antagonists
Agostino et al.,	1992	7 FHD	Sequential UL movements	Slowness (specifically referred as bradykinesia) with no sequence effect
Inzelberg et al.	1995	8 ITD	Kinematic analysis of UL reaching movements	Normal RTs. Slowness (specifically referred as bradykinesia) of reaching movements
Horstink et al.,	1997	10 FHD	Pegboard test	No bradykinesia

Currà et al.	2000	9 GD, 6 FHD	Externally triggered and self-initiated sequential rapid UL movements	Prolonged RTs in GD; normale RTs in FHD; slowness of movement, longer pauses between movements in both groups
Murase et al.	2000	10 FHD	RT task (finger extension)	Normal RTs
Buccolieri et al.	2004	6 FHD, 5 CD, 5 multifocal dystonia	RT task (arm flexion), EMG recordings of UL movements	Normal RTs. Impaired muscles relaxation of arm flexions
Jabush et al.	2004	8 FHD	Finger movements	Altered timing parameters
MacKinnon et al.	2004	9 FHD	RT task and EMG recordings of ballistic wrist movements	Normal RTs. Reduced antagonist muscle activity
Carboncini et al.	2004	CD	EMG and kinematic recordings of horizontal arm extensions	Slowness (specifically referred as bradykinesia) due to the reduced recruitment in the initial phase of the agonist muscle activity
Prodoehl et al.	2008	18 FHD	EMG recordings of fast wrist and elbow flexions movements	Slowness (specifically referred as bradykinesia) due to the underactivation of the first agonist burst
Gregori et al.	2008	15 CD	Kinematic recordings of fast rotational, flexion and extension neck movements	Prolonged movement time, reduced peak angular velocity and amplitude (specifically referred as bradykinesia) of neck movements
Pelosin et al.	2009	10 CD	Kinematic recordings of UL reaching movements	Impaired reaching movements, with altered trajectories and lower velocity and acceleration peaks
Furuya et al.	2013	17 FHD	Finger	Stronger keystrokes,

			movements	slowness and rhythmic inconsistency.
Jankowski et al.	2013	18 FHD	RT task (finger movements)	Normal RTs
Simonyan et al.	2013	18 spasmodic dysphonia	RT task and analysis of finger tapping	Prolonged RTs. Normal number of taps and accuracy
Katschnig-Winter et al.	2014	12 CD	Fast UL movements (using a joystick to move a cursor) .	Normal motor performance, except for an higher peak velocity, normal motor sequence learning and a visuomotor adaptation task
Shaikh et al.	2015	11 CD	Head saccades recorded by a magnetic search coil technique	Longer duration due to multiple pauses in the trajectory of the head movement. No appropriateness of the terms 'slowing' or 'bradykinesia'
Bologna et al.	2016	13 FHD and 13 CD	Kinematic recording of UL reaching movements and head movements	Normal kinematics of upper limb reaching movements, lower amplitude and velocity of neck movements in CD patients
Kishore et al.	2018	37 FHD	Choice RT tack (reaching movements)	Normal RTs
Conte et al.	2018	24 BPS, 31 CD, 16 FHD	EMG and kinematic recordings of ballistic finger movements	Normal root mean square amplitude of EMG activity and normal velocity
Furuya et al.	2018	20 FHD	Sequential finger movements (strikes of piano keys)	Inconsistent and prolonged keypresses

Abbreviations: BPS: blepharospams; CD: cervical dystonia; EMG: electromyography; FHD: focal hand dystonia: GD: generalized dystonia; ITD: idiopathic torsion dystonia; RTs: reaction times; UL: upper limbs

Table 1. Clinical and neurophysiological results on bradykinesia in dystonia

Study	Year	Patients	Methodology	Major Findings/ Terminology
Clinical studies				
Hamilton et al.	1908	27 HD	Clinical description	Slowness of movement
Herz et al	1931	HD	Clinical description	Slowness and irregularity of movement (specifically referred as 'asynergy')
Campbell et al.	1961	2 HD	Clinical description and pathological observation	Parkinsonism
Neurophysiological studies				
Hefter et al.	1987	22 HD	Accelerometric recordings of finger extensions and alternating movements	Slowness of movements
Thompson et al.	1988	10 HD	Fast simple wrist flexion movements	Slowness (specifically referred as bradykinesia) and greater movement variability
Agostino et al.,	1992	9 HD	Sequential UL movements	Slowness (specifically referred as bradykinesia) with no sequence effect
Bradshaw et al.	1992	18 HD	Sequential button pressing task	Prolonged movement initiation and duration
Jahanshahi et al.	1993	7 HD	RTs (finger movements)	Prolonged RTs
Georgiou et al.	1995	20 HD	Button-presses series	Slowness (specifically referred as bradykinesia)
Garcia Ruiz et al.	2000 and 2002	18 HD /20 HD	Different timed tests (Pronation-supination, finger dexterity, movement between two points and	Altered movement parameters (specifically referred as bradykinesia), progressively

			walking test)	worsening during time
Johnson et al.	2000	12 HD	Bimanual cranking task	Variability and low accurancy
van Vugt et al.	2004	76 HD	RT task (finger movements)	Prolonged RTs, slowness (specifically referred as bradykinesia)
Andrich et al.	2007	42 HD	Tapping test	Reduced taping rate decreasing during time
Hinton et al	2007	29 pre-HD	Paced finger-tapping task	Motor timing variability
Bechtel et al.	2010	120 pre-HD, 123 HD	Metronome tapping task	Higher tapping variability than normal
Rowe et al.	2010	747 pre-HD	Paced tapping task	Low timing precision
Martinez Pueyo et al.	2013	30 HD	RT task (finger movement) and self-paced timing precision task	Slowness (specifically referred as bradykinesia) and altered rhythm

Abbreviations: HD: Hungtington's disease; RT: reaction time

Table 2. Clinical and neurophysiological results on bradykinesia in Hungtington's disease

Study	Year	Patients	Methodology	Major Findings/ Terminology
Clinical studies				
Hornabrook and Nagurney	1976	175 ET	Epidemiologic study	3/175 ET presented hypokinesis, increase in tone and poverty of associated movements
Geragthy et al.	1985	130 ET	Clinical description	25 ETPD with bradykinesia
Cleeves at al.	1988	237 ET	Clinical description	4.2% of patients presented parkinsonism (2 patients with UL bradykinesia)
Lou and Jankovic	1991	350 ET	Clinical description from a database	20.2% of patients presented parkinsonism
Koller et al.	1994	678 ET	Clinical description	6.1% of patients presented parkinsonism
Tallòn-Barranco et al.	1997	365 ET	Clinical description	8.7% of patients presented parkinsonism
Fekete at al.	2013	2 ET	Clinical description	Bilateral UL bradykinesia on finger tapping hand grips, hand pronation/supination as well as on foot taps and heel taps
Jiménez-Jiméeza et al.	2010	61 ET	Clinical description	Slowness in finger tapping (specifically referred as bradykinesia), normal values of pronation-supination, movement between two points and walking test

Neurophysiological studies				
Elble et al.	1994	10 ET	Timing analysis of rapid wrist flexion	Normal RTs and MTs
Deuschl et al.	2000	26 ET	Kinematic analysis of grasping	Slowing of the total reach-to-grasp movement in ET with kinetic tremor
Montgomery et al.	2000	8 ET	RT task (wrist flexions and extensions)	Decreased movement velocity (specifically referred as bradykinesia) and tendency toward increased RTs (specifically referred as akinesia)
Özekmekçi et al.	2005	17 ET	Movement times around metacarpophalangeal,wrist, elbow, and shoulder joints	Normal movement times except for slight prolongation of shoulder movements, ascribed to tremor, not to bradykinesia
Duval et al.	2006	10 ET	Rapid alternating movements (fast pronation–supination at the wrist)	Increase of pronation–supination cycle duration (specifically referred as bradykinesia)
Farkas et a.	2006	34 ET	Regularity and the maximum frequency of auditory paced repetitive movements (finger tapping and alternating hand movements)	High rhythm variability
Heroux et al.	2006	31 ET	UL dexterity tests	Altered measures of upper extremity function
Costa et al.	2010	18 ET	Accelerometric analysis of finger-tapping and unbounded forearm	Slowness in execution of repetitive

			movements between two points	oscillatory movements (specifically referred as bradykinesia)
Jiménez-Jiménez et al.	2010	61 ET	Speed for pressing repetitively a key, visual reaction time and movement time	Impairment of speed for pressing repetitively a key and of visual reaction time (specifically referred as bradykinesia); normal movement time
Goubault et al.	2017	15 ET	'Counting money' counting task	Prolonger duration of pronation–supination cycle (specifically referred as bradykinesia) with no reduced amplitude of movement
Bologna et al.	2020	90 ET	Kinematic analysis of finger tapping	Slowness of movements with no sequence effect (specifically referred as bradykinesia)

Abbreviations: ET: essential tremor; MT: movement time; PD: Parkinson's disease;RT: reaction time; UL: upper limbs

Table 3. Clinical and neurophysiological results on bradykinesia in essential tremor

Study	Year	Patients	Methodology	Major Findings/ Terminology
Clinical studies				
Takiyama et al.	1994	30 genetic cerebellar patients	Clinical description	Slowness of movements
Stoodley et al.	2016	18 cerebellar stroke patients	Clinical evaluation of UL motor functions (including finger tapping)	Impaired performance in patients with anterior lobe lesion
Neurophysiological studies				
Beppu et al.	1984	15 cerebellar patients	Visuomotor tracking movements (elbow flexions)	Prolonged RTs, altered amplitude of the initial peak velocity in proportion to the target velocity; altered smoothness; delayed initiation of deceleration phase; irregular EMG activity in the agonist muscles and co-contraction of the antagonistic muscles
Avarello et al.	1988	10 cerebellar patients	Analysis of rapid isometric force changes	Slowness of the force increasing phases
Mai et al.	1988	31 chronic cerebellar disease patients	Continuous measurement of finger force during different tasks	Slowing of the speed in repetitive force changes
Fujita and Nakamura	1989	9 spinocerebellar degeneration patients	Force analysis of knee extensor muscles	Longer time from the rise of tension to its maximum
Becker et al.	1990	3 cerebellar patients	EMG recordings of threwing a ball at a target	Abnormal EMG antagonist onset times; abnormal visual-motor

				coordination
Brown et al	1990	9 cerebellar patients	Visually guided, step tracking movements about the elbow	Short acceleration and long deceleration durations
Hallett et al.	1991	13 cerebellar patients	EMG recordings of elbow flexion movements at different angular distances	Prolonged duration and acceleration time of the first agonist burst.
Hore et al.	1991	9 cerebellar patients	Kinematic and EMG recordings of large and small movements at the elbow, wrist, and finger	Decreased peak accelerations and increased peak decelerations; more gradual buildup; prolongation of agonist activity and delayed onset of antagonist activity
Diener et al.	1992	18 cerebellar patients	Displacements of the center of foot pressure and EMG recordings during rising on tiptoes	Tonic EMG activity, altered latencies of the EMG activity with increased time interval between motor preparation and execution, increased variability
Jahanshahi et al.	1993	8 cerebellar patients	RTs (finger movements)	Prolonged simple and choice RTs
Bonnefoi-Kyriacou et al.	1995	12 cerebellar patients	RTs (UL movements)	Prolonged RTs and MTs
Bastian et al.	1996	7 cerebellar patients	Kinamatic analysis of reaching UL movements	Slowness of movement with altered wrist paths and force torque
Wild et al.	1997	18 cerebellar patients	Analysis of fast goal-directed and no targeted wrist flexions	Slowness of movements due to a decreased acceleration peak
Day et al.	1998	17 cerebellar patients	Kinematic analysis of reaching arm movements	Prolonged RTs; Slowness of movement; altered spatial paths; lower

				accurancy; increased variability
Topka et al.	1998	9 cerebellar patients	Kinematic analysis of reaching arm movements	Deficit in generating appropriate levels of muscular force
Konczak et al.	2010	16 cerebellar stroke patiens	Kinematics of goal-directed and unconstrained finger-pointing movements	Slowness of movements (specifically referred as bradykinesia)

Abbreviations: EMG: electromyography; MT: movement time; RT: reaction time; UL: upper limbs

Table 4. Clinical and neurophysiological results on bradykinesia in cerebellar disorders

Study	Year	Patients	Methodology	Major Findings/ Terminology
Clinical studies				
Williams et al.,	1995	1 PMA	Clinical description	Parkinsonism
Qureshi et al.	1996	13 ALS	Clinical description	Bradykinesia
Desai and Swash	1999	3 ALS	Clinical description	Hypokinesia
D'Ascenzo et al	2012	16 ALS with predominan involvement of the upper motor neurons	Clinical description	Bradykinesia
Pupillo et al.	2015	146 ALS	Clinical description	Bradykinesia
Neurophysiological studies				
Hallett et al.	1979	27 ALS	EMG recordings of rapid elbow flexions	Prolongation of the first agonist and antagonist bursts
Oskarsson et al.	2016	10 ALS	3D kinematic assessment of the reachable workspace	Decreased reachable workspace, reflecting arm dysfunction
Shellikeri et al.	2016	33 ALS	3D electromagnetic articulography of tongue and jaw movements	Reduced tongue movement size and speed
De Bie et al.	2017	10 ALS	3D kinematic assessment of the reachable workspace (longitudinal evaluation)	Progressive reduction of the reachable workspace, able to quantify declines in upper extremity ability over time
Kuruvilla-Dugdale M and Chuquilin-Arista	2017	7 ALS	3D electromagnetic articulography of orofacial movements	Decreased velocity, reduced range of movement and longer utterance durations.

Abbreviations: ALS: amyiotrophic lateral sclerosis; EMG: electromyography; PMA: progressive muscular atrophy

Table 5. Clinical and neurophysiological results on bradykinesia in motoneuron diseases

Study	Year	Patients	Methodology	Major Findings/ Terminology adopted
Clinical studies				
Tsolaki et al.,	2001	126 AD	Clinical description	Bradykinesia
Scarmeas et al.	2004	474 AD	Clinical description	Bradykinesia
Louis et al.	2005	608 MCI	Clinical description	Mild bradykinesia
Scarmeas et al	2005	533 AD	Clinical description	Bradykinesia-hypokinesia
Aggarwal et al.	2006	198 MCI and 60 AD	Clinical description (longitudinal cohort study)	Bradykinesia, lower extremity motor performance and parkinsonian gait in MCI, inversely related to risk of AD
Israeli-Korn et al	2010	173 MCI	Clinical description	Limb bradykinesia
Schirinzi et al.	2018	37 AD	Clinical description	Mild presence of extrapyramidal signs
Vöglein et al.	2019	433 autosomal dominant AD	Clinical description	Bradykinesia
Neurophysiological studies				
Kluger et al.	1997	25 MCI and 25 mild AD	Nine motor function tests (including finger and toe tapping, hand dynamometer, Purdue Pegboard Test, drawing test)	Slowness in finger tapping and impaired Hand steadiness in AD
Schröter et al.	2003	39 MCI and 35 AD	Kinematic handwriting analysis	Low regularity and accuracy in AD
Camarda et al.	2007	11 MCI and 11 AD	Kinematic analysis of goal-directed movement	Slight motor dysfunction in MCI; remarkable slowing down of pointing in AD
Yan et al.	2008	9 MCI and 9 AD	Analysis of handwriting	Slower, less smooth, less coordinated, and

			movement on a digitizer	less consistent handwriting movements in AD and MCI
Rabinowitz and Lavner	2014	170 elderly participants	Finger tapping analysis through a touchpad mounted on a pressure transducer	Increased length and variability of the finger-touch phase in participants with MCI or dementia compared to participants with no cognitive impairment
Roalf et al.	2018	46 MCI and 131 AD	Finger tapping analysis through a highly sensitive light-diode finger tapper	Fewer taps than healthy controls, with longer inter-tap interval and higher intra-individual variability
Suzumura et al.	2018	15 MCI and 31 AD	Finger dexterity using a smart terminal device	Abnormal response time, rhythm, and contact duration in AD
Bologna et al.	2020	20 AD	Kinematic analysis of repetitive finger-tapping	Slowness of movement and altered rhythm compared
Colella et al.	2020	14 MCI	Kinematic analysis of repetitive finger-tapping	Altered rhythm

Abbreviations: AD: Alzheimer disease; MCI: Mild Cognitive Impairment

Table 6. Clinical and neurophysiological results on bradykinesia in Alzheimer disease and Mild Cognitive Impairment

Study	Year	Patients	Methodology	Major Findings/ Terminology adopted
Clinical studies				
Vieregge et al.	1992	2 MS	Clinical description	Bradykinesia
Maranhão-Filho et al.	1995	1 MS	Clinical description	Hypokinesia
Burn and Cartlidge	1996	1 MS	Clinical description	Orofacial bradykinesia, general akinesia
Federlein et al.	1997	1 MS	Clinical description	Parkinsonism
Ozturk et al	2002	1 MS	Clinical description	Slow progressive bradykinesia
Folgar et al.	2003	1 MS	Clinical description	Parkinsonism
Barun et al.	2008	2 MS	Clinical description	Bradykinesia in one case, marked rigidity and monolateral rest tremor in the other
Nociti et al.	2008	733 consecutive recruited MS patients	Clinical description	3 patients showed parkinsonism
Drori et al.	2018	22 MS	Clinical description	Very mild parkinsonian signs in 5 patients(i.e. rigidity and hypomimia). No bradykinesia
Neurophysiological studies				
Kujala et al.	1994	45 MS	Simple and choice RTs (finger movements)	Prolonged RTs in MS patients with cognitive deterioration
Kail et al.	1998	11 MS	Choice RTs (finger movements)	Prolonged RTs
De Sonneville et al.	2002	53 MS	RTs task	Prolonged RTs
Morgante et al.	2011	33 MS	Simple RTs (finger movements)	Prolonged RTs
Cabib et al.	2015	20 MS	Simple RTs	Not significantly

			(finger movements)	prolonged RTs.
Beste et al.	2018	21 MS	Dual Task	Impaired accuracy. Normal speed of responding
Shribman et al.	2018	39 MS	The BRadykinesia Akinesia INcordination (BRAIN) test	The number of taps, the mean dwell time on each key and the variance of travelling time between keys correlated with EDSS scores
Lubrini et al.	2020	66 MS	RTs tasks (finger tapping)	Prolonged RTs

Abbreviations: EDSS: Expanded Disability Status Scale; MS: multiple sclerosis; RTs: reaction times

Table 7. Clinical and neurophysiological results on bradykinesia in multiple sclerosis

	ET (90)	PD (84)	HCs (84)
Gender	37F/53M	22F/62M	36F/48M
Age (years)	68.1±11.46	65.46±9.56	63.95±10.25
Age at onset (years)	55.41±19.96	61.64±9.52	-
Disease duration (years)	12.66±12.99	3.5±2.83	-
Familial history	50 Y/40 N	3 Y/81 N	-
Head tremor	21 Y/69 N	-	-
FTMTRS tot	19.10±11.33	-	-
MDS-UPDRS III	5.5±2.62	30.36±13.35	-
Postural tremor frequency	7.72±6.38	-	-
Postural tremor amplitude	0.56±0.34	-	-

ET: essential tremor patients; PD: Parkinson's disease patients; HCs: healthy controls; F: female; M: male; FTMTRS: Fahn-Tolosa-Marin Tremor Rating Scale; MDS-UPDRS III: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale motor section (part III).

Table 8. Clinical and demographic features in patients with essential tremor (ET), Parkinson's disease (PD), and healthy controls (HCs)

	Age	Gender	Time to diagnosis	MMSE	FAB	BDI-II	UPDRS-III
1	81	F	36	22	15	13	3
2	77	M	1	20	13	4	9
3	72	M	1	15	10	14	8
4	75	M	24	23	14	8	1
5	85	F	36	22	4	21	31
6	87	M	24	26	15	3	0
7	83	F	12	24	14	6	5
8	78	M	24	23	12	16	23
9	79	F	6	24	10	15	1
10	60	F	12	20	13	15	7
11	73	F	4	21	7	16	1
12	88	F	3	16	8	18	0
13	76	M	36	20	13	6	1
14	88	M	60	14	10	0	13
15	77	F	18	16	3	8	18
16	71	M	24	13	3	11	7
17	79	F	12	18	8	13	2
18	59	M	6	22	12	15	0
19	71	M	4	20	16	10	5
20	82	M	24	17	6	7	1

F = female, M = male; Time to diagnosis is expressed in months and refers to the time between the diagnosis of Alzheimer's disease and the clinical-neurophysiological assessment; MMSE = Mini Mental State Examination; FAB = Frontal Assessment Battery; BDI-II = Beck Depression Inventory; UPDRS-III = Unified Parkinson's Disease Rating Scale, part III.

Table 9. Clinical and demographic features in patients with characteristics of patients with Alzheimer's disease.

	SICI	SAI	M1 plasticity
Coefficient of variation	0.07 (0.77)	-0.10 (0.68)	-0.03 (0.90)
Velocity intercept	-0.14 (0.56)	**-0.58 (0.008)**	-0.06 (0.81)

Pearson's correlation coefficient is shown out of brackets, while the P value is shown within brackets. Significant correlations are in bold. SICI = short-interval intracortical inhibition, average SICI at 2 and 4 ms; SAI = short-latency afferent inhibition, average SAI at 22 and 24 ms; M1 plasticity = average changes in MEP amplitude after iTBS across the three measurement time points.

Table 10. Correlations between kinematic and TMS measures in patients with Alzheimer's disease.

	MMSE	FAB
Coefficient of variation	0.46 (0.04)	**-0.59 (0.006)**
Velocity intercept	0.12 (0.62)	0.31 (0.19)

Spearman's rank correlation coefficient is shown out of brackets, while the P value is shown within brackets. Significant correlations are in bold. MMSE = Mini Mental State Examination; FAB = Frontal Assessment Battery. Note that the corrected alpha level for this set of correlations is 0.0125.

Table 11. Correlations between kinematic and clinical scales in patients with Alzheimer's disease.

	MMSE	FAB
SICI	-0.03 (0.89)	0.09 (0.69)
SAI	-0.15 (0.52)	-0.20 (0.41)
M1 plasticity	-0.36 (0.12)	-0.03 (0.90)

Spearman's rank correlation coefficient is shown out of brackets, while the P value is shown within brackets. Significant correlations are in bold. SICI = short-interval intracortical inhibition, average SICI at 2 and 4 ms; SAI = short-latency afferent inhibition, average SAI at 22 and 24 ms; M1 plasticity = average changes in MEP amplitude after iTBS across the three measurement time points. Note that the corrected alpha level for this set of correlations is 0.008.

Table 12. Correlations between TMS measures and clinical scales in patients with Alzheimer's disease.

	Gender	Age (Years)	Disease duration (months)	MoCa	FAB	BDI-II	UPDRS-III	ALSFRS-R
1	F	82	48	26	18	14	24	35
2	F	72	10	26	17	4	23	37
3	M	68	24	27	17	4	0	48
4	F	61	29	26	18	5	35	37
5	M	58	28	25	17	12	7	42
6	M	63	12	28	16	34	0	39
7	M	73	60	20	18	5	27	37
8	M	64	20	27	17	13	8	42
9	F	64	9	28	17	12	18	40
10	M	49	8	26	18	2	4	47
11	M	81	24	26	14	15	28	46
12	F	65	72	25	18	12	30	34
13	F	62	40	20	16	31	50	30
Mean	-	66.3	29.53	25.38	17	12.53	19.53	39.31
SD	-	9.04	20.23	2.56	1.51	9.92	15.09	1.51

ALSFRS-R= ALS Functional Rating Scale-Revised; BDI-II = Beck Depression IInventory, part II; F= female; M = male; FAB = Frontal Assessment Battery; MoCA = Montreal Cognitive Assessment; UPDRS-III = Unified Parkinson's Disease Rating Scale, part III; SD = standard deviation.

Table 13. Clinical-demographic characteristics of patients with amyotrophic lateral sclerosis.

9. FIGURES

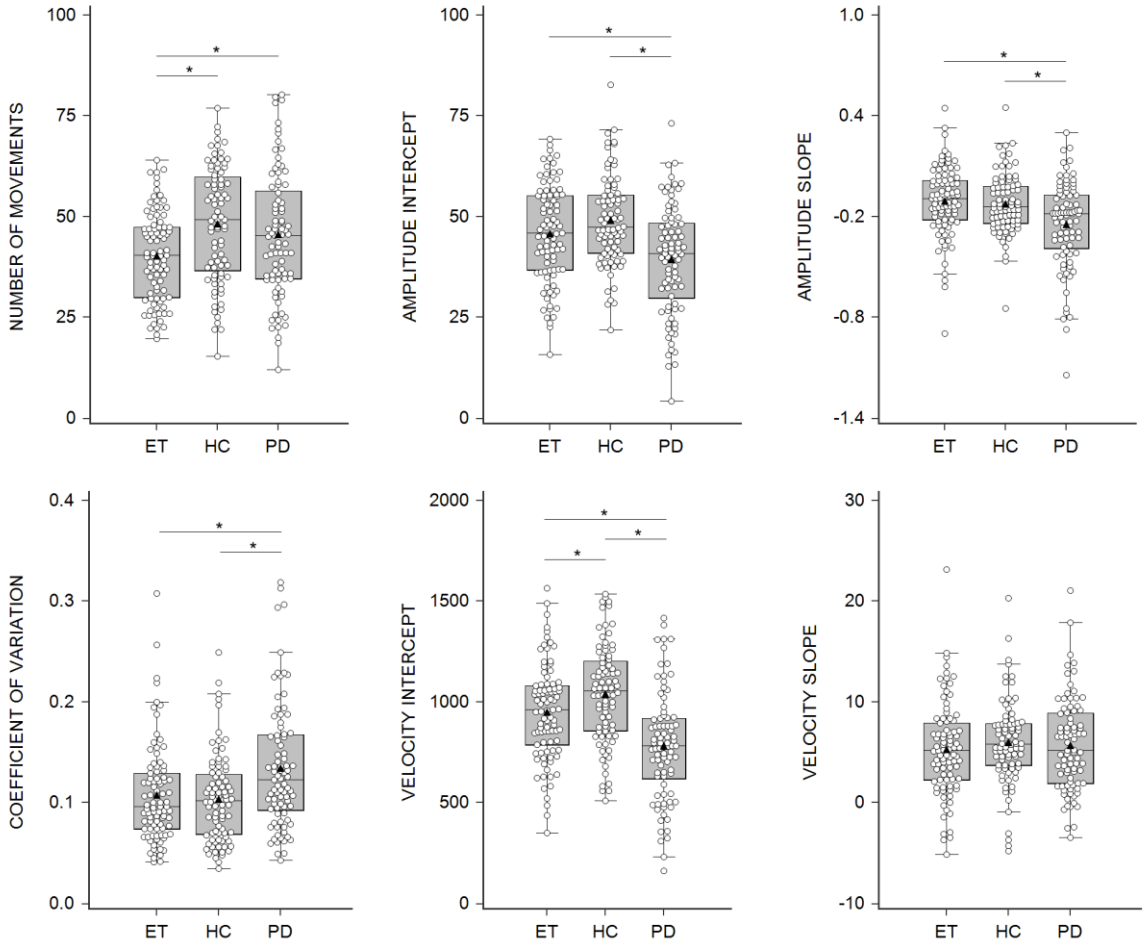


Figure 1: Kinematic variables of repetitive finger movements in patients with essential tremor (ET) and Parkinson's disease (PD) and in healthy controls (HCs). Number of movements reflect the movements performed in the 15 sec recording. Amplitude intercept is expressed in degrees, amplitude slope in degrees/n mov, velocity intercept in degrees/sec, and velocity slope in (degrees/sec)/n mov. Coefficient of variation reflects the variability of the inter-tapping intervals (with higher values representing higher movement irregularity). Triangles indicate the mean values, boxes indicate ± 1 standard error of the mean; whiskers indicate ± 1 standard deviation of the mean. Circles indicate each individual value in the three groups. Asterisks indicate $P < 0.05$ in the post-hoc comparisons.

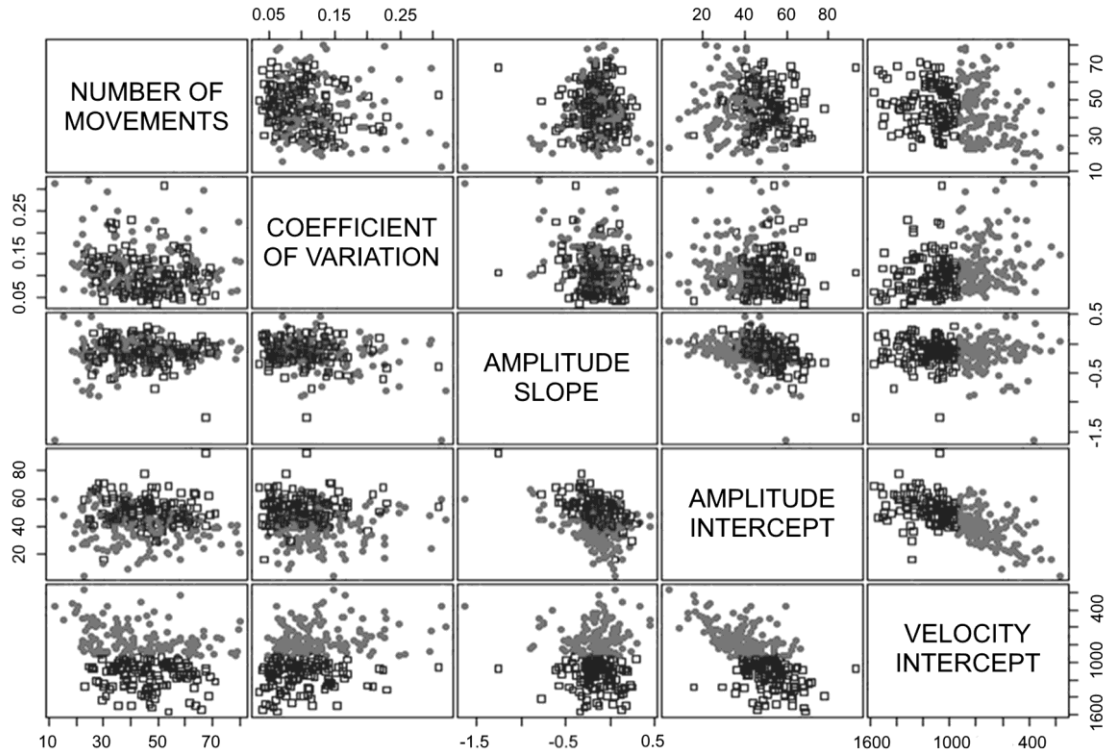


Figure 2: Cluster analysis. Kinematic variables of repetitive finger movements in subjects in cluster 1 (white squares) and cluster 2 (grey circles). The coefficient of variation (CV) of the inter-tap intervals refers to the movement rhythm (with higher values representing lower regularity of repetitive movements). The amplitude slope (representing amplitude decrement across the 15-s trials) refers to the sequence effect. Velocity slope was not included in the cluster analysis because it did not differ between ET patients, PD patients, and HCs, as demonstrated by ANOVA. Notably, participant categorization into the two groups was mainly due to the presence of movement slowness, reduced movement amplitude, and irregular rhythm, while sequence effect had less influence on data categorization.

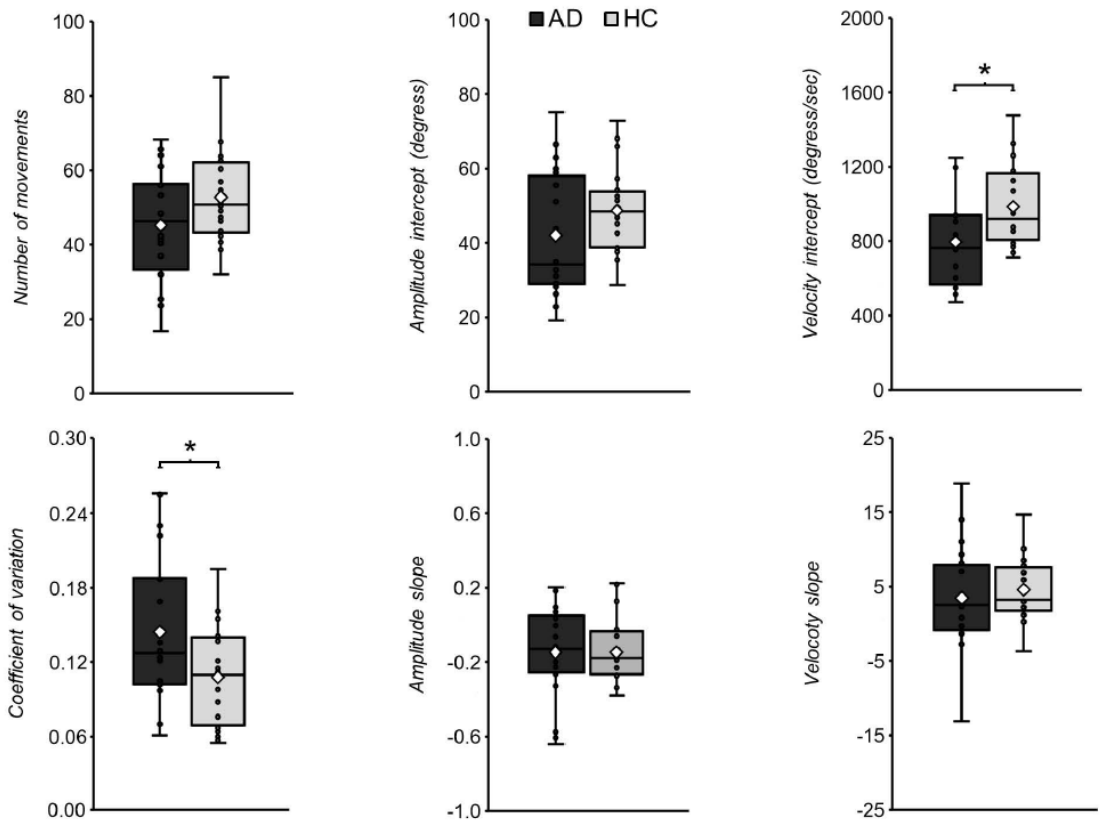


Figure 3: Kinematic measures of finger tapping in Alzheimer's disease (AD) and healthy controls (HC). Dots indicate individual data. White diamonds indicate the average values. Horizontal lines denote the median value (50th percentile). The boxes contain the 25th to 75th percentiles of dataset. Asterisks indicate significant differences between groups at post-hoc analyses.

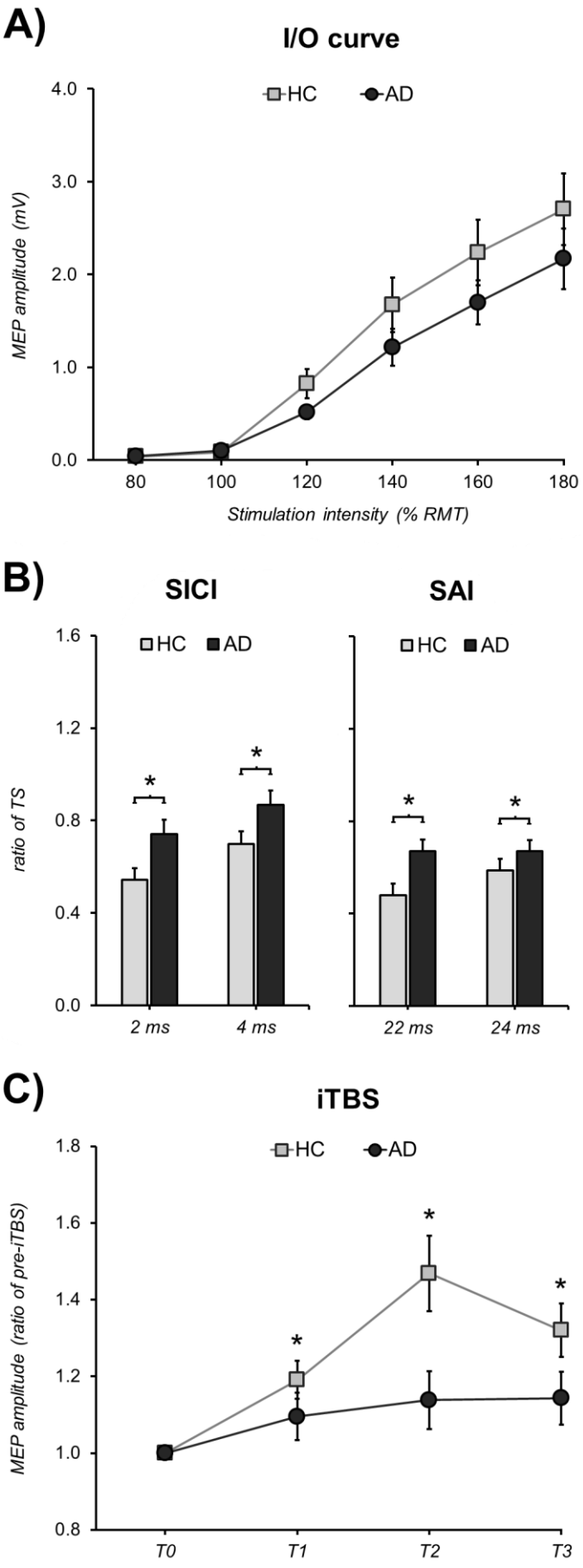

A)
I/O curve
HC
AD
MEP amplitude (mV)
4.0
3.0
2.0
1.0
0.0
80
100
120
140
160
180
Stimulation intensity (% RMT)
B)
SICI
SAI
HC
AD
ratio of TS
1.6
1.2
0.8
0.4
0.0
2 ms
4 ms
22 ms
24 ms
C)
iTBS
MEP amplitude (ratio of pre-iTBS)
1.8
1.6
1.4
1.2
1.0
0.8
T0
T1
T2
T3

Figure 4: TMS measures recorded in Alzheimer's disease (AD) and healthy controls (HC). *Panel A.* The input-output curve of MEPs in patients with AD and HC. The y-axis shows the MEP amplitude (mV); the x-axis shows the six stimulation intensities tested (80, 100, 120, 140, 160 and 180 % of the resting motor threshold – RMT). *Panel B.* Short-interval intracortical inhibition (SICI) and short-latency afferent inhibition (SAI) in AD patients and HC. The y-axis shows the ratio between conditioned and unconditioned MEP amplitudes; the x-axis shows the interstimulus intervals tested (2 and 4 ms for SICI, 22 and 24 ms for SAI). *Panel C.* Changes in MEP amplitude after the intermittent theta-burst stimulation (iTBS) protocol in AD patients and HC. The y-axis shows MEP amplitudes normalized to baseline (T0); the x-axis shows measurements at the four time points: before iTBS (T0) and 5 (T1), 15 (T2) and 30 minutes (T3) after iTBS. Asterisks indicate significant differences between groups at post-hoc analyses.

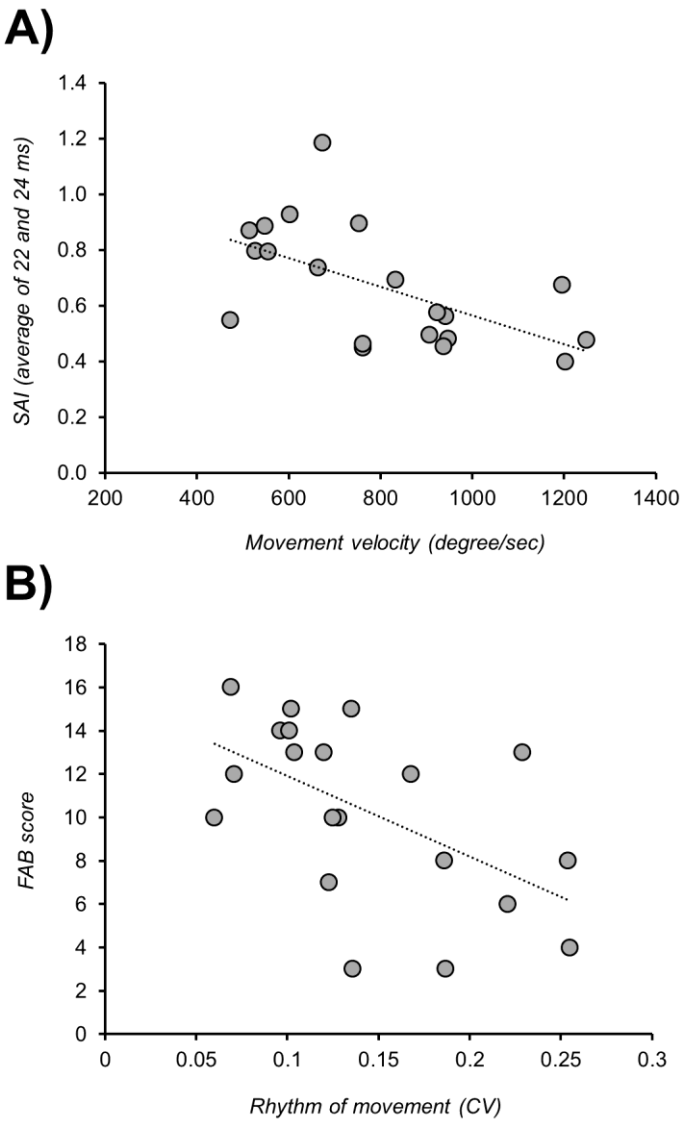


Figure 5: Neurophysiological and clinical-neurophysiological correlations in patients with Alzheimer's disease. *Panel A.* Relationship between movement velocity (i.e. velocity intercept) and short-afferent inhibition (SAI). *Panel B.* Relationship between movement rhythm (i.e. coefficient of variation – CV) and Frontal Assessment Battery (FAB) scores.

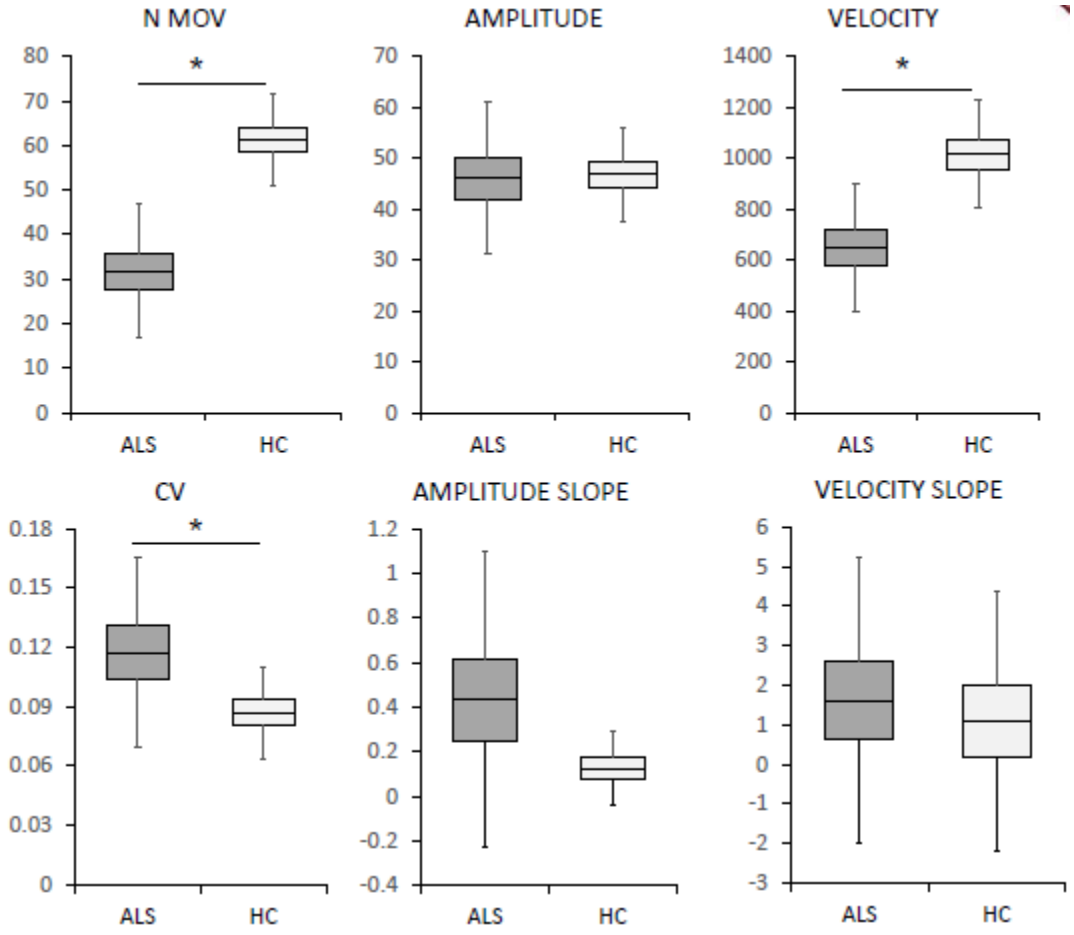


Figure 6: Kinematic variables of repetitive finger movements in patients with amyotroc lateral sclerosis - ALS (dark grey) and in healthy controls - HCs (light grey). Data were compared by a one-way ANOVAs. Horizontal lines denote the average values. The boxes contain the mean value ± 1 SE of the mean. Whiskers contain the mean value ± 1 SD of the mean. Asterisks indicate $P < 0.05$.

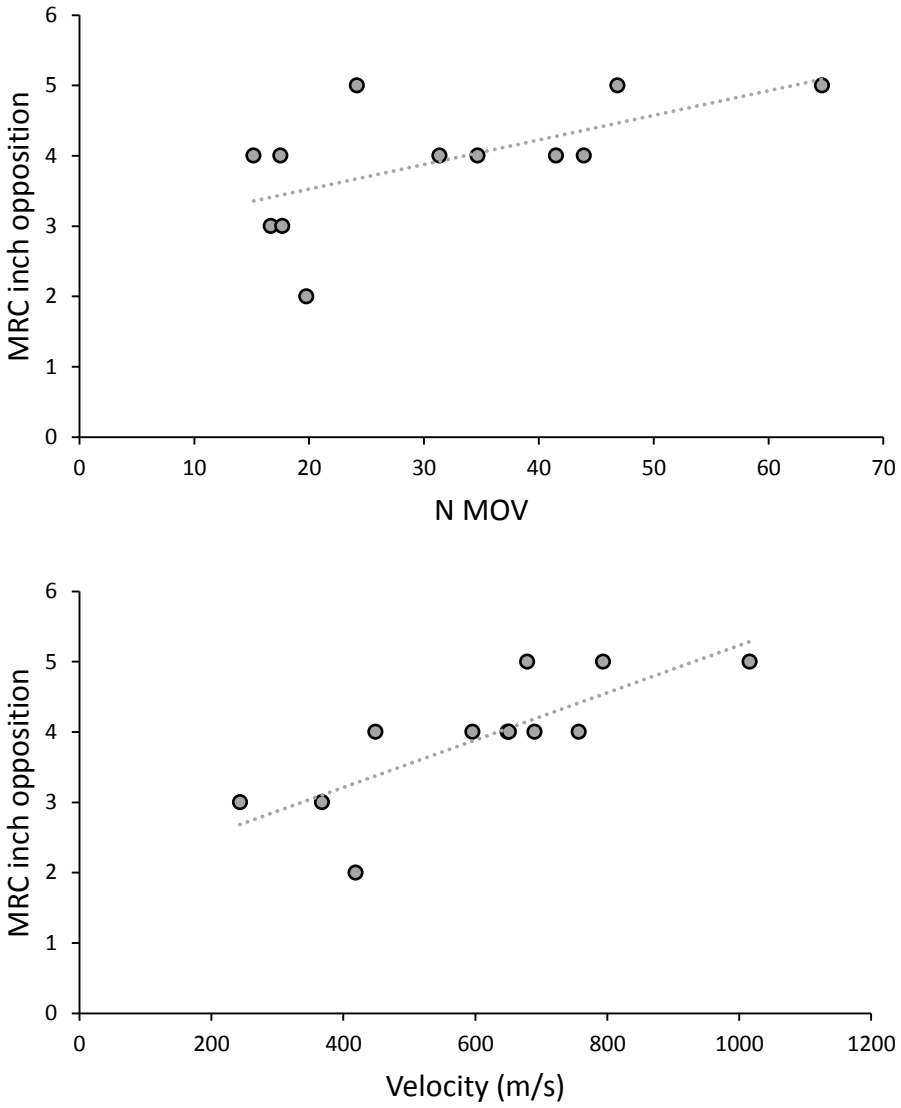
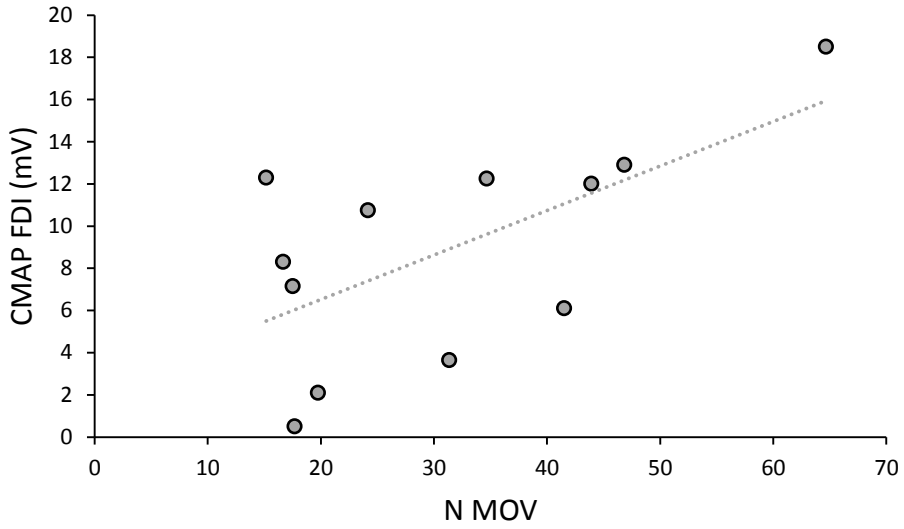
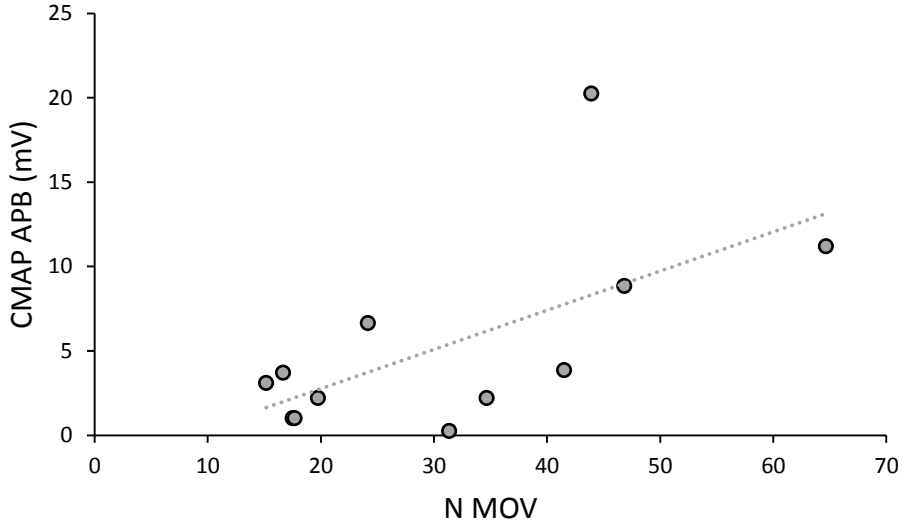


Figure 7: Correlation between the number of movements (upper figure) and the velocity peak (bottom figure) in amyotrophic lateral sclerosis patients during the finger tapping and the MRC score in inch opposition.


CMAP FDI (mV)
N MOV
0
2
4
6
8
10
12
14
16
18
20
0
10
20
30
40
50
60
70


CMAP APB (mV)
N MOV
0
5
10
15
20
25
0
10
20
30
40
50
60
70

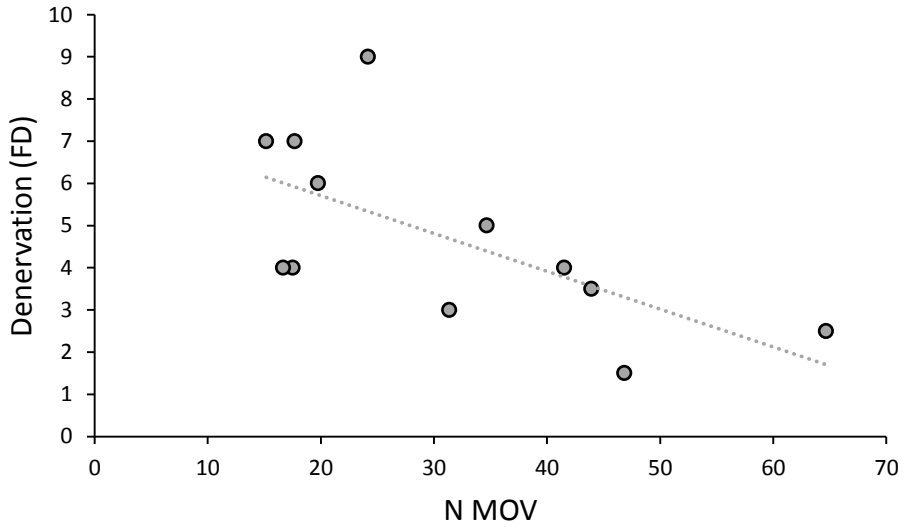

Denervation (FD)
N MOV
0
1
2
3
4
5
6
7
8
9
10
0
10
20
30
40
50
60
70

Figure 8: Correlation between the number of movements and the compound muscle action potential (CMAP) recorded from the first dorsal interosseus (FDI) (upper figure), the CMAP recorded from the abductor pollicis brevis (APB) (in the middle) and the denervation from the FDI (bottom figure) in patients with amyotrophic lateral sclerosis.

10. SUPPLEMENTAL MATIERIAL

	ET RH	ET LH	P value
Number of movements	38.6±12.6	37.6±12.2	0.10
Coefficient of variation	0.109±0.04	0.108±0.04	0.93
Amplitude intercept	46.5±11.3	47.8±10.7	0.51
Amplitude slope	-0.08±0.19	-0.08±0.23	0.91
Velocity intercept	944.5±252.5	938.0±263.9	0.83
Velocity slope	5.15±4.1	5.37±5.4	0.74

Supplementary Table 1. No difference emerged when comparing kinematic features of voluntary movements between the right hand (RH) and left hand (LH) in a subgroup of 50 ET patients. P values result from unpaired t-tests.

	PD RH (43)	PD LH (41)	P value
Number of movements	42.4±15.5	48.8±15.1	0.07
Coefficient of variation	0.142±0.06	0.129±0.07	0.33
Amplitude intercept	40.2±14.7	38.3±12.7	0.54
Amplitude slope	-0.29±0.32	-0.21±0.25	0.19
Velocity intercept	777.6±293.9	778.5±245.3	0.99
Velocity slope	6.24±4.8	5.11±4.4	0.27

Supplementary Table 2. No difference emerged when comparing kinematic features of finger tapping between PD patients whose most affected side was the right (RH) vs. the left (LH). P values result from unpaired t-tests.