The continuum between neurodegeneration, brain plasticity, and movement: a critical appraisal

**Introduction**

It is now increasingly recognized that motor and cognitive decline characterize the aging process. Both motor and cognitive abnormalities contribute to the so-called frailty syndrome, intended as the reduction of the individual’s homeostatic reserves that leads to an increased vulnerability to stressors and to a higher risk for adverse outcomes (Canale et al. 2017). Several constructs such as motoric cognitive risk syndrome (Vergehe et al. 2013), and cognitive frailty (Kelaifiti et al. 2013), have been used in order to explore the combined effect of these dysfunctions on the individual risk and health profiles. Along the same lines, motor and cognitive abilities are incorporated in recent models that have been developed to tentatively measure and monitor longitudinally the composite of all the capacities of a person for personalized interventions (Cesari et al. 2018). Aging is associated with cognitive decline, mainly in learning and memory abilities, and is accompanied by multi-factorial changes within the hippocampus, including volumetric reduction, atrophy, neuroinflammation, and reduced trophic support (Bettio et al. 2017). While the “physiological” aging process might be associated with declines in certain motor and cognitive features, these changes should not result in a significant impairment in function (Schott 2017).

Beyond the “physiological” aging processes, motor and cognitive impairment constitute the most common phenotypic expressions of pathological aging, due to neurodegeneration. Both manifestations frequently coexist in the same disease entity, thus making difficult to detect “pure” motor or cognitive conditions. From one side, movement disorders are conceptualized as neurological syndromes in which the “motor” phenomena represent the main clinical manifestation. However, growing evidence indicate that these conditions are often characterized by the co-occurrence of cognitive disturbances (Table 1). Likewise, in neurodegenerative dementias, commonly intended as the prototype of cognitive disorders, a sizeable proportion of patients with dementia exhibit the occurrence of movement disorders at various disease stages (Merello and Starkstein 2014). In neurodegenerative conditions, including movement disorders and dementia, the deterioration in both motor and cognitive features result in functional impairment (Gale et al. 2018).
In the present article, we will review motor and cognitive features characterizing “physiological” aging. We will then move on summarizing the clinical and pathophysiological aspects of neurodegeneration in animal models as well as in humans with motor and cognitive impairment in order to disclose commonalities in clinical entities traditionally considered distinct. Also, we will discuss overlapping neurodegenerative aspects with a focus on synaptopathy and oscillopathy as the common pathogenic background. Finally, we will discuss the possible role of movement as a putative neuroprotective intervention in neurodegenerative conditions. The present review could be critical to draw the next steps for the possible neuroprotective strategies and the future directions of research studies in neurodegenerative disorders (Figure 1).

Physiological aging

Human brain undergoes several changes due to “physiological” aging, such as brain atrophy (Seidler et al. 2010), small vessels disease (Pantoni 2010), and aggregation of misfolded proteins like α-synuclein, tau, 42-amyloid-β peptide (Aβ42) (Markesbery et al. 2009). All these changes have been documented in the brain of cognitively normal

Table 1: Clinical overlap between motor and cognitive features in neurodegeneration.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Main protein accumulation</th>
<th>Main motor features</th>
<th>Main cognitive features*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s disease</td>
<td>α-syn</td>
<td>Tremor, rigidity, bradykinesia, postural instability (Postuma et al. 2015).</td>
<td>Impairment in executive, memory, learning, visuospatial domains (Kehagia et al. 2010).</td>
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<tr>
<td>Multiple system atrophy</td>
<td>α-syn</td>
<td>Same as Parkinson’s disease but more severe and poorly levodopa responsive; ataxia in cerebellar type (Gilman et al. 2008).</td>
<td>Frontal-executive dysfunction, memory and visuospatial impairments (Santangelo et al. 2018).</td>
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<tr>
<td>Progressive supranuclear palsy</td>
<td>4-R-Tau</td>
<td>Akinetic-rigid, predominantly axial and levodopa resistant parkinsonism; gait impairment with recurrent falls; ocular motor dysfunction (Höglinger et al. 2017).</td>
<td>Speech/language disturbances, bradyphrenia, dys-executive syndrome, apraxia, behavioral changes (e.g., apathy, impulsivity, disinhibition, perseveration) (Höglinger et al. 2017).</td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Amyloid-β 3-R-Tau</td>
<td>Bradykinesia, rigidity, postural or resting tremor, altered speech and facial expression (McKann et al. 2011).</td>
<td>Amnestic presentation: impairment in learning and recall of recently learned information. Non-amnestic presentations: prominence of language or visuospatial or executive dysfunctions. Progression to widespread dementia (McKann et al. 2011).</td>
</tr>
<tr>
<td>Frontotemporal dementias</td>
<td>4-R-Tau</td>
<td>Parkinsonism, motor neuron disease, motor stereotypies, gait disturbances (Rascovsky et al. 2011).</td>
<td>Behavioral variant: disinhibition, apathy, perseverative/stereotyped behaviors, hyperorality and dietary changes, executive dysfunction. Linguistic variants: progressive aphasias with prominent nonflucent/agrammatic or semantic, or logopenic characteristics (Rascovsky et al. 2011).</td>
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<tr>
<td>Essential tremor</td>
<td></td>
<td>Upper limb tremor ± head, voice, or tremor in other body regions (Bhatia et al. 2018).</td>
<td>Mostly executive dysfunction but also impairments in language, memory and visuospatial abilities (Bologna et al. 2019b).</td>
</tr>
</tbody>
</table>

α-syn, Alpha synuclein; 4-R-Tau, four-repeat-Tau protein; 3-R-Tau, three-repeat-Tau protein; HTT, Huntingtin.

*These cognitive disturbances can exhibit a varying severity, ranging from mild cognitive impairment to overt dementia.
and relatively healthy older individuals (Espay et al. 2019; Markesbery et al. 2009), and are reflected by modifications at the cellular/molecular levels (mitochondrial dysfunction, oxidative distress, abnormal calcium signaling, neuroinflammation) (DiSabato et al. 2016; Mattson and Arumugam 2018). During aging, the network activity within and between brain areas can be altered with important implications. For instance, the excitatory imbalance resulting from an impaired inhibitory signaling (GABA) can result in hyperexcitability and excitotoxicity. The dysregulation of other neurotransmitter systems (acetylcholine, dopamine, serotonin) has been linked with neurodegeneration and impaired brain functions (Mattson and Arumugam 2018). As a consequence, synaptic plasticity mechanisms are also affected during “physiological” aging, as shown by non-invasive brain stimulation studies (Freitas et al. 2011). Taken together, these observations contribute to the clinical features detectable in the “healthy” elderly. For instance, an increased muscle tone associated with a concomitant decrease of muscle strength, is reported with aging, as well as other mild motor signs (slowness of movement, resting tremor, and gait/postural abnormalities) (Bennett et al. 1996). Along the same line, declines in individual’s cognitive functioning (language, visuospatial, and executive functions) are considered as unavoidable with aging, although age-related changes in cognition are not uniform across all older individuals and an extreme heterogeneity in term of cognitive performance is observed among older people (Glisky 2007).

### Pathological aging due to neurodegeneration

Pathological aging is associated with several neurodegenerative changes resulting in structural and functional abnormalities within the nervous system. Thus, most neurodegenerative conditions share cognitive and motor abnormalities.

### Cognitive features in movement disorders

Patients with pathological aging, namely Parkinson’s disease (PD) and atypical parkinsonisms, the most common neurodegenerative movement disorders, may present with various neuropsychological deficits within the executive, memory, learning and visuospatial domains, and are at increased risk of developing mild cognitive impairment (MCI) and dementia (Armstrong et al. 2013; Fabbrini et al. 2019; Höglinger et al. 2017; Kehagia et al. 2010; McKeith et al. 2017). Both PD and multiple system atrophy (MSA) patients show a similar impairment in executive functions (Santangelo et al. 2018). Cognitive and behavioral abnormalities may be present at onset or even before motor symptoms become manifest in progressive supranuclear palsy (PSP) patients with a prevalence ranging from 15 to 50% (Fabbrini et al. 2019). Patients with Corticobasal degeneration (CBD) often develop abnormalities in attention/concentration, social
cognition, executive functions, verbal fluency, language, and visuospatial functioning (Fabbrini et al. 2019). However, motor signs referred to as “higher order motor disorders” consisting in disorders of disinhibition and motor intention, alien limb syndrome, and motor overflow phenomena, also occur in Corticobasal degeneration (Kojović and Bhatia 2019). Dementia with Lewy bodies (DLB) patients may show variable degree of cognitive impairment, associated with neuropsychiatric symptoms such as visual hallucinations and paranoid delusions (McKeith et al. 2017). PD and atypical parkinsonisms are also characterized by mood disorders, which may be misdiagnosed as classical non-motor symptoms, such as apathy and anedonia (Aarsland et al. 2011; Galts et al. 2019). Up to 30–40% of Parkinsonian patients are affected by some form of mood depression during the course of disease (Reijnders et al. 2008). Considered to be one of the most influential factors over patient quality of life (Schrag et al. 2000), mood disorders can be present from early to late stages of Parkinsonian diseases (Starkstein et al. 1990).

Other non-Parkinsonian neurodegenerative movement disorders such as Huntington disease (HD) and essential tremor may present comorbid neurocognitive and psychiatric dysfunctions as well (Bologna et al. 2019; Maurage et al. 2016). Huntington disease patients often exhibit mood disorders, personality changes (e.g., manic and depressive disturbances), and slowed intellectual processes, of which onset can precede that of core motor symptoms by decades (Dewhurst 1970; Galts et al. 2019; Gil and Rego 2008; Jensen et al. 1993; Rizvi et al. 2017).

Motor features in dementias

Motor features are described in up to one fourth of and hippocampus respectively (AD) cases and have been associated with poorer cognitive and functional outcomes (Portet et al. 2009; Scarmeas et al. 2004). Namely, patients with AD can develop limb/axial bradykinesia and rigidity, postural or resting tremor as well as altered speech and facial expression. Based on the frequent occurrence of these manifestations, the existence of a “cognitive and motor” phenotype of AD is postulated (Montero-Odasso et al. 2017). In this framework, both cognitive and motor symptoms are considered concomitant phenotypic expressions of the disease (Scarmeas et al. 2004, 2005). Besides AD, patients with frontotemporal dementia (FTD) also present motor disorders associated with modifications in personal and social conduct, disinhibition, and progressive changes in language (Baizabal-Carvallo et al. 2016). Accordingly, FTD can be associated with a wide spectrum of hypokinetic as well as hyperkinetic movement disorders (Baizabal-Carvallo et al. 2016). Parkinsonian motor signs are a distinctive feature of DLB and are considered as a core criterion for its clinical diagnosis (Marsili et al. 2019; McKeith et al. 2017). Accumulating evidence suggests that a varying degree of motor dysfunction may precede the onset of cognitive disturbances and appear in the preclinical phase of dementias (Buchman and Bennett 2011).

Motor dysfunction reflects systemic neurodegeneration in movement disorders and dementias

Quantitative motor assessment allows to precisely describing the impairment in different movement types and it is commonly used as a measure of bradykinesia and fine motor abilities in PD (Bologna et al. 2016, 2019b; Espay et al. 2011; Maetzler et al. 2015). Likewise, a recent study by Roalf et al. (2018), found that PD, AD, and MCI patients had fine motor impairments in finger tapping tested through kinaesthetic quantitative measures, compared to age-matched healthy subjects (HS). Jeppesen Kragh et al. (2018) have quantitatively assessed motor dysfunction in AD, FTD, and DLB patients, without finding any difference in the finger tapping between these pathological conditions and HS. By contrast, the pronation/supination task did differ in the dementia group compared to HS. These apparently conflicting results might be due to several factors, including the different methods used in the two studies (kinematic quantitative measures vs. Q-motor test), as well as the medication status (“ON” vs. “OFF” dopaminergic therapy). In another study by Goldman et al. (1999), finger tapping, and reaction times were assessed in AD patients without clinical evidence of motor signs. The authors documented a general “motor slowing” in all measures suggesting that AD may be associated with motor slowing in a stage-dependent manner. Abnormal finger tapping correlating with disease severity have been also recently documented, through kinematic quantitative measures, in AD patients by Bologna and colleagues (2020).

Gait analysis in advanced stages of PD is known to be characterized by a reduced cadence and short and slow steps and strides compared to HS (Creaby and Cole 2018). Also in AD and other dementias, gait slowness has been documented through wearable sensors analyses. In particular, reduction of speed, stride length, and the
increase of the cycle time have been documented in AD and FTD, being more severe in the latter (Rucco et al. 2017). Again, Choi et al. (2018) showed that all gait parameters (cadence, step and stride time, walking speed, step and stride length) are significantly altered in AD as well as MCI patients, being significantly correlated with the impairment in cognitive tests. Taken together, these observations suggest that motor control is impaired not only in movement disorders, but also in dementias.

**Synaptopathy as a common background for neurodegenerative conditions**

The clinical overlap of different neurodegenerative diseases inevitably implies common pathophysiological mechanisms, which essentially comprise the impairment of synaptic transmission across the various functional systems of the brain.

Physiological neural transmission relies on the “health” of synapses and on the efficiency of synaptic communication, which also include phenomena of activity-dependent modifications of the synaptic strength, the so-called “synaptic plasticity” (Cooke and Bliss 2006), which, in turn represents the neurobiological substrate of learning and memory (Mango et al. 2019). Synaptic plasticity has been long studied and many experimental paradigms have been developed to evaluate such a critical property directly on brain tissue of animal models or in vivo in humans. Briefly, mechanisms of synaptic plasticity include long-term potentiation (LTP) and long-term depression (LTD), consisting into up- or down-regulation of synaptic strength, respectively (Cooke and Bliss 2006). While animal models allow exploring synaptic plasticity over the entire brain, for example at hippocampal level to study episodic memory and cognition or at cortico-striatal level for motor learning (Schirinzi et al. 2016), in humans synaptic plasticity is mainly tested over the primary motor cortex (MI) (Huang et al. 2017; Suppa et al. 2016a, 2017; Ziemann and Siebner 2008).

Abnormalities in synaptic structure and function have been recently defined with the term “synaptopathy” (Busche and Konnerth 2015; Schirinzi et al. 2016). Of interest, a large body of evidence demonstrated that synaptopathy is a common feature among different neurodegenerative conditions, appearing at early stages and progressing along the clinical-pathological course. Therefore, the synaptopathy seems to be the common pathogenic background of different neurodegenerative diseases, but also a dynamic phenomenon occurring in a critical time-window, in which a therapeutic intervention can be effective, reverting functional abnormalities and preventing the consequences of neurodegeneration (Imbriani et al. 2018; Schirinzi et al. 2016, 2019).

**Animal models of Parkinson and Alzheimer diseases: a source to dissect neurodegeneration and attempt novel neuroprotective strategies**

Discoveries in the genetic makeup of neurodegenerative diseases have led to the use of animal models to further explore synaptic abnormalities. Compelling evidence demonstrates that synaptopathy, independent from the modeled molecular breakdown, affects brain areas critically involved in PD and AD (motor circuits and hippocampus respectively) over the entire course of neurodegeneration (Dietrich et al. 2018; Imbriani et al. 2018) (summarized in Table 2).

Synaptic dysfunctions occurring at early stages of neurodegeneration are the most relevant to neuroprotection because they represent a functional impairment, possibly reversible through appropriate interventions. In this regard, evidence from PD animal models is paradigmatic. PD is a multifactorial disorder, due to the concurrence of synucleinopathy, mitochondrial dysfunction, oxidative stress, neuroinflammation, and proteasomal/lysosomal impairment, which collectively lead to nigrostriatal deafferentation (Kalia and Lang 2015; Obeso et al. 2017). Regardless of the initial cause or the presence of neuropathological phenomena, once the dopaminergic signaling is weakened, plasticity of cortico-striatal synapses is disrupted (Imbriani et al. 2018; Schirinzi et al. 2016). Cortico-striatal synaptopathy, in turn, impairs the physiological transmission through the cortex-basal ganglia loops, accounting for abnormalities in motor behavior. During early stages of dopaminergic denervation, massive compensatory mechanisms keep such abnormalities at subclinical level (Beeler et al. 2013). However, in the absence of disease-modifying treatments, neurodegeneration progresses, causing breakdown of motor networks and overt signs of PD (tremor, rigidity, Bradykinesia). Conversely, an appropriate intervention counteracting pathogenic events may interrupt this cascade, preventing the clinical onset of the disease (Martella et al. 2016; Schirinzi et al. 2016, 2019).

Findings from AD models are similar. Indeed, neurochemical alterations and synaptopathy preceding plaque deposition, tau accumulation, and neural loss in
Table 2: Synaptopathies in animal models of Parkinson’s and Alzheimer’s diseases: synoptic table.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Disease model</th>
<th>Hallmarks</th>
<th>Phenotype</th>
<th>Synaptic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parkinson’s disease</strong></td>
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<tr>
<td>Garcia-Reitbock et al. (2010)</td>
<td>α-synuclein transgenic mice</td>
<td>Expression of truncated human α-synuclein</td>
<td>Reduced locomotion</td>
<td>Reduction of dopamine release in age-dependent manner</td>
</tr>
<tr>
<td>Janezic et al. (2013)</td>
<td>BAC transgenic mice</td>
<td>Overexpression of human wild-type α-synuclein</td>
<td>Motor abnormalities</td>
<td>Impairment in synaptic transmission of Substantia Nigra pars compacta dopaminergic cells</td>
</tr>
<tr>
<td>Paillé et al. (2010)</td>
<td>Unilateral 6-OHDA rat</td>
<td>Dopamine denervation</td>
<td>Motor abnormalities</td>
<td>Selective impairment of LTP at corticostriatal synapses</td>
</tr>
<tr>
<td>Chou et al. (2014)</td>
<td>LRRK2 transgenic mice</td>
<td>Expression of G2019S mutant LRRK2</td>
<td>Motor abnormalities</td>
<td>Impairment in synaptic transmission of Substantia Nigra pars compacta dopaminergic cells</td>
</tr>
<tr>
<td>Sloan et al. (2016)</td>
<td>LRRK2 BAC transgenic rats</td>
<td>Expression of G2019S or R1441C mutant LRRK2</td>
<td>Motor abnormalities</td>
<td>Selective impairment of LTD at corticostriatal synapses</td>
</tr>
<tr>
<td>Ginns et al. (2014)</td>
<td>CBE mouse</td>
<td>Subchronic CBE exposure to inhibit GCase</td>
<td>Motor abnormalities</td>
<td>Reduction of dopamine release</td>
</tr>
<tr>
<td>Mercado et al. (2018)</td>
<td>Unilateral 6-OHDA mouse</td>
<td>Dopamine denervation</td>
<td>Motor abnormalities</td>
<td>Reduction of dopamine release</td>
</tr>
<tr>
<td>Kitada et al. (2007)</td>
<td>PINK1&lt;sup&gt;−/−&lt;/sup&gt; mice</td>
<td>Homozygous PINK1 knockout mice</td>
<td>No</td>
<td>Reduction of dopamine release</td>
</tr>
<tr>
<td>Madeo et al. (2014)</td>
<td>PINK1&lt;sup&gt;−/−&lt;/sup&gt; mice</td>
<td>Heterozygous PINK1 knockout mice</td>
<td>No</td>
<td>Reduction of dopamine release</td>
</tr>
<tr>
<td>Molina-Luna et al. (2009)</td>
<td>6-OHDA lesioned rat</td>
<td>Dopamine denervation</td>
<td>Motor abnormalities</td>
<td>Reduction of dopaminergic terminals in M1</td>
</tr>
<tr>
<td>Matheus et al. (2016)</td>
<td>6-OHDA lesioned rat</td>
<td>Dopamine denervation</td>
<td>Motor abnormalities</td>
<td>Reduction in optical density of TH in PFC</td>
</tr>
<tr>
<td>Guo et al. (2015)</td>
<td>6-OHDA lesioned - reserpine injection</td>
<td>Dopamine denervation</td>
<td>Motor abnormalities</td>
<td>Structural changes in M1</td>
</tr>
<tr>
<td><strong>Alzheimer’s disease</strong></td>
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<tr>
<td>Bouter et al. (2013)</td>
<td>Tg4-42 transgenic mice</td>
<td>Expression of human Aβ&lt;sub&gt;42&lt;/sub&gt;</td>
<td>Spatial memory deficit</td>
<td>Abnormal transmission and impaired synaptic activity in CA1 subfield of hippocampus</td>
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<tr>
<td>Alexandru et al. (2011)</td>
<td>TBA2.1hom transgenic mice</td>
<td>Expression of N-truncated Aβ</td>
<td>Behavioral and motor abnormalities</td>
<td>Impairment of synaptic activity in CA1 subfield of hippocampus</td>
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<tr>
<td>D’amelio et al. (2011)</td>
<td>Tg2576 transgenic mice</td>
<td>Expression of human mutated APP</td>
<td>Memory deficit</td>
<td>Impairment of morphology and activity in synapses of CA1 hippocampal subfield</td>
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<tr>
<td>Chapman et al. (1999)</td>
<td>PD-APP transgenic mouse</td>
<td>Expression of PDGF–APP transgene</td>
<td>NA</td>
<td>Impairment in transmission and plasticity in synapses of CA1 hippocampal subfield</td>
</tr>
</tbody>
</table>

728  T. Schirinzi et al.: Neurodegeneration, plasticity, and movement
<table>
<thead>
<tr>
<th>Author, year</th>
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<th>Hallmarks</th>
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</thead>
<tbody>
<tr>
<td>Sturchler-Pierrat et al. (1997)</td>
<td>APP23 transgenic mice</td>
<td>Expression human or murine Thy-1 and human APP</td>
<td>NA</td>
<td>Impaired synaptic transmission in CA1 hippocampal subfield</td>
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<td>Kuo et al. (2001)</td>
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<td>Roder et al. (2003)</td>
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<td>Oakley et al. (2006)</td>
<td>SxFAD transgenic mice</td>
<td>Co-overexpression of human APP and PS1 harboring five familial AD mutations</td>
<td>Memory deficit</td>
<td>Impaired transmission and plasticity in synapses of CA1 hippocampal subfield</td>
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<td>Jawhar et al. (2012)</td>
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<td>Wittnam et al. (2012)</td>
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<td>Kimura and Ohno (2009)</td>
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<td>Crouzin et al. (2013)</td>
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<td>Casas et al. (2006)</td>
<td>APPS1PS1KI transgenic mice</td>
<td>Knock-in mutations in presenilin-1 and overexpression mutated human APP</td>
<td>NA</td>
<td>Impaired transmission and plasticity in synapses of CA1 hippocampal subfield</td>
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<td>Christensen et al. (2008)</td>
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<td>Breyhan et al. (2009)</td>
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<td>Savonenko et al. (2005)</td>
<td>APPswe/PS1dE9 transgenic mice</td>
<td>Expression of a chimeric mouse/human mutated APP plus mutated PS1</td>
<td>Memory deficit</td>
<td>Impaired synaptic activity within hippocampus</td>
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<td>Busche et al. (2012)</td>
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<td>Jolas et al. (2002)</td>
<td>TgCRND8 transgenic mice</td>
<td>Increased Aβ load</td>
<td>Memory deficit</td>
<td>Impaired transmission and plasticity in synapses of CA1 hippocampal subfield</td>
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<tr>
<td>Oddo et al. (2003)</td>
<td>3×Tg-AD transgenic mice</td>
<td>Increased Aβ load</td>
<td>Memory deficit</td>
<td>Impaired transmission and plasticity in synapses of CA1 hippocampal subfield</td>
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<td>Clark et al. (2015)</td>
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BAC, bacterial artificial chromosome; 6-OHDA, 6-Hydroxy-Dopamine; SNpc, substantia nigra pars compacta; LTD, long-term depression; LTP, long-term potentiation; M1, primary motor cortex; TH, tyrosine hydroxylase; PFC, prefrontal cortex; NA, not available; CBE, conduritol-β-epoxide; GCase, glucocerebrosidase; Aβ, amyloid-β; APP, amyloid precursor protein; PS1, presenilin-1; PDGF, platelet-derived growth factor; TBA, tert-butyl alcohol.

The data support the hypothesis that reverting synaptopathy at early stages of neurodegeneration may prevent the clinical and pathological progression of the disease.

**Altered plasticity at cortical synapses in humans with movement disorders and dementias**

Neurodegeneration processes, as a result of the accumulation of both α-synuclein (α-synucleinopathies: PD, MSA, DLB) and/or tau protein (tauopathies: AD, PSP, CBD, FTDP) have several pathophysiological consequences. Impairment of dopaminergic and cholinergic neurotransmission is a well-recognized consequence of α-synucleinopathies (Calabresi et al. 2006). Similarly, tauopathies also lead to an impaired cholinergic, GABA-ergic, and glutamatergic neurotransmission (Busche et al. 2012; Cespón et al. 2018). In addition, dopaminergic dysregulation in the ventral tegmental area has been recently demonstrated since early stages of AD (Serra et al. 2018). From a physiological standpoint, α-synuclein and tau deposition directly impairs brain plasticity mechanisms (Bologna et al. 2012, 2017a, b; Conte et al. 2012; Di Lorenzo et al. 2016; Di Stasio et al. 2018; Ghiglieri et al. 2018; Koch et al. 2014; Suppa et al. 2010, 2014). Thus, neurodegeneration is reflected in abnormal neural excitability and brain plasticity mechanisms (Cespón et al. 2018; Heuninckx et al. 2008).

Cortical plasticity, intended as activity-dependent changes in synaptic transmission, may be tested in vivo in humans with non-invasive brain stimulation techniques as repetitive transcranial magnetic stimulation (rTMS) (Suppa et al. 2016a, 2017; Ziemann et al. 2008). In rTMS studies, plasticity refers to changes in motor evoked potential amplitudes during brain stimulation or outlasting it by seconds (short-term plasticity) or minutes (long-term plasticity) (Suppa et al. 2016a, 2017). The rTMS techniques have been largely employed to examine M1 plasticity in

Hippocampus (Dietrich et al. 2018) can be rescued by drugs interfering with the amyloid cascade (Busche et al. 2012). These data support the hypothesis that reverting synaptopathy at early stages of neurodegeneration may prevent the clinical and pathological progression of the disease.
PD patients. The rationale is that since M1 is an important
target of basal ganglia output, it may show secondary
modifications due to chronic changes in the pattern of
activity it receives. Neurophysiological studies in patients
with PD have documented changes in M1 plasticity
(Bologna et al. 2018; Eggers et al. 2010; Suppa et al. 2011,
2016a, 2017). Abnormal M1 synaptic plasticity has been
documented also in atypical Parkinsonian syndromes,
either α-synucleinopathies as multiple system atrophy
(Suppa et al. 2014), or tauopathies as progressive supra-
nuclear palsy (Bologna 2017a; Conte et al. 2012) and
corticobasal syndrome (Di Stasio et al. 2019; Suppa et al.
2016b), with possibly distinctive patterns (Bologna et al.
2017b).

Also, among AD and other neurodegenerative de-
dentias, M1 plasticity has been found to be abnormal. TMS
studies have shown impaired LTP-like (Inghilleri et al.
2006; Trebbastoni et al. 2015), but normal LTD-like (Koch
et al. 2014) cortical plasticity in AD. These alterations have
been documented since early phases of AD, showing that
cortical LTP-like plasticity disruption is a central mecha-
nism, independent from age of onset (Di Lorenzo et al.
2016). Ferreri et al. (2016) have demonstrated that in “mild”
AD the sensorimotor system is hyperexcitable, despite the
lack of clinical motor manifestations; similar observations
have been also reported in the “early” phase of PD (Kishore
et al. 2012). Recently, Di Stasio et al. (2018) have docu-
mented abnormal M1 long-term potentiation/LTD-like
plasticity tested by TBS in patients with “FTD and Parkin-
sonian symptoms”, suggesting neurodegenerative pro-
cesses similar to those described in PD, in the cortico-basal
ganglia network in this patients’ subgroup.

These observations suggest the intimate relationship
at physiological network level between motor and cogni-
tive circuits, in neurodegenerative diseases mediated by
accumulation of α-synuclein as well as tau proteins.

The unifying concept of “oscillopathies”

Synaptic transmission functionally connects distinct
neuronal networks throughout the brain. The synchroni-
ation of synaptic activity creates electrical rhythms or
“oscillations”, recordable by neurophysiological tech-
niques (Nimmrich et al. 2015). Such oscillations reflect the
dynamics of neural circuits and have both temporal and
causal relationships with behavioral phenotypes. Accord-
ingly, the term “oscillopathies” refers to all conditions
characterized by abnormal oscillatory brain activity
following the disruption of a neural network at microscopic
or macroscopic levels (Takeuchi and Berényi 2020).

Neurodegenerative disorders exhibit peculiar patterns
of brain oscillations that correlate with motor or cognitive
disturbances, even independently from the etiology of the
underlying disease (Chan et al. 2016; Li et al. 2015). More-
over, neuronal oscillations might track common pathogenic
pathways across different clinical entities (Chan et al. 2016).

From this perspective, “oscillopathy” represents an
emerging concept that provides a unified view of neuro-
degenerative diseases and possibly a path for novel clinical
approaches, considering that network impairment prevails
over molecular events in every single disorder (Chan et al.
2016; Nimmrich et al. 2015).

Movement as a neuroprotective
intervention: environmental
enrichment and physical exercise

Motricity has a peculiar bidirectional relationship with
synaptic activity. Indeed, motor impairment, either as an
overt clinical sign or an “endophenotypic” trait, may
mirror synaptopathy underlying the different neurode-
generative diseases (Ferreri et al. 2016; Schirinzi et al. 2016)
conversely, motor exercise initiates a number of processes,
which directly or indirectly supports the synaptic “health”
of the brain, providing neuroprotective effects.

These latter data came from studies on environmental
enrichment, an experimental setting in which animal
models are kept in a stimulating environment that poten-
tiates social interactions, learning and memory, and
sensory-motor stimulation, which collectively promote
several neuroprotective mechanisms and stimulate multi-
ple neurotransmitter systems (Mattson and Magnus 2006;
Mora et al. 2007). More recently, other experiments dis-
closed that practicing motor activity might modulate brain
synapses in a neuroprotective manner (Table 3). In fact, PD
mice models forced to perform physical exercise, exhibited
increased synaptogenesis and neural connectivity at
striatal level (Garcia et al. 2017), which suggests that motor
exercise may restore and enhance synaptic function even
into the site primarily affected by synaptopathy in PD,
highlighting the potential role as a neuroprotective inter-
vention. Likewise, also in animal models of AD interesting
results have been reported. Namely, in 5×FAD mice it has
been demonstrated that physical exercise boosts adult
hippocampal neurogenesis and ameliorates both neuro-
pathology and cognitive deficits, favoring the release of
neurotrophins and growth factors, stimulating synaptic
activity, and reducing neuroinflammation (Choi et al.
2018).
Table 3: Major pre-clinical studies in animal models of Parkinson’s or Alzheimer’s diseases that have evaluated the potential beneficial effects of physical exercise on brain plasticity: synoptic Table.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Disease model</th>
<th>Aims</th>
<th>Study settings</th>
<th>Main results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parkinson’s disease</strong></td>
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<tr>
<td>Chen et al. (2018)</td>
<td>6-OHDA PD-mice model</td>
<td>To determine the influences of exercise on motor deficits and dopaminergic transmission in a hemiparkinson animal model</td>
<td>6-OHDA PD-mice with exercise vs. no exercise</td>
<td>Exercise could improve motor walking speed. Exercise also ameliorated spatiotemporal impairments in gait in PD animals. Exercise increased the parameters of synaptic plasticity formation in the corticostriatal pathway as well as the dynamics of dopamine transmission.</td>
<td>Treadmill training could ameliorate spatial-temporal gait impairment, improve walking speed, dopamine transmission as well as corticostriatal synaptic plasticity in the unilateral 6-OHDA rat model.</td>
</tr>
<tr>
<td>Garcia et al. (2017)</td>
<td>OHDA PD-mice model</td>
<td>To study the impact of short and long-term treadmill exercise during evolution of the unilateral 6-hydroxyl-dopamine (6-OHDA) animal model of PD</td>
<td>Sedentary vs. exercise rats</td>
<td>Higher reduction of corticostriatal glutamatergic synaptic drive in sedentary groups when compared to exercised groups.</td>
<td>These modifications may be relevant for corticostriatal circuits in PD, since the exercise-dependent plasticity can modulate glutamate receptors expression and neuronal excitability.</td>
</tr>
<tr>
<td>Shin et al. (2016)</td>
<td>MPTP PD-mice model</td>
<td>To study the effect of exercise in synapse and dendritic spine of nigrostriatal dopaminergic neurons on mice with PD</td>
<td>Sham group, sham-exercise treated group, MPTP-treated group, and MPTP-exercise treated group</td>
<td>MPTP treated group displayed poor coordination ability compared with sham group. MPTP-exercise treated group showed good coordination ability compared with MPTP treated group</td>
<td>Exercise may give beneficial effects to patients with PD by facilitating synaptic plasticity and increasing dendritic spines.</td>
</tr>
<tr>
<td>Wu et al. (2011)</td>
<td>LPS PD-mice model</td>
<td>To study whether exercise protects dopaminergic neurons against inflammation-induced injury in the substantia nigra</td>
<td>LPS and wild type with and without exercise</td>
<td>Four weeks of exercise before LPS treatment completely prevented the LPS-induced loss of dopaminergic neurons, reduction of dopamine levels and dysfunction of motor movement.</td>
<td>Exercise protects dopaminergic neurons against inflammation-induced insults.</td>
</tr>
<tr>
<td>Van Leeuwen et al. (2010)</td>
<td>MPTP PD-mice model</td>
<td>To see the effect of treadmill exercise on fast excitatory neurotransmission in the brain, and on synaptic strength and synaptic neuroplasticity</td>
<td>MPTP and wild type mice</td>
<td>Treadmill exercise increased synaptic strength.</td>
<td>These findings suggest a role for the beneficial effects of exercise in modulating experience-dependent neuroplasticity of the injured basal ganglia.</td>
</tr>
<tr>
<td>Petzinger et al. (2007)</td>
<td>MPTP PD-mice model</td>
<td>To determine changes in striatal dopamine by means of intensive treadmill exercise,</td>
<td>MPTP and wild type with and without exercise</td>
<td>Treadmill running improved motor velocity in both exercise groups. All exercised animals also showed increased latency to fall using the accelerating rotarod compared with non-exercised mice. Exercised OHD-infused mice showed improved motor outcomes relative to sedentary lesioned controls.</td>
<td>The benefits of treadmill exercise on motor performance may be accompanied by changes in dopaminergic neurotransmission that vary in the 2 groups.</td>
</tr>
<tr>
<td>O’Dell et al. (2006)</td>
<td>OHDA PD-mice model</td>
<td>1. To see whether a form of voluntary exercise, wheel running, would improve motor performance in rats with such lesions</td>
<td>Exercised vs. sedentary OHDA mice</td>
<td></td>
<td>Exercise facilitates recovery from nigrostriatal injury, but it does so without evident sparing of dopamine nerve terminals.</td>
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<td>Tillerson et al. (2003)</td>
<td>MPTP and 6-OHDA PD-mice models</td>
<td>To see whether any beneficial effects of wheel running are attributable to ameliorating the dopaminergic damage.</td>
<td>Unilateral 6-OHDA vs. bilateral MPTP lesioned mice</td>
<td>Motorized treadmill running improved the neurochemical and behavioral outcomes</td>
<td>Exercise following nigrostriatal damage ameliorates related motor symptoms and neurochemical deficits</td>
</tr>
<tr>
<td>Lourenco et al. (2019)</td>
<td>FNDC5 AD-mice model</td>
<td>To test the hypothesis that FNDC5 could be a key mediator of the beneficial effects of exercise on synaptic plasticity and memory in AD models</td>
<td>FNDC5 vs. wild type mice</td>
<td>Peripheral overexpression of FNDC5 rescued memory impairment, whereas blockade of either peripheral or brain FNDC5 attenuated the neuroprotective actions of physical exercise on synaptic plasticity and memory in AD mice</td>
<td>FNDC5 is a novel agent capable of opposing synapse failure and memory impairment in AD</td>
</tr>
<tr>
<td>Choi et al. (2018)</td>
<td>5XFAD AD-mice model</td>
<td>1. To enhance hippocampal neurogenesis (AHN) for therapeutic purposes 2. To see whether AHN impairment mediates aspects of AD pathogenesis or is a neuroadaptive response to the pathological events of the disease</td>
<td>Mimicking of the effects of exercise on AD mice by genetica lly and pharmacologically inducing AHN in combination with elevating BDNF levels</td>
<td>Exercise provided cognitive benefit to 5XFAD mice, a mouse model of AD, by inducing AHN and elevating levels of brain-derived neurotrophic factor (BDNF). Supressing AHN later led to worsened cognitive performance and loss of pre-existing dentate neurons.</td>
<td>Pharmacological mimetic of exercise, enhancing AHN and elevating BDNF levels, may improve cognition in AD.</td>
</tr>
<tr>
<td>Sun et al. (2018)</td>
<td>Aβ AD–mice model</td>
<td>To see whether exercise could reserve the neural dysfunctions in AD model and its possible neurobiological mechanism</td>
<td>Pre vs. post exercise</td>
<td>Physical exercise increased the neurogenesis and releases the immune response in hippocampal dentate gyrus (DG) region.</td>
<td>Physical exercise prevented the Aβ-induced cognitive deficits</td>
</tr>
<tr>
<td>Tapia-Rojas et al. (2016)</td>
<td>APPswe/PS1ΔE9 AD-mice model</td>
<td>To assess the effect of running on Aβ deposition</td>
<td>Pre vs. post exercise</td>
<td>Voluntary-wheel running decreased both cognitive decline and histopathological changes</td>
<td>Specific neuroprotective effects of running observed in this study includes decreased Aβ burden and increased cell proliferation and neurogenesis</td>
</tr>
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<tr>
<td>Kim et al. (2014)</td>
<td>Aβ25-35 AD-mice model</td>
<td>To investigate the effects of treadmill exercise on short-term memory in relation with neurogenesis</td>
<td>Exercise vs. sedentary</td>
<td>Treadmill exercise alleviated memory impairment and increased apical dendritic length in the Aβ25-35-injected mice</td>
<td>Treadmill exercise may provide therapeutic value for the alleviating symptoms of AD</td>
</tr>
<tr>
<td>Dao et al. (2015)</td>
<td>Aβ AD–mice model</td>
<td>To study the neuroprotective effects of treadmill exercise on early-phase long-term potentiation (E-LTP) and its molecular signaling pathways in AD mice</td>
<td>Control vs. exercise vs amyloid-infused(Aβ), and exercise + amyloid-infused (Ex/Aβ).</td>
<td>Exercise normalized the basal levels of memory and E-LTP-related signaling molecules</td>
<td>Four weeks of moderate treadmill exercise prevents synaptic deficits and deleterious alterations in signaling pathways associated with AD.</td>
</tr>
<tr>
<td>Yuede et al. (2009)</td>
<td>Tg2576 AD-mice model</td>
<td>To examine the effects of voluntary and forced exercise on memory-related behavior, hippocampal volume, plaque number, and soluble Aβ levels in brain tissue</td>
<td>Voluntary vs. forced running vs. sedentary mice</td>
<td>Voluntary running animals showed fewer plaques than all other groups, whereas forced running animals showed an intermediate number of plaques. Both voluntary and forced running animals had larger hippocampal volumes than sedentary animals.</td>
<td>Voluntary exercise may be superior to forced exercise for reducing certain aspects of AD-like deficits</td>
</tr>
<tr>
<td>Mirochnic et al. (2009)</td>
<td>APP23 AD-mice model</td>
<td>To assess how age affects the response to activity and to study the effects of physical exercise and environmental enrichment</td>
<td>APP23 vs. wild type</td>
<td>At 18 months, both exercise and enrichment increased the number of newborn granule cells of APP23 mice when compared with wild type</td>
<td>Environmental enrichment even more than exercise might contribute to a “neurogenic reserve” despite a stable plaque load and that age affects the outcome</td>
</tr>
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</table>

PD, Parkinson’s disease; 6-OHDA, 6-Hydroxy-Dopamine; MPTP, 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine; LPS, lipopolysaccharide; AD, Alzheimer’s disease; vs., versus; NA, not available; E-LTP, early-phase long-term potentiation; Aβ, amyloid-infused; APPswe/PS1ΔE9, amyloid precursor protein/presenilinDE9; Aβ25-35, amyloid β25-35.
In agreement with preclinical data, it has been demonstrated that patients with mild and initial PD undergoing an intensive physical training showed an improvement of cortical synaptic activity with an increase of M1 excitability, as assessed by TMS (Fisher et al. 2008). Nowadays, cerebral synaptic activity can be also assessed, to some extent, in peripheral human fluids (cerebrospinal fluid –CSF– or blood) by measuring the concentration of proteins involved in molecular processes. For instance, CSF levels of Aβ42 inversely reflect brain amyloid plaques accumulation, such that this biomarker is commonly used either to diagnose AD or to predict future dementia in PD. However, since amyloid peptides play a crucial role in synaptic transmission, the reduction of CSF-Aβ42 might also underlie a widespread loss of synapses in multiple neurochemical systems, even unrelated to brain amyloidopathy (Martorana et al. 2015; Schirinzi et al. 2018a, 2018c). At this regard, it should be noticed that in non-demented PD patients the CSF-Aβ42 content directly correlated with the amount of weekly physical activity, being higher in those practicing vigorous exercise (Alwardat et al. 2019). Of interest, similar findings have been obtained in AD patients too, whose motor ability, in general, declines in parallel with CSF-Aβ42 levels (Schirinzi et al. 2018b).

Mechanisms underlying this movement-related neuroprotection encompass an increased expression of neurotrophic factors and an improvement of bioenergetics via the mitochondria, which in turn maintain synaptic functions and hinder molecular steps of neurodegeneration into the more vulnerable brain areas (Liu et al. 2019). Another hypothesis involves the serotonergic transmission, which is significantly stimulated by physical activity. In facts, serotonergic signaling mediates Aβ42 metabolism and promote synaptogenesis in those sites where synaptopathy typically begins, such as the hippocampus and the basal ganglia (Alwardat et al. 2019; Liu et al. 2019; Pietrelli et al. 2018). Motor activity also improves cerebral perfusion, contributing to the efficiency of the neurovascular unit and the blood-brain-barrier, which together protect from circulating insults (Liu et al. 2019; Pietrelli et al. 2018). The vascular effects of physical exercise positively impact even on clearance mechanisms of the brain, the so-called “glymphatic system”, whose dysfunction leads to protein mismetabolism, an early step of synaptopathy and degeneration (Schirinzi et al. 2017, 2018c). Finally, physical activity intervenes at a systemic level, inhibiting the “chronic inflammation”, a well-known determinant of common age-related chronic disorders (cardiovascular diseases, diabetes, neurodegeneration) (Liu et al. 2019).

Overall, an ever-increasing number of trials now demonstrated the clinical benefits of physical exercise on both motor and cognitive disturbances of patients with neurodegenerative diseases (Ngandu et al. 2015), thus representing a possible strategy to prevent and counteract the progression of such conditions, which could be immediately adopted in clinical practice.

Physical exercise consisting of treadmill training has been documented to improve gait velocity, stride length, and postural stability (thus reducing falls) in patients with mild and moderate PD (Allen et al. 2010; Petzinger et al. 2013). Several randomized clinical trials (RCTs) have shown gait improvements after treadmill training in both short and long term (weeks and months, respectively) in PD (Frazzitta et al. 2012; Miyai et al. 2002). Of note, other PD signs, such as bradykinesia, may improve after treadmill exercise (Frazzitta et al. 2012; Miyai et al. 2002), a phenomenon linked to neuroprotection (Petzinger et al. 2013). Moreover, not only the moderate (4 days per week, 60–65% maximum heart rate) but also the high-intensity (4 days per week, 80–85% maximum heart rate) treadmill exercises are safe and beneficial in patients with early PD (Hoehn and Yahr scores 1 and 2) (Schenkman et al. 2018). Other helpful physical activities in PD include aerobic walking, boxing, tango dancing, and Tai Chi (Combs et al. 2010; Duncan and Earhart 2012; Poier et al. 2019; Uc et al. 2014). RCTs have demonstrated an improvement in postural stability, gait, and dual tasking in PD patients after having partaken in these activities (Duncan and Earhart 2012; Poier et al. 2019).

Physical exercise may also improve cognitive function and decrease the cognitive decline in AD patients (Cass 2017). In particular, exercise has been shown to slow deterioration in activities of daily life in AD patients (Rolland et al. 2007). As a general rule, the earlier in the disease course and the longer the exercise intervention, the better the outcome. This means that patients with advanced AD will not easily benefit from any exercise intervention, whereas at-risk individuals, as well as those with MCI, are the most suitable candidates (Chapman et al. 2013; Gaitán et al. 2019; Hoffmann et al. 2015). As in PD, moderate-to-high intensity aerobic exercise (three times per week) is safe and beneficial in AD (Hoffmann et al. 2015). Recent RCTs have documented that aerobic exercise in early AD is associated with benefits in functional ability, improved memory performance, reduced hippocampal atrophy, and improvement in instrumental activities of daily living (Morris et al. 2017; Vidoni et al. 2015, 2019). Together, these observations support the value of exercise for individuals with cognitive impairment.
Concluding remarks: a common horizon for different conditions

In the present article, we have reviewed physiological and pathological motor and cognitive phenomena that characterize aging. There is a substantial overlap between physiological and pathological aging, as well as within each neurodegenerative condition because of the co-occurrence in variable combination of motor and cognitive features. The overlap is reflected in common pathophysiological mechanisms, which occur despite different pathological substrates. Among these it is worth mentioning various system dysfunctions, and in particular synaptopathies and oscillopathies. Due to the mutual relationship between movement and cognition, an integrated approach should be promoted both in the context of “physiological” aging and neurodegenerative diseases. Undoubtedly, the approach and management of a given movement disorder can be improved by assessing the one’s cognitive functioning, and vice versa. The sharp separation between what is motoric and what is cognitive should accordingly be revised. This bidirectional relationship is qualitatively documented through clinical observations and quantitatively assessed by means of objective motor assessments. At this purpose, the accurate monitoring of movement using wearable motion sensor technologies equipped with gyroscopes and accelerometers should represent a possible important outcome measure for future clinical trials in neurodegenerative conditions (Marsili et al. 2018). The study of M1 plasticity in patients with neurodegenerative disorders by means of non-invasive brain stimulation techniques, and in animal models through basic electrophysiology could help disentangling the underlying pathological mechanisms, especially when correlated with fluid biomarkers of neurodegeneration (Krashia et al. 2019). These observations reflect the most recent theories on the pathogenesis of neurodegenerative disorders: they should not be considered as unique and distinct disorders, but as heterogenic group of conditions that, while related by common degeneration, exhibit unique genetic, biological, and molecular abnormalities, with several related disease courses (Espay et al. 2017, 2019). Only by understanding this breakthrough concept, it will be possible to achieve personalized neuroprotective interventions (Espay et al. 2019). Neuroprotection may benefit from “precision medicine” paradigms (with interventions targeting specific altered biological processes), and from validated measures that stimulate synapto genesis. While precision medicine treatments will be further developed, other more easily applicable neuroprotective strategies aimed at strengthening motor synapses through physical exercises could be practical approaches to test in future clinical trials alone or in combination with different drugs (Villeneuve 2019).

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References


