

Review article

The Neurodegenerative Elderly Syndrome (NES) hypothesis: Alzheimer and Parkinson are two faces of the same disease

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ABSTRACT

Increasing evidence suggests that Alzheimer's disease (AD) and Parkinson's disease (PD) share monoamine and alpha-synuclein (α Syn) dysfunctions, often beginning years before clinical manifestations onset. The triggers for these impairments and the causes leading these early neurodegenerative processes to become AD or PD remain unclear. We address these issues by proposing a radically new perspective to frame AD and PD: they are different manifestations of one only disease we call "Neurodegenerative Elderly Syndrome (NES)". NES goes through three phases. The seeding stage, which starts years before clinical signs, and where the part of the brain-body affected by the initial α Syn and monoamine dysfunctions, influences the future possible progression of NES towards PD or AD. The compensatory stage, where the clinical symptoms are still silent thanks to compensatory mechanisms keeping monoamine concentrations homeostasis. The bifurcation stage, where NES becomes AD or PD. We present recent literature supporting NES and discuss how this hypothesis could radically change the comprehension of AD and PD comorbidities and the design of novel system-level diagnostic and therapeutic actions.

1. Introduction

Alzheimer's disease (AD) and Parkinson's disease (PD) are the two most diffused neurodegenerative disorders worldwide. Globally, AD affects an estimated 44 million people, whereas PD affects over six million people (Dorsey et al., 2018; Dumurgier and Sabia, 2020). AD causes a gradual progression of memory loss and deficits in other cognitive domains, including language, visuospatial skills, and executive functions. In the early and middle stages of the disease progression, depression and apathy are also frequent. In the later stages, motor impairments may also appear (e.g., dystonia, tremor) (Scheltens, 2000). A first neuropathological feature characterizing AD is the abnormal accumulation of extracellular amyloid- β ($A\beta$) oligomers leading to plaque formation. A second one is the aggregation of hyperphosphorylated tau protein into neurofibrillary tangles. Both phenomena produce cytotoxic effects leading to cortical cell death (Binder et al., 2005; Hardy and Higgins, 1992). Another neuropathological finding is the loss of cholinergic neurons in the nucleus basalis of Meynert (Schliebs and

Arendt, 2011). This produces impairments in cholinergic neurotransmission in the cerebral cortex and causes deficits in other target areas involved in learning, memory, and emotional regulation (e.g., hippocampus and amygdala) (Hasselmo, 2006; He et al., 2014; Maurer and Williams, 2017), ultimately leading to the deterioration of cognitive functions (Pinto et al., 2011). Several works also suggest abnormalities in the principal dopaminergic nuclei, such as the ventral tegmental area (VTA) and the substantia nigra pars compacta (SNc) (Burns et al., 2005; Gibb et al., 1989; Storga et al., 1996). Pathological alterations of the dopamine (DA) meso-corticolimbic circuit contribute to cognitive and behavioral signs and occur early in the disease progression (Caligiore et al., 2020; Nobili et al., 2017). By contrast, the impairments of the DA meso-striatal system contribute to the development of extrapyramidal motor deficits, usually occurring in the later stages of AD (Martorana and Koch, 2014). Impairments in serotonin (5-HT) production and transmission could also affect AD pathogenesis (Ceyzériat et al., 2021; Vakalopoulos, 2017; Whitley et al., 2021; Xie et al., 2019). Finally, the locus coeruleus (LC), the dorsal pontine nucleus that synthesizes

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noradrenaline (NA), which is involved in attention, memory, and various other aspects of cognition, could show impairments in the early stages of disease progression (Bondareff et al., 1987; Braak et al., 2011; Mather and Harley, 2016; Simić et al., 2017; Weinschenker, 2018; Zarow et al., 2003).

Differently from AD, PD involves more precociously and pervasively motor functions. The main PD motor symptoms include bradykinesia, resting tremor, rigidity, and freezing of gait (Caligiore et al., 2019; Jankovic and Kapadia, 2001; Obeso et al., 2010). Some neuropsychological disorders such as anxiety or depression often develop several years before typical motor symptoms (Faivre et al., 2019). Cognitive impairments might be evident at the time of diagnosis, even though they significantly manifest in the later stage of the disease progression (Aarsland et al., 2009; Williams-Gray et al., 2007). The core pathologic feature of PD is the loss of dopaminergic neurons in the SNc. Alpha-synuclein (α Syn) is the major protein associated with the hallmark protein deposit in PD, the Lewy body (Polymeropoulos, 1997; Polymeropoulos et al., 1996; Spillantini et al., 1997). Some works suggest that the α Syn abnormal accumulation contributes to dopaminergic cell death in the SNc (Mahul-Mellier et al., 2020; Rajagopalan and Andersen, 2001). The dopaminergic deficit also involves the VTA, even though its contribution to the emergence and progression of motor and non-motor PD features is unclear (Alberico et al., 2015; Narayanan et al., 2013). Aside from the dopaminergic system, PD could also involve dysfunction of cholinergic, noradrenergic, and serotonergic neuronal populations (Jellinger, 1991; Perez-Lloret and Barrantes, 2016; Singh, 2020; Wilson et al., 2019). In PD, loss of LC neurons begins before nigral pathology and appears to be more severe (Brunnström et al., 2011; Delaville et al., 2011, 2012; German et al., 1992). There is also a serotonergic dysfunction beginning earlier than the dopaminergic one and involved with the development of both non-motor and motor symptoms (Jankovic, 2018; Muñoz et al., 2020; Pasquini et al., 2018; Politis and Niccolini, 2015).

Increasing evidence suggests that AD and PD neurodegenerative processes involve a *network of areas* and circuits interacting dynamically and influencing each other, rather than specific regions and molecular mechanisms working in isolation (Caligiore et al., 2016, 2017; 2020; Castrillo and Oliver, 2016; Helmich, 2018). For this reason, the two diseases share several features, including the increased incidence with age, some clinical manifestations, chronic and progressive early cell death in the brainstem monoaminergic nuclei, and the conspicuous presence of protein aggregates. Aside from the aggregation of $A\beta$ oligomers and the hyperphosphorylated tau protein, increasing evidence also supports a central role of α Syn, the major protein associated with the abnormal protein deposit in PD, in the pathogenesis of AD. Furthermore, the mixed pathology consisting of Lewy bodies and $A\beta$ -amyloid plaques supports a faster progression of extrapyramidal motor signs in patients with AD (Iwai et al., 1995a; 1995b; Iwai, 2000; Twohig and Nielsen, 2019).

AD and PD could also share overlapping dysfunctions in monoamine interactions (Babić et al., 2021; Huot and Fox, 2013; Scatton et al., 1983; Simić et al., 2009; Storga et al., 1996; Trillo et al., 2013). For example, data coming from both experimental models and human postmortem brains have demonstrated a profound impairment of the noradrenergic system in both PD and AD pathogenesis (Singh, 2020 for a recent review). Reduced 5-HT transporter availability could be present in mild cognitive impairment in cortical and limbic areas typically affected by AD (Smith et al., 2017). Degeneration of dopaminergic and serotonergic axons could affect α Syn aggregation at the onset of neurodegeneration (Grosch et al., 2016).

Often these overlapping neurodegenerative mechanisms begin many years before the onset of cognitive and motor manifestations in AD and PD. Many experimental and clinical studies have provided solid evidence supporting the early cellular and molecular alterations associated with the presence of α Syn aggregates and neurodegeneration before AD or PD clinical signs (Beason-Held et al., 2013; Butkovich et al., 2018;

Ghiglieri et al., 2018; Gonera et al., 1997; Rajan et al., 2015).

The *overlapping of AD and PD neurodegenerative processes involving the monoaminergic nuclei* and their *occurrence decades before overt clinical manifestations* posit several open questions. Among these, what are the triggers of these impairments? How do they affect each other? What are the causes leading the early neurodegenerative processes to develop AD or PD? This article addresses these issues by proposing a radically new perspective to frame AD and PD: they are different manifestations of one only disease that we call “*Neurodegenerative Elderly Syndrome (NES)*”. More in detail, NES is characterized by three progressive stages. The overlapping between α Syn and monoamine system-level dysfunctions in AD and PD raises the possibility that a seeding mechanism is involved in the pathogenesis and progression of these diseases. Starting from this perspective, we consider a first NES phase where dysfunctions of mainly NA and 5-HT and α Syn begin but are too weak to produce overt clinical symptoms. Different seeds could trigger these early impairments. The type of seed could influence the future development of NES in AD or PD. For this reason, we indicate the first NES stage as the “*seeding stage*”. In the second NES stage, there are also dysfunctions of DA producing systems. However, the overt clinical symptoms are still silent thanks to compensatory mechanisms keeping different monoamine concentrations homeostasis. We indicate this NES phase as the “*compensation stage*”. Finally, in the light of recent literature evidencing the importance of VTA degeneration in the early stages of AD pathogenesis (Caligiore et al., 2020; De Marco and Venneri, 2018; Nobili et al., 2017), we suggest that in the third “*bifurcation stage*”, NES respectively becomes AD or PD, depending on which dopaminergic area is most affected (VTA or SNc). Genetic, environmental, and lifestyle factors affect the triggering event, causing the initial neurodegenerative process during the seeding stage. These factors also could confirm or change the initial neurodegenerative trajectory during the bifurcation stage.

In the rest of the paper, we discuss the recent literature supporting the NES core idea and present the three NES stages in more detail. Then we highlight how NES could be important for early diagnosis and advanced therapies. Finally, we draw conclusions proposing possible experiments to verify the NES perspective.

2. NES core idea

We could distinguish three different progressive stages in the development of the NES.

2.1. First NES stage: seeding

2.1.1. α Syn, NA and 5-HT early dysfunctions

In the first NES stage, there are mainly NA, 5-HT, and the α Syn dysfunctions. These impairments are strongly related and influence each other. Many experimental and clinical studies have provided solid evidence supporting the early cellular and molecular alterations associated with the presence of α Syn aggregates and neurodegeneration before clinical manifestations (Fricova et al., 2020; Ghiglieri et al., 2018; Twohig and Nielsen, 2019).

Studies using double transgenic mice demonstrated, in some cases, overlapping pathological alterations regarding α Syn/ $A\beta$ -amyloid (Swirski et al., 2014). In dementia with Lewy bodies, the $A\beta$ -amyloid and α Syn may interact to promote neurodegeneration and cognitive decline. The detailed mechanisms about the cross-influence between those two proteins are still unclear. The presence of Lewy-type synucleinopathy in AD has a significant impact on future clinical symptoms (Savica et al., 2019). In the early stage of AD, the α Syn abnormal accumulation at the presynaptic site supports aberrant synapse formation (Brookes and St Clair, 1994; Kim et al., 2004; Twohig and Nielsen, 2019). Recent experiments using recombinant and brain-derived tau and α Syn oligomers to seed monomeric tau aggregation in vitro and in vivo have shown that α Syn enhances the harmful effects of tau, thus contributing to AD progression (Castillo-Carranza et al., 2018).

The initiating event causing the abnormal accumulation of α Syn protein is unknown. It could be due to a combination of environmental, genetic, and lifestyle factors (Lashuel et al., 2013; Twohig and Nielsen, 2019; Villar-Piqué et al., 2016). Exposure to heavy metals or pesticides could increase the risk for abnormal α Syn aggregation (Kozlowski et al., 2009; Uversky et al., 2001; Willis et al., 2010). Neuroinflammation, oxidative stress, mitochondrial dysfunctions, and genetic polymorphisms contribute to creating the conditions for developing an abnormal α Syn accumulation (Klein and Schlossmacher, 2006; Roberts and Brown, 2015). High-stress conditions support mitochondrial cell death mechanisms leading to α Syn aggregates (McCann et al., 2016). Age-related decline in the efficiency of the proteolytic mechanism also supports the accumulation of α Syn (Kaushik and Cuervo, 2015).

The α Syn pathology could appear in LC neurons before than in the dopaminergic nuclei (Gcwenza et al., 2021; Hansen, 2021). The LC dysfunctions often precede the primary symptoms of each disorder (dementia in AD and motor dysfunction in PD), suggesting that LC loss may contribute to disease initiation, progression, and severity, rather than merely representing collateral damage (Braak and Del Tredici, 2017; Mather and Harley, 2016; Rüb et al., 2016; Theofilas et al., 2017; Vermeiren and De Deyn, 2017). LC neurons have several anatomical, morphological, and neurochemical characteristics that might contribute to their vulnerability, especially with age progression (Betts et al., 2019; Weinschenker, 2018). These cells synthesize neuromelanin, a granular pigment that binds iron and other heavy metals, as well as chemical toxicants and even α Syn. Neuromelanin may initially protect LC neurons by chelating heavy metals but eventually aggravate neurodegeneration by releasing the toxins later in life (Pamphlett, 2014). In addition, prolonged LC abnormal activity (e.g., due to chronic stress, a risk factor for neurodegenerative disease) may increase oxidative stress. The LC cell bodies proximity to the ventricle affords easy access to the cerebrospinal fluid. The latter can therefore work as a diffusion mean for chemical toxicants and neuroinflammatory molecules. The LC is also densely exposed to brain capillaries and thus can be selectively targeted by toxicants from the blood, even those present at low levels (Pamphlett, 2014).

Another key neuromodulator early involved in the NES progression is the 5-HT, whose main telencephalic sources are the median and dorsal raphe nuclei (MRN and DRN respectively). This neuromodulator is involved both in AD and PD (Babić et al., 2021; Huot and Fox, 2013; Scatton et al., 1983; Simic et al., 2009; Storga et al., 1996; Trillo et al., 2013). It is involved in affective and cognitive functions and with the early cognitive decline related to neurodegeneration. The dysfunction of the serotonergic system projecting to the hippocampus might contribute to early non-motor symptoms such as anxiety and depression. Several data support the presence of 5-HT malfunctioning in the early stages of PD. People with hereditary risks of developing PD show 5-HT loss in several brain areas (Wilson et al., 2019). There is a reduction in raphe 5-HT transporter availability in the early phases of PD (Pasquini et al., 2020). 5-HT afferents modulate SNc and VTA DA neurons oppositely (Gervais and Rouillard, 2000). The selective stimulation of the various 5-HT receptor subtypes differentially distributed throughout the brain likely supports this process (Di Giovanni et al., 2001; Hoyer et al., 1994). Differential modulation of VTA and SNc DA neurons by 5-HT afferents from the DRN could have important implications for the progression of NES until it becomes AD or PD (Babić et al., 2021; Wilson et al., 2019). If the initial dysfunctional seed mainly involves the 5-HT-VTA circuit, it is more likely that NES could become AD. Otherwise, if the initial dysfunctional process includes the 5-HT-SNc network, NES could become PD (see “2.3 Third NES stage: Bifurcation”).

These dysfunctions are reciprocally related to the one causing an abnormal α Syn production. Extracellular α Syn aggregates, indeed, could support an early DRN and LC degeneration (Yavich et al., 2006; Wan et al., 2016; Wersinger et al., 2006). α Syn can influence NA metabolism, and this, in turn, could impact α Syn expression (Butkovich et al., 2018; Wan et al., 2016). Other relevant factors determine different

propagation of α Syn across brainstem nuclei. The isoform LRRK2 kinase coded by the gene variation G2019S changes the diffusion pathway, making both VTA, SNc, and hippocampus vulnerable to α Syn accumulation (Henderson et al., 2019; Kim et al., 2019). In this line, recent evidence shows that transgenic mice overexpressing human α Syn in NA neurons develop LC pathology and non-motor features of PD (Butkovich et al., 2020). 5-HT supports the initiation and propagation of α Syn aggregation in the nervous system (Falsone et al., 2011; Hijaz and Volpicelli-Daley, 2020). The raphe nuclei show early intracellular accumulation of α Syn accompanied by the loss of serotonergic neurons (Braak et al., 2003; Halliday et al., 1990).

2.1.2. The entry point of α Syn, NA, and 5-HT dysfunctions affect the NES seeding mechanism

We propose that in the first NES stage, the part of the brain-body system where the α Syn, 5-HT, and NA dysfunctions initially originate, which we call “entry point”, could critically influence the progression of NES towards further explicit PD or AD neurodegeneration. Below we describe two entry points mainly involved in NES: the enteric and limbic pathways.

Increasing evidence showed changes in gut microbiota composition in association with AD and PD (Bhattarai and Kashyap, 2020; Janeiro et al., 2021; Kaur et al., 2021; Marizzoni et al., 2020; Rajput et al., 2021; Romano et al., 2021; Shabbir et al., 2021; Shen et al., 2021). Pivoting on data suggesting that microbiota unbalance can trigger α Syn misfolding, several works investigate the pathology-related changes in the distribution of α Syn in enteric neurons. Based on the pattern of Lewy body pathology observed in the postmortem human brain, Braak and colleagues proposed that α Syn pathology could diffuse from the gastrointestinal tract via the vagus nerve to the ventral midbrain (Braak et al., 2003, 2004). This hypothesis has been recently empirically validated through a novel gut-to-brain α Syn transmission mouse model, with an injection of α Syn preformed fibrils into the duodenal and pyloric muscularis layer. The spread of α Syn dysfunction in the brain was observed first in the vagus dorsal motor nucleus, then in caudal portions of the hindbrain, including LC. Much later, in the basolateral amygdala, the DRN, and the SNc. Truncal vagotomy prevented the gut-to-brain spread of α Synucleinopathy and associated neurodegeneration (Kim et al., 2019). Gold and colleagues used immunohistochemical techniques to study the age α Syn enteric distribution in the general autopsy population and age-matched PD and AD populations. They found that all PD subjects were α Syn positive, with higher prevalence and grade than age-matched controls. AD subjects were no more likely to be α Syn positive than controls (Gold et al., 2013).

Gut microbiota could also regulate the bidirectional vagus nerve communication by directly affecting release and receptor expression of 5-HT, NA, and DA (Bhattarai and Kashyap, 2020; Galland, 2014; González-Arancibia et al., 2019; Shishov et al., 2009; Strandwitz, 2018; Tsavkelova et al., 2000). Several recent works underline how gut microbiota dysbiosis contributes to producing initial monoamine dysfunctions leading to AD or PD (Jiang et al., 2017; Kowalski and Mulak, 2019; Rani and Mondal, 2021; Shabbir et al., 2021). Emerging evidence is demonstrating specific microbiota alterations. In AD, for example, there is a lower abundance in Bifidobacterium and a greater prevalence of Blautia (Miyake et al., 2015; Shen et al., 2021). Despite these encouraging data, many questions remain, and more research is needed to exploit the gut microbiota analysis as a discriminative tool to study AD and PD pathogenesis (Castillo-Álvarez and Marzo-Sola, 2021; Gerhardt and Mohajeri, 2018).

Overall, these data suggest that the enteric system could be a critical seeding site for both α Syn and monoamine dysfunctions. These trigger the neurodegenerative processes leading to AD and PD. In particular, enteric α Syn malfunctioning could mainly support the neurodegenerative trajectory leading to PD but not to AD (Fricova et al., 2020; Gold et al., 2013). The gut microbiota dysbiosis could instead contribute to producing initial monoamine dysfunctions leading to AD or PD

(Kowalski and Mulak, 2019; Rani and Mondal, 2021; Shabbir et al., 2021).

A second “entry point” could be the limbic system. Several works demonstrated that the limbic system is critically involved in the malfunctioning of α Syn in AD and PD (Braak et al., 2005; Hamilton, 2000; Kalaitzakis et al., 2009; Twhig and Nielsen, 2019; Uchikado et al., 2006). Studies on a large cohort of familial AD cases with mutations in presenilin PSEN genes found that the amygdala is the most vulnerable site for α Syn abnormal accumulation (Leverenz et al., 2006; Lipka et al., 1998; Sorrentino et al., 2019). α Syn burden in the limbic regions could differentiate demented from non-demented PD cases with high sensitivity and specificity (Apaydin et al., 2002; Braak et al., 2005; Kalaitzakis et al., 2009). Biochemical studies demonstrated that the amygdala in PD prominently contained specific carboxy-truncated forms of α Syn, which are highly prone to aggregate to initiate the development of α Syn pathology. By contrast, the α Syn amygdala aggregates could contribute to triggering AD pathophysiological mechanisms through indirect routes. The amygdala projects to VTA, and its dysfunctions generated by the α Syn abnormal accumulation could, in turn, contribute to triggering dopaminergic impairments in VTA (Cardinal et al., 2002; Fudge and Haber, 2000). Similarly, α Syn aggregation could enhance the harmful effects of tau, thus contributing to AD progression (Castillo-Carranza et al., 2018). Moreover, α Syn and A β -amyloid can synergistically interact to promote AD neurodegeneration and cognitive decline (Crews et al., 2009; Marsh and Blurton-Jones, 2012).

The triggering event causing the initial implicit neurodegenerative trajectory during NES stage one depends on a combination of several genetic, environmental, and lifestyle factors. For example, there is accumulating evidence that alcohol intake affects the functioning of the microbiota-gut-brain axis. The changes it produces in the microbiome support neuroinflammation and could alter the neuroimmune functions (Hillemacher et al., 2018). Excessive amounts of alcohol interact with the neurotransmitter system and increase blood-brain barrier permeability, resulting in brain damage and dysfunction (Gushcha et al., 2019). Experimental animal studies indicate that chronic heavy alcohol consumption may have DA neurotoxic effects (Eriksson et al., 2013). Chronic alcohol exposure decreases DA levels and increases the amount of α Syn (Rotermund et al., 2017; Trantham-Davidson and Chandler, 2015). The assumption of nicotine and coffee influence the microbiota-gut-brain axis involving bacterial strains such as Bifidobacterium (Derkinderen et al., 2014). In the absence of coffee drinking and cigarette smoking, the microbiota would shift toward a pro-inflammatory state which promotes chronic gastrointestinal inflammation and an enteric glial reaction, which occurs in the early stage of PD (Devos et al., 2013). In addition, the local inflammation supports the α Syn aggregation within the adjacent submucosal neurons (Lema Tomé et al., 2013; Pouclet et al., 2012). Some lifestyles can influence the limbic system, in particular the amygdala and hippocampus (Gerritsen et al., 2015). The high education and low lifetime smoking status were associated with larger hippocampal volumes, which mediated indirect effects on episodic memory, processing speed, and global cognition (Schreiber et al., 2016).

Crucially, the same features could confirm or change the course of the initial neurodegenerative trajectory. The involvement of these factors depends on the subjects. For subjects where the genetic aspects play a principal role, it is hard to frame and affect the causality of brain events producing NES because the hereditary features are often less manipulable. By contrast, for subjects where environmental and lifestyle factors are more critical, the causality of the brain events producing NES could be easier to understand and manipulate. In this case, we could make the course of the neurodegenerative trajectory slower or even interrupt it. We discuss all these aspects more in detail in the section focused on the third NES stage.

2.2. Second NES stage: compensation

The prolonged malfunctioning of the NA and 5-HT circuits and the abnormal α Syn production mechanisms could, in the long run, contribute to producing neurodegeneration within the VTA and SNc. These two nuclei start to work in the wrong way leading to DA loss (Zhang et al., 2005). However, the brain still shows normal functioning with no overt motor or non-motor dysfunctions. The neurodegenerative trajectory leading to AD or PD is not yet confirmed. At this stage, the ubiquitous influence of NA and 5-HT leads to several system-level compensatory processes to recover the DA loss (Jiménez-Sánchez et al., 2020; Merlo et al., 2019). For this reason, we indicate this second NES phase as the *compensation stage*. Even though monoamines play different functions, they could influence each other. LC neurons receive excitatory input from DA neurons in the VTA and send noradrenergic innervations to the DA neurons in the VTA and SNc (Bari et al., 2020; Mejias-Aponte, 2016; Rommelfanger et al., 2007). DRN receives projections from both VTA and SNc. It also projects to DA cells in the VTA and the SNc and their terminal fields in the nucleus accumbens, prefrontal cortex, and striatum (Moukhles et al., 1997; Van Bockstaele et al., 1993; Van Bockstaele and Pickel, 1993; Kirouac et al., 2004). These pathways support the reciprocal influence between different neuromodulators, often through compensatory mechanisms. Here, we use the term “compensation” to indicate the action of NA and 5-HT neurons to partially boost the functions of the remaining DA neurons. When there is a VTA or SNc dysfunction leading to an impairment of the DA production, NA and 5-HT could act against this dysfunction modulating DA concentration through the projection (direct and indirect) of LC and DRN to VTA and SNc, or by directly modulating DA release in other brain regions (Zhang et al., 2016). For example, synaptic dopamine is captured by both NA and DA transporters (Carboni et al., 2006), and extracellular DA in the cerebral cortex originates also from terminals of NA neurons (Devoto and Flore, 2006).

LC or DRN impairments could also contribute to producing a DA release dysfunction (cf., Sec. “2.1 First NES stage: seeding”). For example, experimental findings using animal models of PD suggest that the loss of NA brain neurons might exacerbate DA neuron damage and that NA could be neuroprotective (Fornai et al., 1997; Marien et al., 2004; Rommelfanger et al., 2004). The abnormal A β amyloid and α Syn accumulation in the LC contributes to NA release dysfunctions in both AD and PD (Heneka, 2006; Mather and Harley, 2016; Oliveira et al., 2017; van Dijk et al., 2012). If the LC neurons loss supports the DA release dysfunctions, DRN could be involved in the compensation mechanisms. In particular, DRN could support the VTA/SNc DA release through the projection it sent to these dopaminergic areas. Alternatively, if the DRN impairment contributes to DA release loss, the LC could compensate by supporting VTA/SNc activity. Postmortem data on humans suggest an inverse relationship between brain NA level and DA loss (Tong et al., 2006). Combining clinical and imaging data of a cohort of PD patients at an early clinical stage (Hoehn and Yahr stage 1–2) has been found an LC compensating activity for the degeneration of DA nigrostriatal projections (Isaias et al., 2011). Evidence about a possible LC involvement in compensation mechanisms also comes from digit span task experiments comparing the performance of patients with mild cognitive impairments, AD patients, and human control (Granholm et al., 2017; Hoogendijk et al., 1999). LC activity measured using pupil dilation (Larsen and Waters, 2018) follows an inverted U-shape pattern, with an increase followed by a dropping in the degree of neurodegeneration. LC temporary compensation reduces the performance drop and counteracts the tendency of refusing to engage in the task (resilience to apathy, an early AD sign). Similarly, computational modeling research on AD progression showed that LC response follows an inverted U shape with the disease progression. More in detail, the LC overactivation compensates for the effects of initial VTA degeneration characterizing the early stage of the disease progression (De Marco and Venneri, 2018; Nobili et al., 2017). This compensation keeps behavioral

performance stable and leads to no manifest symptoms. However, with a more severe VTA lesion, the LC becomes under-activated, leading to an abrupt performance drop (Caligiore et al., 2020).

Several works support the involvement of DRN in compensation processes (Ceyzeriat et al., 2021; Jiménez-Sánchez et al., 2020; Merlo et al., 2019). DRN could modulate DA concentration through the 5-HT projections it sends to VTA and SNc (Bara-Jimenez et al., 2005; Di Matteo et al., 2008; Kirouac et al., 2004; Politis and Niccolini, 2015).

Works on humans show a compensatory upregulation of hippocampal 5-HT_{1A} receptor density in the early stage of mild cognitive impairment and a dramatic decline of it at later stages (Truchot et al., 2007). In the AD prodromal stage, 5-HT could also compensate for VTA DA loss indirectly through the projections toward LC (Babić et al., 2021; Hoogendijk et al., 1999). The 5-HT compensatory mechanisms also take place to maintain normal function for a prolonged pre-diagnostic period in PD (Bezard et al., 2003; Blesa et al., 2017; Pagano et al., 2018). For example, a study with rats found that 5-HT hyperinnervation into the striatum compensates for the loss of DA function (Maeda et al., 2005). Increased striatal serotonergic activity has been proposed as a possible compensatory mechanism (Boulet et al., 2008). However, data provide contradictory results, showing depletion and increasing of serotonergic markers (Huot et al., 2011). These different results could be due to the variety of distinct receptors mediating various physiological effects of 5-HT on striatal DA release. 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT₃, and 5-HT₄ receptors facilitate neuronal DA function and release (Caligiore et al., 2021; Jiménez-Sánchez et al., 2020). By contrast, the 5-HT_{2C} receptor mediates an inhibitory effect of 5-HT on the basal electrical activity of DA neurons and DA release stimulating a GABA-containing interneuron (Di Giovanni et al., 2001; Di Matteo et al., 2001).

2.3. Third NES stage: bifurcation

In the third NES stage, the compensatory mechanisms operating during the previous NES phase cannot further handle the progression of neurodegeneration. The compensation stage, indeed, could only slow down the course of the neurodegenerative trajectory but not interrupt it. For example, the 5-HT overactivity supports the partial recovery of the DA function that in turn could inhibit fibrillization and contrasts the polymerization of α Syn and A β aggregates. However in the long run, the 5-HT overactivity could contribute to the initiation and propagation of α Syn aggregation (Falsone et al., 2011; Hijaz and Volpicelli-Daley, 2020), triggering a vicious circle leading to neurodegeneration. The end of the compensatory effects accelerates the course of the neurodegenerative trajectory but does not affect its direction established during the seeding stage. This trajectory could be confirmed or changed by lifestyle, genetics, and environmental aspects (see Sec. “2.3.1 Lifestyle, genetic, and environmental factors supporting bifurcation” for more details).

Thus, the end of the compensation effect and the lifestyle, genetics, and environmental aspects contribute to obtain a bifurcation effect boosting the malfunctioning of one of the two DA areas. If the increasing malfunctioning involves VTA, subjects start to show AD overt cognitive symptoms (Nobili et al., 2017). The chronic malfunctioning of the VTA-LC system might affect the functioning of the nucleus basalis of Meynert. This area receives the DA input from VTA, NA input from LC and provides the principal source of acetylcholine for the prefrontal cortex, amygdala, and hippocampus (Gaykema and Zaborszky, 1996; Mesulam, 2013; Smiley and Mesulam, 1999). The cholinergic axons degeneration contributes to the worsening of AD symptoms (Liu et al., 2015). By contrast, if the increasing impairment mainly converges towards SNc, subjects show overt motor symptoms typical of PD. Note that the bifurcation could not be fully net, producing a partial VTA impairment in PD subjects, so they show cognitive deficits (Alberico et al., 2015; Narayanan et al., 2013). SNc could become partially impaired also in AD subjects, so they show abnormal motor behavior (Martorana and Koch, 2014). It is a matter of weight, AD could include some PD features,

or PD could embed some AD features. Thus, in patients with comorbidity, the bifurcation is low.

A *cost-benefit mechanism* as those recently proposed in neuro-computational literature (Caligiore et al., 2020; Silveti et al., 2019; Silveti et al., 2018) could support the transition from compensation to bifurcation. The cortical-subcortical circuit involving the anterior cingulate cortex (ACC) and the brainstem monoaminergic nuclei could regulate the compensation mechanism (Caligiore et al., 2020; Celada et al., 2013; Silveti et al., 2018; 2019). For example, if the neuronal loss strikes mostly the VTA, ACC will mostly upregulate the LC activity. The subsequent LC overactivation compensates for the effects of VTA neural degeneration. The ACC boosts monoamine release to keep cognitive and behavioral performance within the limits of efficiency. It is a cost-benefit process where the cognitive and behavioral benefits counterbalances the cost of boosting and vice-versa (Caligiore et al., 2020). This optimization mechanism leads to a compensatory boosting signal following an inverted U shape. When the brainstem neuronal loss is mild, the ACC upregulates monoamine release as a form of compensation. This compensatory mechanism increases as a function of brainstem neuronal loss *until compensation costs overcome the cognitive and behavioral benefits*. At that point, the ACC operates a progressive “shutdown” of the boosting signal promoting monoamine release. There is an abrupt decrease in monoamine production, and in particular in DA nuclei. If the DA loss mainly involves VTA, there is an increasing malfunctioning of brain areas associated with AD (e.g., hippocampus, amygdala, nucleus basalis of Meynert, prefrontal cortical areas) (Caligiore et al., 2020; De Marco and Venneri, 2018; Nobili et al., 2017). By contrast, when the DA loss mainly involves SNc, there is an increasing malfunctioning of brain areas associated with PD (e.g., basal ganglia, cerebellum, and thalamocortical loops) (Caligiore et al., 2016; 2019; Helmich, 2018). In both cases, the result is an acceleration of the rise of overt clinical symptoms. The compensation becomes bifurcation. Fig. 1 summarizes the three stages of the NES progression.

Pathological alterations of DA production by VTA might contribute to cognitive and behavioral signs that may occur early in the disease progression (Gibb et al., 1989; Martorana and Koch, 2014; Storga et al., 1996). In this regard, a recent work investigating the structural alterations of the midbrain DA system in an animal model of AD (Tg2576 mouse), found an age-dependent dopaminergic neuron loss in the VTA at a stage when A β -plaque deposition, hyperphosphorylated tau tangles, or any sign of neurodegeneration in hippocampal and cortical regions involved in memory deficits has not yet occurred (Nobili et al., 2017). The VTA degeneration results in a lower DA outflow in the nucleus accumbens and hippocampus and this is associated with dysfunctions in memory performance, food reward processing, cost-benefit decision-making, and depressive-like symptoms (Ito and Hayden, 2011). A magnetic resonance imaging study supported this finding by showing a positive correlation between the VTA volume, hippocampal size, and memory performance in a cohort of patients compared with healthy controls (De Marco and Venneri, 2018). Another work used functional magnetic resonance imaging to study the VTA-driven modulation of connectivity in AD brains and its impact on behavioral symptoms (Serra et al., 2021). Finally, it has been recently reported a positive correlation of atrophy in VTA projecting areas with severity of depression, apathy, and anxiety in the prodromal phase of AD while no metabolic connectivity changes have been detected within nigrostriatal pathway (Iaccarino et al., 2020). Despite these data started to explain the relationship between DA dysfunctions, structural and cognitive and non-cognitive alterations along the AD stages, further research will be necessary to provide a unifying theory on the causal relations between A β oligomers formation and DA dysregulation, suggesting the need of integrating these phenomena within a system-neuroscience approach (Caligiore et al., 2020; Henstridge et al., 2019).

2.3.1. Lifestyle, genetic, and environmental factors supporting bifurcation

The neurodegenerative trajectory triggered during the first NES stage

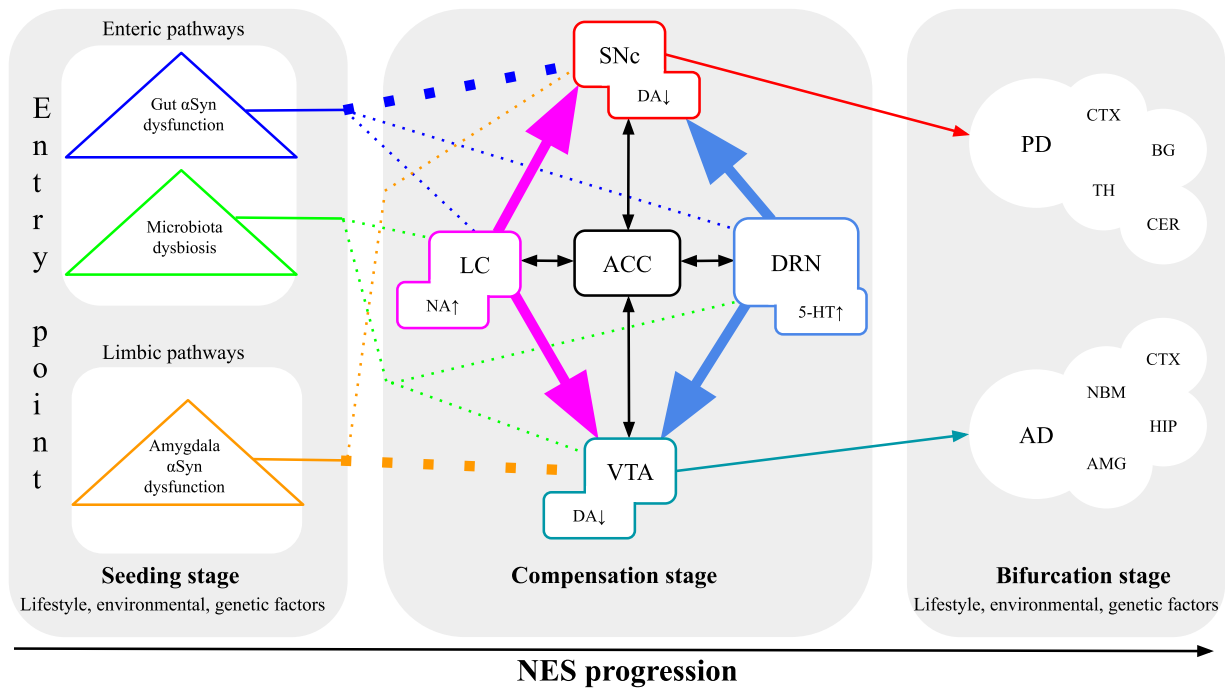


Fig. 1. The progression of the three NES stages. During the *seeding stage* (left) the different types of seed could set different initial pathways (dashed lines) towards a possible future development of NES in AD or PD. The different dashed line thickness indicates the different initial probability that NES could become AD or PD (large thickness, greater probability). The initial neurodegenerative trajectory is influenced by lifestyle, genetics, and environmental factors (bifurcation stage), which make the seeding stage determine only probabilistically the future outcome of the bifurcation stage leading to AD or PD. In the compensation stage (middle) the ACC could upregulate the LC and/or DRN activity to recover the DA loss in SNc or VTA (thicker arrows), according to a cost-benefit trade-off. In the bifurcation stage (right) NES becomes AD or PD. Lifestyle, environmental and genetic factors could affect both the seeding and the bifurcation stages. Abbreviations: AD: Alzheimer’s disease; α Syn: alpha-synuclein; AMG: amygdala; BG: basal ganglia; 5-HT: serotonin; CER: cerebellum; CTX: cortex; DA: dopamine; DRN: dorsal raphe nucleus; HIP: hippocampus; LC: locus coeruleus; ACC: anterior cingulate cortex; NA: noradrenaline; NBM: nucleus basalis of Meynert; SNc: substantia nigra pars compacta; PD: Parkinson’s disease; TH: thalamus; VTA: ventral tegmental area.

could be confirmed or changed by lifestyle, genetics, and environmental aspects (Table 1). The degree of involvement of these factors is different for each subject. For subjects where the genetic features play the principal role, it is more difficult to understand the brain events transforming NES in PD or AD because the hereditary features are often latent. By contrast, for subjects where environmental and lifestyle factors are more critical, the brain events leading to PD or AD could be easier to understand. In this case, indeed, we could build on the increasing literature linking early NA, 5-HT, and α Syn dysfunctions with several environmental and lifestyle factors and with the risk of developing neurodegeneration (Betts et al., 2019; Lashuel et al., 2013; Weinschenker, 2018), trying to isolate the bifurcation causes.

Table 1
Lifestyle, environmental, and genetic factors that affect the *seeding* and the *bifurcation stages*.

| | Alzheimer’s Disease | Parkinson’s Disease |
|----------------|---|--|
| Increased risk | <ul style="list-style-type: none"> Nicotine Alcohol Pesticides High cholesterol High iron intake SNCA gene (rs6532190, rs3775430, and rs10516846) 5-HTT polymorphism (short variant of the 5-HTTPLR) MAOA-GT allele 113 | <ul style="list-style-type: none"> High iron intake Pesticides SNCA gene (rs2301134, rs2301135, and rs11931074) DA polymorphism (COMT Val158Met) allele > 188 bp of the MAOB (GT)_n polymorphism |
| Reduced risk | <ul style="list-style-type: none"> Coffee DA polymorphism (COMT Val158Met) | <ul style="list-style-type: none"> Nicotine Alcohol High cholesterol 5-HTT polymorphism MAOA-GT or MAOB-GT polymorphisms |

The first lifestyle risk factor is nicotine. It stimulates DA neurons, inhibits α Syn fibril formation, and lessens symptoms of PD (Bono et al., 2019; Wirdefeldt et al., 2011). By contrast, nicotine increases the risk of developing AD (Peters et al., 2008). It contributes to the emergence of neurobiological abnormalities in the amygdala, hippocampus, and prefrontal cortex (Kalivas and Volkow, 2005; Krueger et al., 2010; Makris et al., 2008; Volkov et al., 2021). Furthermore, cigarettes contain non-negligible metal concentrations such as copper, iron, and zinc. These could support the tau tangles formation, display specific binding to the A β peptide and modulate its aggregation pathways (Sayre et al., 2000; Wärmländer et al., 2013). Thus, while nicotine could not support the early PD trajectory triggered during NES stage one, it confirms the initial AD trajectory set during the same stage. Another risk factor identified is alcohol. Depending on the amounts, it may have dual roles in worsening or in protecting against neurodegenerative diseases. Epidemiological studies reported a reduction in the prevalence of AD in individuals who drink low amounts of alcohol (Muñoz et al., 2015); low or moderate concentrations of ethanol protect against A β -amyloid toxicity in hippocampal neurons (Ormeño et al., 2013), whereas excessive amounts of ethanol increase the accumulation of A β and tau phosphorylation (Huang et al., 2018). By contrast, alcohol abuse increases the blood-brain barrier permeability, resulting in brain damage and dysfunction (Gushcha et al., 2019). Experimental animal studies indicate that chronic heavy alcohol consumption may have DA neurotoxic effects (Eriksson et al., 2013). Chronic alcohol exposure decreased the levels of DA and increased the amount of α Syn (Rotermund et al., 2017; Trantham-Davidson and Chandler, 2015). Other lifestyle risk factors are cholesterol and pesticides. In vitro and in vivo experiments suggest that high levels of blood cholesterol increase the production of A β (Daneshvar et al., 2015). By contrast, high blood cholesterol is a lower risk of PD (de Lau et al., 2006; Huang et al., 2008). Pesticides

destroy DA neurons, which is why many PD animal models use them. Several studies prove a higher relationship between PD and AD development and exposure to pesticides (Bonetta, 2002; Freire and Koifman, 2012; Hayden et al., 2010; Parrón et al., 2011; Van Maele-Fabry et al., 2012). Finally, elevated levels of iron increases the risk of developing PD and AD (Ayton et al., 2015; Ayton et al., 2017; Belaidi and Bush, 2016), whereas coffee promotes beneficial effects on cognition and resistance to AD development (Camandola et al., 2019).

Aside from lifestyle and environmental aspects, genetic factors could also change or confirm the neurodegenerative trajectory triggered during the first NES stage. In this respect, several works demonstrated how genetic polymorphism is critical to understanding individual differences in risk for developing neurodegenerative diseases (Bogdan et al., 2013; Pang et al., 2019). There is a relationship between changes in the binding of transcription factors produced by various α Syn gene SNCA (Synuclein Alpha) polymorphisms and the individual risk of PD and AD development (Alkanli and Ay, 2020; Matsubara et al., 2001; Wang et al., 2016; Rahimi et al., 2017). Polymorphisms of DA-related genes lead to the variation of frontostriatal pathway functions that, in turn, could support PD development (Bogdan et al., 2013; Nikolova et al., 2011; Wong et al., 2012), furthermore the DA-polymorphism can be a risk to develop PD or AD (Lee and Song, 2014; Yan et al., 2016; Wang et al., 2019). Two proteins critically involved in regulating 5-HT levels in the brain are the serotonin transporter (5HTT), carrying 5-HT from the extracellular space, and the monoamine oxidase A (MAOA), responsible for degrading serotonin. Both genes encoding these proteins hold genetic polymorphisms in their promoter regions that affect their transcriptional activity (Bennett et al., 2002; Nordquist and Orelund, 2010; Sabol et al., 1998) and can influence the further development in AD or PD disorder (Oliveira et al., 1998; Gao and Gao, 2014; Takehashi et al., 2002; Nanko et al., 1996; Williams-Gray et al., 2009). Studying these genetic variants could help understand the individual differences in the pathological pathway leading to PD (Cacabelos et al., 2021; Mössner and Riederer, 2007; Zhang et al., 2014) and AD (Assal et al., 2004; Quaranta et al., 2009; Takehashi et al., 2002; Yamazaki et al., 2016).

3. NES hypothesis supports early diagnosis and advanced therapies for AD and PD

Early and reliable diagnosis of AD and PD could provide new treatment options for patients and improve their quality of life. At present, diagnosis mainly relies on clinical symptoms. Only postmortem pathological confirmation of dopaminergic and cholinergic neuronal degeneration could produce a definitive diagnosis. However, the neurodegenerative mechanisms leading to AD or PD begin many years before the onset of cognitive and motor manifestations. For example, in PD initial estimates based on striatal DA imaging or nigral neuropathological findings suggest a five-year preclinical period. However, more recent data of Lewy body pathology in other neuronal populations preceding nigral involvement suggest that the preclinical phase may be much longer. Epidemiologic studies of non-motor manifestations, such as constipation, anxiety disorders, rapid eye movement, sleep behavior disorder, and anemia, suggest that the preclinical period extends at least 20 years before the motor symptoms. Olfactory impairment and depression may also precede the onset of motor manifestations (Abbott et al., 2005; Berg et al., 2021; Heii et al., 1992; Ross et al., 2008; Savica et al., 2010; Smith et al., 2017).

In addition, the similarity of the clinical, cognitive, and neuropathological features between AD and PD calls for new biomarkers suitable for differential diagnosis. The NES hypothesis suggests that the primary pathogenesis occurs several years before the onset of typical AD and PD cognitive and motor symptoms. In addition, the early dysfunctions involve other body parts (e.g., gut), peripheral tissues, and brain regions traditionally weakly or even not considered in AD and PD literature. In particular, our analysis suggests that α Syn impairments at the level of gastrointestinal tissues could be critical for the early diagnosis of PD

before the onset of clinical features. Hence, gastrointestinal α Syn could be used as a biomarker to distinguish PD and AD. Several new techniques can improve α Syn detection in gastrointestinal tissues (Fricova et al., 2020; Visanji et al., 2014). Among these, the nanoparticle-based methodologies, including sensor-based approaches, could be used to increase sensitivity (Jang et al., 2020; Kumar et al., 2020). Monitoring the differential microbiota alterations for AD and PD could also support early diagnosis (Castillo-Álvarez and Marzo-Sola, 2021; Gerhardt and Mohajeri, 2018). The NES hypothesis also supports the monitoring of LC and DRN activity as indicative early diagnostic markers for both PD and AD pathogenesis, specifically during the presymptomatic phase. The LC output could augment or decrease depending on the AD disease progression (Betts et al., 2019; Hoogendijk et al., 1999). During the compensation phase (NES stage two), LC follows an inverted U-shape pattern, with an increase followed by a dropping in the degree of AD neurodegeneration. More in detail, the LC overactivation compensates for the effects of initial VTA degeneration characterizing the early stage of the disease progression (De Marco and Venneri, 2018; Nobili et al., 2017). This compensation keeps behavioral performance stable. However, with a more severe VTA lesion, the LC becomes under-activated, leading to an abrupt performance drop (Caligiore et al., 2020; Granholm et al., 2017; Hoogendijk et al., 1999). Similarly, several studies showed that LC burden precedes SNc neurons degradation, making the LC a good candidate for PD preclinical diagnosis (Braak et al., 2004; Seidel et al., 2015; Zarow et al., 2003). Measuring pupil dilation could be an effective non-invasive way to monitor LC activity for early diagnosis (Joshi et al., 2016; Kremen et al., 2019). Alternatively, could be used traditional but more expensive magnetic resonance imaging approaches (Betts et al., 2019; Hou et al., 2021; Liu et al., 2017). Another early diagnosis action could be monitoring 5-HT release through, for example, high-resolution PET imaging. Recent data, indeed, reveals progressive loss of DRN 5-HT in early PD (Fazio et al., 2020; Pasquini et al., 2020).

The NES system-level hypothesis suggests new therapeutic actions for AD and PD, based on the interactions between monoamine and α Syn dynamics. Several data have shown that DA and its precursor L-dopa could inhibit fibrillization and dissolve existing α Syn and A β -amyloid aggregates (Bharath and Andersen, 2004; Li et al., 2004). In this way, DA could contribute to reversing conformational changes necessary for fibril formation. These data are of particular interest because they suggest a common strategy for therapeutic intervention in both AD and PD. In particular, treatments that act to raise brain levels of L-dopa or DA in AD or PD patients may prevent and even reverse aggregate formation. The treatments may include L-dopa administration, monoamine oxidase inhibitors which prevent its catabolism, or DA agonists, which act to mimic its effects. Early recognition of the various clinical manifestations associated with NA deficiency in the brain and elsewhere, which may precede the development of motor and cognitive symptoms, could provide a window of opportunity for neuroprotective interventions (Espay et al., 2014). Administration of selective serotonin reuptake inhibitors (SSRIs) reduced the production of toxic A β proteins. Chronic administration of the SSRI citalopram blocked plaque growth in transgenic AD mice (Sheline et al., 2014). In addition, clinical studies on humans revealed lower cortical amyloid levels in participants who had taken SSRIs within the past five years versus those who had not been treated with SSRI (Cirrito et al., 2011).

Despite these encouraging results, translating the NES ideas to the clinic is challenging. It is necessary to investigate the mechanisms underlying neurotransmitter interactions to determine optimal compounds and doses for effective therapies producing the maximal benefit with minimal adverse events. In addition, a critical issue is to treat patients in the very early stages of the disease. Treatments should start at the prodromal phase, or even before, or in MCI patients, even if it is impossible to know if their symptoms will evolve and if they will develop AD or PD. Such preventive clinical trials are already underway for genetic forms of AD and PD (Berg et al., 2021; Claeysen et al., 2015; Shihabuddin et al.,

2018).

4. Conclusions

Increasing evidence supports the central role of α Syn and monoamine dysfunctions beginning years before AD and PD clinical manifestations. However, many questions remain unclear, including the triggers for these impairments, their reciprocal influence, and the causes leading these early neurodegenerative processes to develop AD or PD (Lamonaca and Volta, 2020; Savica et al., 2010, 2018; Smith et al., 2017; Twohig and Nielsen, 2019; Wilson et al., 2019). This article addresses these issues by proposing the Neurodegenerative Elderly Syndrome (NES) hypothesis. AD and PD are different manifestations of one only disorder we call NES. It starts years before the AD and PD clinical manifestation and goes through three progressive phases. The seeding stage, where the part of the brain-body system where the α Syn, 5-HT, and NA dysfunctions initially originate, could critically influence the progression of NES towards further explicit PD or AD neurodegeneration. The compensatory stage, where the degree of impairments started during the seeding phase increases and also begins DA dysfunctions. However, the overt clinical symptoms are still silent thanks to compensatory mechanisms keeping different monoamine concentrations homeostasis. The bifurcation stage, where NES becomes AD or PD. The combination of genetic, environmental, and lifestyle factors could affect the triggering event, causing the initial implicit neurodegenerative process (seeding stage). These factors could also confirm or change the initial neurodegenerative trajectory supporting the development of AD or PD (bifurcation stage).

NES partially supports the stage perspective on PD pathology proposed by Braak and colleagues. This latter view claims that in the first PD pathology stage, α Syn dysfunction appears in brainstem nuclei. It continues along a caudo-rostral axis, with LC pathology appearing at stage two and SNc pathology at stage three before finally extending into cortical regions (Braak et al., 2003; Del Tredici et al., 2002). However, NES extends it in several ways. NES supports the involvement of DRN and proposes that α Syn and monoaminergic system dysfunctions begin years before clinical manifestations and represent a common framework involving not only PD but also AD. In addition, NES underlines the critical role of environmental, lifestyle, and genetic factors for triggering NES and driving its progression towards AD or PD.

Several exams and empirical investigations could validate or disconfirm the NES hypothesis. For example, before overt AD or PD symptoms manifestation, gut biopsy and RNA gene expression analysis (Ambrosini et al., 2019; Cersosimo, 2015; Tang et al., 2020) could be useful to detect α Syn abnormalities (seeding stage). Similarly, monitoring NA or 5-HT alterations through PET or imaging techniques (Chen et al., 2020; Fazio et al., 2020; Watanabe et al., 2019; Wile et al., 2017) could indicate the presence of compensatory mechanisms aiming at recovering initial DA loss (compensatory stage). If confirmed by future empirical works, the NES hypothesis could radically change the comprehension of AD and PD pathophysiology. In this way, it could be possible to shed light on AD and PD comorbidities and devise novel precision system-level diagnostic and therapeutic actions. Combining empirical and artificial intelligence approaches could be a way to frame the progression of NES. Future research, indeed, could design machine learning algorithms to predict the probability of developing AD or PD based on the analysis of the heterogeneous data collected to monitor the seeding and compensatory NES stages (Grassi et al., 2019; Myszczyńska et al., 2020).

Author contributions

Daniele Caligiore: Conceptualization, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing, Funding acquisition, Project administration, Supervision. **Flora Giocundo:** Investigation, Methodology, Visualization, Writing – review &

editing. **Massimo Silvetti:** Investigation, Methodology, Writing – review & editing, Funding acquisition. All authors contributed to the article and approved the submitted version.

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Ethical statement

The authors declare that the work described has not involved experimentation on humans or animals. Additionally, the authors declare that this report does not contain personal information that could lead to the identification of the patients.

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