



The degeneration and replacement of dopamine cells in Parkinson's disease: the role of aging

Manuel Rodríguez^{1,2*}, Ingrid Morales^{1,2}, Clara Rodríguez-Sabate², Alberto Sánchez¹, Rafael Castro¹, Jose Miguel Brito¹ and Magdalena Sabate³

¹ Laboratory of Neurobiology and Experimental Neurology, Department of Physiology, Faculty of Medicine, University of La Laguna, La Laguna, Tenerife, Canary Islands, Spain

² Center for Networked Biomedical Research in Neurodegenerative Diseases (CIBERNED), Madrid, Spain

³ Rehabilitation Service, Department of Physical Medicine and Pharmacology, Faculty of Medicine, University of La Laguna, La Laguna, Tenerife, Canary Islands, Spain

Edited by:

Javier Blesa, Columbia University, USA

Reviewed by:

Javier Blesa, Columbia University, USA

Vernice Ruffin Jackson-Lewis, Columbia University, USA

*Correspondence:

Manuel Rodríguez, Laboratory of Neurobiology and Experimental Neurology, Department of Physiology, Faculty of Medicine, University of La Laguna, 38200 La Laguna, Tenerife, Canary Islands, Spain
e-mail: mrdiaz@ull.es

Available data show marked similarities for the degeneration of dopamine cells in Parkinson's disease (PD) and aging. The etio-pathogenic agents involved are very similar in both cases, and include free radicals, different mitochondrial disturbances, alterations of the mitophagy and the ubiquitin-proteasome system. Proteins involved in PD such as α -synuclein, UCH-L1, PINK1 or DJ-1, are also involved in aging. The anomalous behavior of astrocytes, microglia and stem cells of the subventricular zone (SVZ) also changes similarly in aging brains and PD. Present data suggest that PD could be the expression of aging on a cell population with high vulnerability to aging. The future knowledge of mechanisms involved in aging could be critical for both understanding the etiology of PD and developing etiologic treatments to prevent the onset of this neurodegenerative illness and to control its progression.

Keywords: Parkinson's disease, aging, dopamine, nigrostriatal cells, etiopathology

Parkinson's disease (PD) is a neurodegenerative illness whose onset and progression is clearly linked to aging (Driver et al., 2009; Buchman et al., 2012). The discovery of cell loss and eosinophilic intracitoplasmic aggregates (Lewy bodies) in the substantia nigra (SN) of these patients during the early twentieth century (Greenfield and Bosanquet, 1953) led a number of groups to investigate the etio-pathology of PD in this center. Although recent studies have reported neurodegeneration in many other brain centers, the degeneration of SN cells is still the hallmark for a diagnosis of PD.

In the 1960s Hornykiewicz reported a decrease of striatal dopamine (DA) and an effective therapeutic response to levodopa (a DA precursor) suggesting that nigrostriatal DA-cells (nsDac) are the SN cells which mainly degenerate in PD, a possibility also supported by the loss of neuromelanin+ cells in this center (this pigment is a by-product of DA oxidation) (Hornykiewicz, 1966, 2010; Hirsch et al., 1988). This possibility was then supported by studies showing that most degenerated cells express proteins involved in the synthesis (e.g., tyrosine hydroxylase -TH- and l-dopa decarboxylase -DD-), degradation (monoamine oxidase -MAO-), and transport (dopamine transporter, DAT) of DA (Lloyd and Hornykiewicz, 1970; Kastner et al., 1993). The aforementioned findings are frequently used to support the possibility that the nigral DA cell (Dac) loss is a specific characteristic of PD. However, a similar degeneration has been observed in the SN of aged healthy subjects

who also show a decrease in the number of: (1) total SN neurons (Hirai, 1968; McGeer et al., 1977; Stark and Pakkenberg, 2004; Morterá and Herculano-Houzel, 2012); (2) pigmented SN neurons (which decrease 7–10% per decade) (Ma et al., 1999; Stark and Pakkenberg, 2004; Rudow et al., 2008); (3) TH+ and DAT+ neurons (Kastner et al., 1993; Rudow et al., 2008; Kordower et al., 2013); (4) DD+ neurons (Lloyd and Hornykiewicz, 1970); and (5) MAO+ neurons (Saura et al., 1997). Thus, the nsDac loss cannot be considered as a discriminating characteristic of PD.

It has been suggested that the nigral DA-cell subgroups (González-Hernández and Rodríguez, 2000) which degenerate in PD are not the same subgroups which degenerate during the normal aging. PD degeneration mainly affects snDac located in the ventral tier of the posterior-lateral regions of the SN compacta (Fearnley and Lees, 1991; Damier et al., 1999) which innervate the dorsal-lateral region of the striatum (Kish et al., 1988; Hornykiewicz, 1989). However, this snDac subgroup also shows the highest degeneration rate during aging, a fact observed in both monkeys (Kanaan et al., 2008; Collier et al., 2011) and humans (Reeve et al., 2014). In addition, the striatal distribution of the DA denervation is also similar in PD (Kish et al., 1988; Hornykiewicz, 1989) and aging (Kish et al., 1992; Haycock et al., 2003). Therefore, the difference between the DA-cell degeneration in PD and aging may be the intensity of the degeneration process more than the type of cells which degenerate.

Both PD (Olanow and Tatton, 1999; Obeso et al., 2010) and aging (Olson, 1987; Peto and Doll, 1997) are probably the consequence of the simultaneous and persistent action of a number of damaging agents, with oxidative stress being one of the most relevant factors in both cases. *Oxidative stress* has proved to be critical for aging (Gerschman et al., 1954; Brack et al., 2000; Toussaint et al., 2000), affecting proteins, lipids, and nucleic acids in a variety of organs and animals (Sohal and Weindruch, 1996; Perez et al., 2009; Oliveira et al., 2010). The oxidative stress in mammals is mainly generated by the mitochondrial production of energy. The nsDAC has an unmyelinated axon (Orimo et al., 2011) and a large number of synaptic terminals (hundreds of thousands) (Matsuda et al., 2009) which require a high amount of energy, thereby increasing oxidative stress. The metabolism and autooxidation of DA, together with the high concentration of intracellular iron, are additional sources of free radicals in these cells (Kidd, 2000; Berg and Hochstrasser, 2006). These characteristics increase the vulnerability of the snDAC to the aging process.

The DAC is protected from oxidative stress by different mechanisms including the superoxide dismutase and glutathione peroxidase activity (which prevent the oxidant action of oxygen species), and by the DAT and the vesicular monoamine transporter 2 activity (which moves DA from the extracellular medium to synaptic vesicles preventing its metabolism and self-oxidation). These protecting mechanisms are altered in PD where a disruption of the mitochondrial electron transport chain increases the generation of free radicals (Parker et al., 1989; Bender et al., 2006). This, and the down-regulation of the superoxide dismutase, glutathione peroxidase, DAT and vesicular monoamine transporter 2 activities observed in PD (Riederer et al., 1989; Zeevalk et al., 2008), suggest high oxidative stress in the SN of these patients. This possibility is also supported by the high oxidative damage of lipids (Bosco et al., 2006), proteins and DNA (Nakabeppu et al., 2007) found in the SN of these patients (Jenner, 2007). However, all these facts have also been observed in the aged brain and cannot be considered as a selective characteristic of the PD brain (Sohal and Brunk, 1992; Oliveira et al., 2010). In fact, increasing the resistance to oxidative stress via caloric restriction is often considered as the most effective way of delaying aging in animals (Yu, 1996; Bokov et al., 2004), although this neuroprotecting possibility is still to be properly tested in PD.

The most direct impact of oxidative stress is produced on the *mitochondria*. The DNA of mitochondria (mtDNA) is highly vulnerable to mutations because it is located near the mitochondrial source of free radicals (electron transport chain) and because it is not protected by histones. mtDNA shows a high number of deletions in PD patients, and epidemiological studies and cybrid models have suggested that the mtDNA damage is important in PD (Gu et al., 1998; Kraytsberg et al., 2006). Similar mtDNA damage has been observed in the healthy brain, where the mtDNA mutations normally accumulate with aging (Linnane et al., 1989; Bender et al., 2006). Sporadic mtDNA mutations in single mitochondria are not enough to induce severe cell damage, but the aggregation of random mutations in an increasing number of mitochondria can reduce cell viability. This fact probably enhances neurodegeneration in both aged and age-associated

diseases such as PD (Cantuti-Castelvetri et al., 2005; Smigrodzki and Khan, 2005; Maruszak et al., 2006).

The mitochondrial population of cells is normally protected from damage by different repair mechanisms, including *fission/fusion processes* (which use healthy mitochondria to recuperate the functions of damaged mitochondria) and *mitophagy* (an autophagic process which eliminates the most damaged mitochondria preventing their accumulation). Proteins involved in these repair mechanisms (e.g., parkin and PINK1) behave anomalously in both PD (Ethell and Fei, 2009) and aging (Palikaras and Tavernarakis, 2012), with autophagy also being altered in both cases (Cuervo et al., 2004; Ethell and Fei, 2009; Hubbard et al., 2012). The movement of mitochondria across the axon is necessary to preserve an efficient quality control of neuronal mitochondria. Most synaptic mitochondria are synthesized in the neuronal somata and moved along axons (anterograde motion). Axonal transport is also necessary to move dysfunctional mitochondria from synaptic bottoms to the cell somata (retrograde motion) where they can be destroyed by mitophagy and other mechanisms (Cheng et al., 2010). Different proteins involved in the axonal transport (e.g., α -synuclein, parkin and PINK1-Miro-Milton complex) are involved in both PD and aging as well. The axonal damage observed in DAC of the PD brain (Cheng et al., 2010) has been found in the aging brain too (Gilley et al., 2012), which shows that the anomalous behavior of axons is also a characteristic shared by the PD and the aging brain.

The anomalous conformations of α -synuclein facilitate the formation of Lewy bodies in the nsDAC of PD patients (Lansbury and Brice, 2002) as well as in healthy aged subjects (Li et al., 2004; Moore et al., 2005). Similarly, the mutation of parkin has been associated to both PD (Lücking et al., 1998; Lücking et al., 2000; Moore et al., 2005; Reeve et al., 2014) and aging (Rodríguez-Navarro et al., 2007; Vincow et al., 2013). The UCH-L1 mutation impairs the ubiquitin-proteasome system (Osaka et al., 2003; Li et al., 2004), promoting both PD (Leroy et al., 1998) and aging (Marzban et al., 2002). PINK1 facilitates axonal transport and degradation of damaged mitochondria (Valente et al., 2004a; Liu, 2014), and this PINK1 activity is altered in both the PD (Valente et al., 2004b; Albanese et al., 2005; Gelmetti et al., 2008) and aging (Wood-Kaczmar et al., 2008; Vincow et al., 2013) brain. The DJ-1 protein protects cells against oxidative stressors (Moore et al., 2005). Its anomalous behavior has been linked to a familiar parkinsonism (Bonifati et al., 2003a,b; Ibanez et al., 2003) and to aging (Marzban et al., 2002; Meulener et al., 2006). These proteins have been associated with the different familiar early onset parkinsonisms which present mutations of their genes, but also with idiopathic (or sporadic) PD and with normal aging where their activity may change (Cookson and Bandmann, 2010).

Many of the altered cell groups in PD show similar changes in the aged brain. This is the case of *astrocytes*, cells whose physiological functions (Sofroniew and Vinters, 2010; Rodriguez et al., 2012) change in PD and aging (Raivich et al., 1999; Morales et al., 2013). Astrocytes prevent neuronal damage by releasing neuroprotecting agents (glutathione, basic fibroblast growth factor, glial cell line-derived neurotrophic factor...) (Saavedra et al., 2006; Deierborg et al., 2008), and by removing toxic molecules from the extracellular medium (e.g., α -synuclein)

(Braak et al., 2007; Lee et al., 2010). The neuroprotecting abilities of astrocytes decrease with age (Pertusa et al., 2007; Mansour et al., 2008; Chinta et al., 2013), which increases DAC vulnerability (Mirza et al., 2000; Song et al., 2009) and enhances the development of PD (Halliday and Stevens, 2011).

It has been suggested that the slow DAC decline during life is normally compensated by a slow cell repopulation provided by the subventricular zone (SVZ; Doetsch et al., 1997, 1999; Quiñones-Hinojosa et al., 2006). SVZ *stem cells* normally differentiate into astrocytes and neuroblasts which later migrate to the olfactory bulb. The differentiation and migration of these cells are modulated by the DA released from nsDAC terminals (Freundlieb et al., 2006; Borta and Höglinger, 2007). Some neurons generated by SVZ stem cells express a DAergic phenotype and migrate to the olfactory bulb where they modulate olfaction. However, neuroblasts can also migrate to other brain loci, particularly when the target areas have been damaged (ictus.) (Macas et al., 2006). It has been suggested that stem cells can migrate to the SN (Kay and Blum, 2000; Zhao et al., 2003; Zhao and Janson Lang, 2009), where they could compensate for the DAC loss induced by aging. Thus, an insufficient repopulation of the DAC loss induced by senescence may also be a cause of PD (Armstrong and Barker, 2001). This possibility is supported by the low neurogenesis observed in the SVZ (Höglinger et al., 2004) and anterior olfactory nucleus (Pearce et al., 1995; Hawkes et al., 1997) of PD patients. A similar low neurogenesis has been observed during aging. Healthy subjects present a noticeable decrease of SVZ stem cell proliferation during the last third of life which is when the incidence of PD increases (Galvan and Jin, 2007; Conover and Shook, 2011). Nevertheless, the cell repopulation hypothesis is currently a matter of debate because the DAergic repopulation of the SN has not been definitively proved (Frielingsdorf et al., 2004). The new astrocytes derived from SVZ stem cells could also prevent DAC degeneration by replacing the damaged astrocytes in PD patients (Gonzalez-Perez and Quiñones-Hinojosa, 2012; Mack and Wolburg, 2013). Bearing in mind the neuroprotecting role of astrocytes, this repopulation could also be necessary to keep the DAC alive in the aged brain. In this case, aging and PD could be the final result of a deficient gliogenesis and of the consequent deterioration of the astrocyte population supporting the snDAC. Therefore, the reduced neurogenesis and gliogenesis secondary to the senescence of the SVZ could be involved in both aging and PD.

The *microglia* has been linked to the neurodegenerating process in PD. *Microglia* is activated in the presence of aggregated forms of α -synuclein (Zhang et al., 2005), expressing macrophage markers and releasing IL-1 β , IL-6 and TNF- α which can damage the DAC (Croisier et al., 2005; Orr et al., 2005). This activation has been found in both PD (Hunot et al., 1996; Knott et al., 2000) and aged brains (Godbout and Johnson, 2004; Gelinas and McLaurin, 2005; Campuzano et al., 2009), suggesting that the neurotoxic action of these cells is similar in both conditions (Ouchi et al., 2005; Streit et al., 2008; Cunningham, 2013).

Recent technological advances have made it possible to obtain *pluripotent stem cells* (iPSC; Takahashi and Yamanaka, 2006) from the skin of healthy subjects and patients with different illnesses including PD (disease-specific iPSC) (Lee and Studer, 2010). The DAC derived from iPSC shows an abnormal phenotype

(with respect to aged-matched controls) when produced from patients with familiar parkinsonisms (PINK1, SNCA, parkin, LRRK2...) (Sánchez-Danés et al., 2013) but not when produced from patients with sporadic PD (Soldner et al., 2009). However, cells from sporadic PD patients show the typical alterations of the nsDAC when they are kept for a long time in a culture medium which *in vitro* simulates *in vivo* aging (more than 2 months in a culture medium which induces chronic cellular stress) (Sánchez-Danés et al., 2012). In these conditions, the DAC derived from iPSC of sporadic PD patients shows morphological (reduced number of neurites and accumulation of autophagic vacuoles) and neurochemical (accumulation of α -synuclein in their cytoplasm) characteristics similar to those of the DAC in PD (Sánchez-Danés et al., 2012). Thus, aging, in this *in vitro* model, seems to be a condition for developing the DAC characteristics observed in PD, which also supports aging as a basic mechanism for PD.

In summary, the studies reviewed above show that the DAC degeneration in PD is similar to that observed in aging, suggesting that aging is not simply another agent to add to the etiology of PD. The progressive course of aging and PD could be induced by the same multi-factorial etiology, including astrocytic and microglia alterations, oxidative stress, anomalous action of different proteins, mitochondrial disturbances, and alterations of the mitophagy and the ubiquitin-proteasome system. To this effect, PD could be the expression of aging on a cell population which, due to its characteristics (number of synaptic terminals, unmyelinated axon etc...), is particularly vulnerable to damage. Repeated injuries accumulated throughout a person's lifespan may go unnoticed until the DAC loss exceeds a critical value. DAC degenerated over the years could be regularly replaced by new neurons derived from brain stem cells. Since stem cells are also affected by aging, the DAC loss induced by aging could be increased by an insufficient cell replacement. The progressive imbalance between the DAC loss and DAC neurogenesis eventually leads to a large enough decrease in the number of DAC to trigger the onset of motor disturbances of PD. This DAC loss is usually considered as a sign of brain aging until it crosses the above mentioned clinical threshold and PD can be diagnosed. In our opinion, a better understanding of the mechanisms involved in aging would help to explain the etiology of PD.

REFERENCES

- Albanese, A., Valente, E. M., Romito, L. M., Bellacchio, E., Elia, A. E., and Dallapiccola, B. (2005). The PINK1 phenotype can be indistinguishable from idiopathic Parkinson disease. *Neurology* 64, 1958–1960. doi: 10.1212/01.wnl.0000163999.72864.fd
- Armstrong, R. J., and Barker, R. A. (2001). Neurodegeneration: a failure of neuroregeneration? *Lancet* 358, 1174–1176. doi: 10.1016/S0140-6736(01)06260-2
- Bender, A., Krishnan, K. J., Morris, C. M., Taylor, G. A., Reeve, A. K., Perry, R. H., et al. (2006). High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nat. Genet.* 38, 515–517. doi: 10.1038/ng1769
- Berg, D., and Hochstrasser, H. (2006). Iron metabolism in Parkinsonian syndromes. *Mov. Disord.* 21, 1299–1310. doi: 10.1002/mds.21020
- Bokov, A., Chaudhuri, A., and Richardson, A. (2004). The role of oxidative damage and stress in aging. *Mech. Ageing Dev.* 125, 811–826. doi: 10.1016/j.mad.2004.07.009
- Bonifati, V., Rizzu, P., Squitieri, F., Krieger, E., Vanacore, N., van Swieten, J. C., et al. (2003a). DJ-1 (PARK7), a novel gene for autosomal recessive,

- early onset parkinsonism. *Neurol. Sci.* 24, 159–160. doi: 10.1007/s10072-003-0108-0
- Bonifati, V., Rizzu, P., van Baren, M. J., Schaap, O., Breedveld, G. J., Krieger, E., et al. (2003b). Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science* 299, 256–259. doi: 10.1126/science.1077209
- Borta, A., and Höglinger, G. U. (2007). Dopamine and adult neurogenesis. *J. Neurochem.* 100, 587–595. doi: 10.1111/j.1471-4159.2006.04241.x
- Bosco, D. A., Fowler, D. M., Zhang, Q., Nieva, J., Powers, E. T., Wentworth, P., et al. (2006). Elevated levels of oxidized cholesterol metabolites in Lewy body disease brains accelerate alpha-synuclein fibrilization. *Nat. Chem. Biol.* 2, 249–253. doi: 10.1038/nchembio782
- Braak, H., Sastre, M., and Del Tredici, K. (2007). Development of alpha-synuclein immunoreactive astrocytes in the forebrain parallels stages of intraneuronal pathology in sporadic Parkinson's disease. *Acta Neuropathol.* 114, 231–241. doi: 10.1007/s00401-007-0244-3
- Brack, C., Lithgow, G., Osiewicz, H., and Toussaint, O. (2000). EMBO WORKSHOP REPORT: molecular and cellular gerontology Serpiano, Switzerland, September 18–22, 1999. *EMBO J.* 19, 1929–1934. doi: 10.1093/emboj/19.9.1929
- Buchman, A. S., Shulman, J. M., Nag, S., Leurgans, S. E., Arnold, S. E., Morris, M. C., et al. (2012). Nigral pathology and parkinsonian signs in elders without Parkinson disease. *Ann. Neurol.* 71, 258–266. doi: 10.1002/ana.22588
- Campuzano, O., Castillo-Ruiz, M. M., Acarin, L., Castellano, B., and Gonzalez, B. (2009). Increased levels of proinflammatory cytokines in the aged rat brain attenuate injury-induced cytokine response after excitotoxic damage. *J. Neurosci. Res.* 87, 2484–2497. doi: 10.1002/jnr.22074
- Cantuti-Castelvetri, I., Lin, M. T., Zheng, K., Keller-McGandy, C. E., Betensky, R. A., Johns, D. R., et al. (2005). Somatic mitochondrial DNA mutations in single neurons and glia. *Neurobiol. Aging* 26, 1343–1355. doi: 10.1016/j.neurobiolaging.2004.11.008
- Cheng, H. C., Ulane, C. M., and Burke, R. E. (2010). Clinical progression in Parkinson disease and the neurobiology of axons. *Ann. Neurol.* 67, 715–725. doi: 10.1002/ana.21995
- Chinta, S. J., Lieu, C. A., Demaria, M., Laberge, R. M., Campisi, J., and Andersen, J. K. (2013). Environmental stress, ageing and glial cell senescence: a novel mechanistic link to Parkinson's disease? *J. Intern. Med.* 273, 429–436. doi: 10.1111/joim.12029
- Collier, T. J., Kanaan, N. M., and Kordower, J. H. (2011). Ageing as a primary risk factor for Parkinson's disease: evidence from studies of non-human primates. *Nat. Rev. Neurosci.* 12, 359–366. doi: 10.1038/nrn3039
- Conover, J. C., and Shook, B. A. (2011). Aging of the subventricular zone neural stem cell niche. *Aging Dis.* 2, 149–163. doi: 10.1016/j.neuroscience.2010.11.032
- Cookson, M. R., and Bandmann, O. (2010). Parkinson's disease: insights from pathways. *Hum. Mol. Genet.* 19, R21–R27. doi: 10.1093/hmg/ddq167
- Croisier, E., Moran, L. B., Dexter, D. T., Pearce, R. K., and Graeber, M. B. (2005). Microglial inflammation in the parkinsonian substantia nigra: relationship to alpha-synuclein deposition. *J. Neuroinflammation* 2:14. doi: 10.1186/1742-2094-2-14
- Cuervo, A. M., Stefanis, L., Fredenburg, R., Lansbury, P. T., and Sulzer, D. (2004). Impaired degradation of mutant alpha-synuclein by chaperone-mediated autophagy. *Science* 305, 1292–1295. doi: 10.1126/science.1101738
- Cunningham, C. (2013). Microglia and neurodegeneration: the role of systemic inflammation. *Glia* 61, 71–90. doi: 10.1002/glia.22350
- Damier, P., Hirsch, E. C., Agid, Y., and Graybiel, A. M. (1999). The substantia nigra of the human brain. II. Patterns of loss of dopamine-containing neurons in Parkinson's disease. *Brain* 122(Pt. 8), 1437–1448. doi: 10.1093/brain/122.8.1437
- Deierborg, T., Soulet, D., Roybon, L., Hall, V., and Brundin, P. (2008). Emerging restorative treatments for Parkinson's disease. *Prog. Neurobiol.* 85, 407–432. doi: 10.1016/j.pneurobio.2008.05.001
- Doetsch, F., Caille, I., Lim, D. A., Garcia-Verdugo, J. M., and Alvarez-Buylla, A. (1999). Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* 97, 703–716. doi: 10.1016/S0092-8674(00)80783-7
- Doetsch, F., Garcia-Verdugo, J. M., and Alvarez-Buylla, A. (1997). Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. *J. Neurosci.* 17, 5046–5061.
- Driver, J. A., Logroscino, G., Gaziano, J. M., and Kurth, T. (2009). Incidence and remaining lifetime risk of Parkinson disease in advanced age. *Neurology* 72, 432–438. doi: 10.1212/01.wnl.0000341769.50075.bb
- Ethell, D. W., and Fei, Q. (2009). Parkinson-linked genes and toxins that affect neuronal cell death through the Bcl-2 family. *Antioxid. Redox. Signal.* 11, 529–540. doi: 10.1089/ARS.2008.2228
- Fearnley, J. M., and Lees, A. J. (1991). Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain* 114(Pt. 5), 2283–2301. doi: 10.1093/brain/114.5.2283
- Freundlieb, N., Francois, C., Tande, D., Oertel, W. H., Hirsch, E. C., and Höglinger, G. U. (2006). Dopaminergic substantia nigra neurons project topographically organized to the subventricular zone and stimulate precursor cell proliferation in aged primates. *J. Neurosci.* 26, 2321–2325. doi: 10.1523/jneurosci.4859-05.2006
- Frielingdorf, H., Schwarz, K., Brundin, P., and Mohapel, P. (2004). No evidence for new dopaminergic neurons in the adult mammalian substantia nigra. *Proc. Natl. Acad. Sci. U S A* 101, 10177–10182. doi: 10.1073/pnas.0401229101
- Galvan, V., and Jin, K. (2007). Neurogenesis in the aging brain. *Clin. Interv. Aging* 2, 605–610. doi: 10.2147/CIA.S1614
- Gelinas, D. S., and McLaurin, J. (2005). PPAR-alpha expression inversely correlates with inflammatory cytokines IL-1beta and TNF-alpha in aging rats. *Neurochem. Res.* 30, 1369–1375. doi: 10.1007/s11064-005-8341-y
- Gelmetti, V., Ferraris, A., Brusa, L., Romano, F., Lombardi, F., Barzaghi, C., et al. (2008). Late onset sporadic Parkinson's disease caused by PINK1 mutations: clinical and functional study. *Mov. Disord.* 23, 881–885. doi: 10.1002/mds.21960
- Gerschman, R., Gilbert, D. L., Nye, S. W., Dwyer, P., and Fenn, W. O. (1954). Oxygen poisoning and x-irradiation: a mechanism in common. *Science* 119, 623–626. doi: 10.1126/science.119.3097.623
- Gilley, J., Seereeram, A., Ando, K., Mosely, S., Andrews, S., Kerschensteiner, M., et al. (2012). Age-dependent axonal transport and locomotor changes and tau hypophosphorylation in a "P301L" tau knockin mouse. *Neurobiol. Aging* 33, 621.e1–621.e15. doi: 10.1016/j.neurobiolaging.2011.02.014
- Godbout, J. P., and Johnson, R. W. (2004). Interleukin-6 in the aging brain. *J. Neuroimmunol.* 147, 141–144. doi: 10.1016/j.jneuroim.2003.10.031
- González-Hernández, T., and Rodriguez, M. (2000). Compartmental organization and chemical profile of dopaminergic and GABAergic neurons in the substantia nigra of the rat. *J. Comp. Neurol.* 421, 107–135. doi: 10.1002/(sici)1096-9861(20000522)421:1<107::aid-cnc7>3.3.co;2-6
- Gonzalez-Perez, O., and Quinones-Hinojosa, A. (2012). Astrocytes as neural stem cells in the adult brain. *J. Stem Cells* 7, 181–188. doi: jsc.2012.7.3.181
- Greenfield, J. G., and Bosanquet, F. D. (1953). The brain-stem lesions in Parkinsonism. *J. Neurol. Neurosurg. Psychiatry* 16, 213–226. doi: 10.1136/jnnp.16.4.213
- Gu, M., Cooper, J. M., Taanman, J. W., and Schapira, A. H. (1998). Mitochondrial DNA transmission of the mitochondrial defect in Parkinson's disease. *Ann. Neurol.* 44, 177–186. doi: 10.1002/ana.410440207
- Halliday, G. M., and Stevens, C. H. (2011). Glia: initiators and progressors of pathology in Parkinson's disease. *Mov. Disord.* 26, 6–17. doi: 10.1002/mds.23455
- Hawkes, C. H., Shephard, B. C., and Daniel, S. E. (1997). Olfactory dysfunction in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry* 62, 436–446. doi: 10.1136/jnnp.62.5.436
- Haycock, J. W., Becker, L., Ang, L., Furukawa, Y., Hornykiewicz, O., and Kish, S. J. (2003). Marked disparity between age-related changes in dopamine and other presynaptic dopaminergic markers in human striatum. *J. Neurochem.* 87, 574–585. doi: 10.1046/j.1471-4159.2003.02017.x
- Hirai, S. (1968). Histochemical study on the regressive degeneration of the senile brain, with special reference to the aging of the substantia nigra. *Shinkei Kenkyu No Shimpo* 12, 845–849.
- Hirsch, E., Graybiel, A. M., and Agid, Y. A. (1988). Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. *Nature* 334, 345–348. doi: 10.1038/334345a0
- Höglinger, G. U., Rizk, P., Muriel, M. P., Duyckaerts, C., Oertel, W. H., Caille, I., et al. (2004). Dopamine depletion impairs precursor cell proliferation in Parkinson disease. *Nat. Neurosci.* 7, 726–735. doi: 10.1038/nn1265
- Hornykiewicz, O. (1966). Dopamine (3-hydroxytyramine) and brain function. *Pharmacol. Rev.* 18, 925–964.

- Hornykiewicz, O. (1989). Ageing and neurotoxins as causative factors in idiopathic Parkinson's disease—a critical analysis of the neurochemical evidence. *Prog. Neuro-psychopharmacol. Biol. Psychiatry* 13, 319–328. doi: 10.1016/0278-5846(89)90121-8
- Hornykiewicz, O. (2010). A brief history of levodopa. *J. Neurol.* 257, S249–S252. doi: 10.1007/s00415-010-5741-y
- Hubbard, V. M., Valdor, R., Macian, F., and Cuervo, A. M. (2012). Selective autophagy in the maintenance of cellular homeostasis in aging organisms. *Biogerontology* 13, 21–35. doi: 10.1007/s10522-011-9331-x
- Hunot, S., Boissiere, F., Faucheux, B., Brugg, B., Mouatt-Prigent, A., Agid, Y., et al. (1996). Nitric oxide synthase and neuronal vulnerability in Parkinson's disease. *Neuroscience* 72, 355–363. doi: 10.1016/0306-4522(95)00578-1
- Ibanez, P., De Michele, G., Bonifati, V., Lohmann, E., Thobois, S., Pollak, P., et al. (2003). Screening for DJ-1 mutations in early onset autosomal recessive parkinsonism. *Neurology* 61, 1429–1431. doi: 10.1212/01.wnl.0000094121.48373.fd
- Jenner, P. (2007). Oxidative stress and Parkinson's disease. *Handb. Clin. Neurol.* 83, 507–520. doi: 10.1016/S0072-9752(07)83024-7
- Kanaan, N. M., Kordower, J. H., and Collier, T. J. (2008). Age-related changes in dopamine transporters and accumulation of 3-nitrotyrosine in rhesus monkey midbrain dopamine neurons: relevance in selective neuronal vulnerability to degeneration. *Eur. J. Neurosci.* 27, 3205–3215. doi: 10.1111/j.1460-9568.2008.06307.x
- Kastner, A., Hirsch, E. C., Herrero, M. T., Javoy-Agid, F., and Agid, Y. (1993). Immunocytochemical quantification of tyrosine hydroxylase at a cellular level in the mesencephalon of control subjects and patients with Parkinson's and Alzheimer's disease. *J. Neurochem.* 61, 1024–1034. doi: 10.1111/j.1471-4159.1993.tb03616.x
- Kay, J. N., and Blum, M. (2000). Differential response of ventral midbrain and striatal progenitor cells to lesions of the nigrostriatal dopaminergic projection. *Dev. Neurosci.* 22, 56–67. doi: 10.1159/000017427
- Kidd, P. M. (2000). Parkinson's disease as multifactorial oxidative neurodegeneration: implications for integrative management. *Altern. Med. Rev.* 5, 502–529.
- Kish, S. J., Shannak, K., and Hornykiewicz, O. (1988). Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. Pathophysiological and clinical implications. *N. Engl. J. Med.* 318, 876–880. doi: 10.1056/nejm198804073181402
- Kish, S. J., Shannak, K., Rajput, A., Deck, J. H., and Hornykiewicz, O. (1992). Aging produces a specific pattern of striatal dopamine loss: implications for the etiology of idiopathic Parkinson's disease. *J. Neurochem.* 58, 642–648. doi: 10.1111/j.1471-4159.1992.tb09766.x
- Knott, C., Stern, G., and Wilkin, G. P. (2000). Inflammatory regulators in Parkinson's disease: iNOS, lipocortin-1 and cyclooxygenases-1 and -2. *Mol. Cell. Neurosci.* 16, 724–739. doi: 10.1006/mcne.2000.0914
- Kordower, J. H., Olanow, C. W., Dodiya, H. B., Chu, Y., Beach, T. G., Adler, C. H., et al. (2013). Disease duration and the integrity of the nigrostriatal system in Parkinson's disease. *Brain* 136, 2419–2431. doi: 10.1093/brain/awt192
- Kraytsberg, Y., Kudryavtseva, E., McKee, A. C., Geula, C., Kowall, N. W., and Khrapko, K. (2006). Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. *Nat. Genet.* 38, 518–520. doi: 10.1038/ng1778
- Lansbury, P. T. Jr., and Brice, A. (2002). Genetics of Parkinson's disease and biochemical studies of implicated gene products. *Curr. Opin. Genet. Dev.* 12, 299–306. doi: 10.1016/S0959-437X(02)00302-7
- Lee, G., and Studer, L. (2010). Induced pluripotent stem cell technology for the study of human disease. *Nat. Methods* 7, 25–27. doi: 10.1038/nmeth.f.283
- Lee, H. J., Suk, J. E., Patrick, C., Bae, E. J., Cho, J. H., Rho, S., et al. (2010). Direct transfer of alpha-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies. *J. Biol. Chem.* 285, 9262–9272. doi: 10.1074/jbc.M109.081125
- Leroy, E., Boyer, R., Auburger, G., Leube, B., Ulm, G., Mezey, E., et al. (1998). The ubiquitin pathway in Parkinson's disease. *Nature* 395, 451–452. doi: 10.1038/26652
- Li, W., Lesuisse, C., Xu, Y., Troncoso, J. C., Price, D. L., and Lee, M. K. (2004). Stabilization of alpha-synuclein protein with aging and familial parkinson's disease-linked A53T mutation. *J. Neurosci.* 24, 7400–7409. doi: 10.1523/jneurosci.1370-04.2004
- Linnane, A. W., Marzuki, S., Ozawa, T., and Tanaka, M. (1989). Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. *Lancet* 1, 642–645. doi: 10.1016/s0140-6736(89)92145-4
- Liu, J. P. (2014). Molecular mechanisms of aging and related diseases. *Clin. Exp. Pharmacol. Physiol.* 41, 445–458. doi: 10.1111/1440-1681.12247
- Lloyd, K., and Hornykiewicz, O. (1970). Parkinson's disease: activity of L-dopa decarboxylase in discrete brain regions. *Science* 170, 1212–1213. doi: 10.1126/science.170.3963.1212
- Lücking, C. B., Abbas, N., Durr, A., Bonifati, V., Bonnet, A. M., de Broucker, T., et al. (1998). Homozygous deletions in parkin gene in European and North African families with autosomal recessive juvenile parkinsonism. The European consortium on genetic susceptibility in Parkinson's disease and the French Parkinson's disease genetics study group. *Lancet* 352, 1355–1356. doi: 10.1016/s0140-6736(05)60746-5
- Lucking, C. B., Durr, A., Bonifati, V., Vaughan, J., De Michele, G., Gasser, T., et al. (2000). Association between early-onset Parkinson's disease and mutations in the parkin gene. *N. Engl. J. Med.* 342, 1560–1567. doi: 10.1056/nejm200005253422103
- Ma, S. Y., Roytt, M., Collan, Y., and Rinne, J. O. (1999). Unbiased morphometrical measurements show loss of pigmented nigral neurones with ageing. *Neuropathol. Appl. Neurobiol.* 25, 394–399. doi: 10.1046/j.1365-2990.1999.00202.x
- Macas, J., Nern, C., Plate, K. H., and Momma, S. (2006). Increased generation of neuronal progenitors after ischemic injury in the aged adult human forebrain. *J. Neurosci.* 26, 13114–13119. doi: 10.1523/jneurosci.4667-06.2006
- Mack, A. F., and Wolburg, H. (2013). A novel look at astrocytes: aquaporins, ionic homeostasis and the role of the microenvironment for regeneration in the CNS. *Neuroscientist* 19, 195–207. doi: 10.1177/1073858412447981
- Mansour, H., Chamberlain, C. G., Weible, M. W. 2nd, Hughes, S., Chu, Y., and Chan-Ling, T. (2008). Aging-related changes in astrocytes in the rat retina: imbalance between cell proliferation and cell death reduces astrocyte availability. *Aging Cell* 7, 526–540. doi: 10.1111/j.1474-9726.2008.00402.x
- Maruszak, A., Gaweda-Walerych, K., Soltyszewski, I., and Zekanowski, C. (2006). Mitochondrial DNA in pathogenesis of Alzheimer's and Parkinson's diseases. *Acta Neurobiol. Exp. (Wars)* 66, 153–176.
- Marzban, G., Grillari, J., Reisinger, E., Hemetsberger, T., Grabherr, R., and Katinger, H. (2002). Age-related alterations in the protein expression profile of C57BL/6J mouse pituitaries. *Exp. Gerontol.* 37, 1451–1460. doi: 10.1016/s0531-5565(02)00117-1
- Matsuda, W., Furuta, T., Nakamura, K. C., Hioki, H., Fujiyama, F., Arai, R., et al. (2009). Single nigrostriatal dopaminergic neurons form widely spread and highly dense axonal arborizations in the neostriatum. *J. Neurosci.* 29, 444–453. doi: 10.1523/JNEUROSCI.4029-08.2009
- McGeer, P. L., McGeer, E. G., and Suzuki, J. S. (1977). Aging and extrapyramidal function. *Arch. Neurol.* 34, 33–35. doi: 10.1001/archneur.1977.00500130053010
- Meulener, M. C., Xu, K., Thomson, L., Ischiropoulos, H., and Bonini, N. M. (2006). Mutational analysis of DJ-1 in *Drosophila* implicates functional inactivation by oxidative damage and aging. *Proc. Natl. Acad. Sci. U S A* 103, 12517–12522. doi: 10.1073/pnas.0601891103
- Mirza, B., Hadberg, H., Thomsen, P., and Moos, T. (2000). The absence of reactive astrocytosis is indicative of a unique inflammatory process in Parkinson's disease. *Neuroscience* 95, 425–432. doi: 10.1016/s0306-4522(99)00455-8
- Moore, D. J., West, A. B., Dawson, V. L., and Dawson, T. M. (2005). Molecular pathophysiology of Parkinson's disease. *Annu. Rev. Neurosci.* 28, 57–87. doi: 10.1146/annurev.neuro.28.061604.135718
- Morales, I., Sabate, M., and Rodriguez, M. (2013). Striatal glutamate induces retrograde excitotoxicity and neuronal degeneration of intralaminar thalamic nuclei: their potential relevance for Parkinson's disease. *Eur. J. Neurosci.* 38, 2172–2182. doi: 10.1111/ejn.12205
- Mortera, P., and Herculano-Houzel, S. (2012). Age-related neuronal loss in the rat brain starts at the end of adolescence. *Front. Neuroanat.* 6:45. doi: 10.3389/fnana.2012.00045
- Nakabeppu, Y., Tsuchimoto, D., Yamaguchi, H., and Sakumi, K. (2007). Oxidative damage in nucleic acids and Parkinson's disease. *J. Neurosci. Res.* 85, 919–934. doi: 10.1002/jnr.21191
- Obeso, J. A., Rodriguez-Oroz, M. C., Goetz, C. G., Marin, C., Kordower, J. H., Rodriguez, M., et al. (2010). Missing pieces in the Parkinson's disease puzzle. *Nat. Med.* 16, 653–661. doi: 10.1038/nm.2165

- Olanow, C. W., and Tatton, W. G. (1999). Etiology and pathogenesis of Parkinson's disease. *Annu. Rev. Neurosci.* 22, 123–144. doi: 10.1146/annurev.neuro.22.1.123
- Oliveira, B. F., Nogueira-Machado, J. A., and Chaves, M. M. (2010). The role of oxidative stress in the aging process. *ScientificWorldJournal* 10, 1121–1128. doi: 10.1100/tsw.2010.94
- Olson, C. B. (1987). A review of why and how we age: a defense of multifactorial aging. *Mech. Ageing Dev.* 41, 1–28. doi: 10.1016/0047-6374(87)90050-9
- Orimo, S., Uchihara, T., Kanazawa, T., Itoh, Y., Wakabayashi, K., Kakita, A., et al. (2011). Unmyelinated axons are more vulnerable to degeneration than myelinated axons of the cardiac nerve in Parkinson's disease. *Neuropathol. Appl. Neurobiol.* 37, 791–802. doi: 10.1111/j.1365-2990.2011.01194.x
- Orr, C. F., Rowe, D. B., Mizuno, Y., Mori, H., and Halliday, G. M. (2005). A possible role for humoral immunity in the pathogenesis of Parkinson's disease. *Brain* 128, 2665–2674. doi: 10.1093/brain/awh625
- Osaka, H., Wang, Y. L., Takada, K., Takizawa, S., Setsuie, R., Li, H., et al. (2003). Ubiquitin carboxy-terminal hydrolase L1 binds to and stabilizes monoubiquitin in neuron. *Hum. Mol. Genet.* 12, 1945–1958. doi: 10.1093/hmg/ddg211
- Ouchi, Y., Yoshikawa, E., Sekine, Y., Futatsubashi, M., Kanno, T., Ogasu, T., et al. (2005). Microglial activation and dopamine terminal loss in early Parkinson's disease. *Ann. Neurol.* 57, 168–175. doi: 10.1002/ana.20338
- Palikaras, K., and Tavernarakis, N. (2012). Mitophagy in neurodegeneration and aging. *Front. Genet.* 3:297. doi: 10.3389/fgene.2012.00297
- Parker, W. D. Jr., Boyson, S. J., and Parks, J. K. (1989). Abnormalities of the electron transport chain in idiopathic Parkinson's disease. *Ann. Neurol.* 26, 719–723. doi: 10.1002/ana.410260606
- Pearce, R. K., Hawkes, C. H., and Daniel, S. E. (1995). The anterior olfactory nucleus in Parkinson's disease. *Mov. Disord.* 10, 283–287. doi: 10.1002/mds.870100309
- Perez, V. I., Buffenstein, R., Masamsetti, V., Leonard, S., Salmon, A. B., Mele, J., et al. (2009). Protein stability and resistance to oxidative stress are determinants of longevity in the longest-living rodent, the naked mole-rat. *Proc. Natl. Acad. Sci. U S A* 106, 3059–3064. doi: 10.1073/pnas.0809620106
- Pertusa, M., Garcia-Matas, S., Rodriguez-Farre, E., Sanfeliu, C., and Cristofol, R. (2007). Astrocytes aged in vitro show a decreased neuroprotective capacity. *J. Neurochem.* 101, 794–805. doi: 10.1111/j.1471-4159.2006.04369.x
- Peto, R., and Doll, R. (1997). There is no such thing as aging. *BMJ* 315, 1030–1032. doi: 10.1136/bmj.315.7115.1030
- Quiñones-Hinojosa, A., Sanai, N., Soriano-Navarro, M., Gonzalez-Perez, O., Mirzadeh, Z., Gil-Perotin, S., et al. (2006). Cellular composition and cytoarchitecture of the adult human subventricular zone: a niche of neural stem cells. *J. Comp. Neurol.* 494, 415–434. doi: 10.1002/cne.20798
- Raivich, G., Bohatschek, M., Kloss, C. U., Werner, A., Jones, L. L., and Kreutzberg, G. W. (1999). Neuroglial activation repertoire in the injured brain: graded response, molecular mechanisms and cues to physiological function. *Brain Res. Brain Res. Rev.* 30, 77–105. doi: 10.1016/s0165-0173(99)00007-7
- Reeve, A., Simcox, E., and Turnbull, D. (2014). Ageing and Parkinson's disease: why is advancing age the biggest risk factor? *Ageing Res. Rev.* 14, 19–30. doi: 10.1016/j.arr.2014.01.004
- Riederer, P., Sofic, E., Rausch, W. D., Schmidt, B., Reynolds, G. P., Jellinger, K., et al. (1989). Transition metals, ferritin, glutathione and ascorbic acid in parkinsonian brains. *J. Neurochem.* 52, 515–520. doi: 10.1111/j.1471-4159.1989.tb09150.x
- Rodriguez, M., Sabate, M., Rodriguez-Sabate, C., and Morales, I. (2012). The role of non-synaptic extracellular glutamate. *Brain Res. Bull.* 93, 17–26. doi: 10.1016/j.brainresbull.2012.09.018
- Rodriguez-Navarro, J. A., Casarejos, M. J., Menendez, J., Solano, R. M., Rodal, I., Gomez, A., et al. (2007). Mortality, oxidative stress and tau accumulation during ageing in parkin null mice. *J. Neurochem.* 103, 98–114. doi: 10.1111/j.1471-4159.2007.04762.x
- Rudow, G., O'Brien, R., Savonenko, A. V., Resnick, S. M., Zonderman, A. B., Pletnikova, O., et al. (2008). Morphometry of the human substantia nigra in ageing and Parkinson's disease. *Acta Neuropathol.* 115, 461–470. doi: 10.1007/s00401-008-0352-8
- Saavedra, A., Baltazar, G., Santos, P., Carvalho, C. M., and Duarte, E. P. (2006). Selective injury to dopaminergic neurons up-regulates GDNF in substantia nigra postnatal cell cultures: role of neuron-glia crosstalk. *Neurobiol. Dis.* 23, 533–542. doi: 10.1016/j.nbd.2006.04.008
- Sánchez-Danés, A., Benzoni, P., Memo, M., Dell'era, P., Raya, A., and Consiglio, A. (2013). Induced pluripotent stem cell-based studies of Parkinson's disease: challenges and promises. *CNS Neurol. Disord. Drug Targets* 12, 1114–1127. doi: 10.2174/187152731131200128
- Sánchez-Danés, A., Richaud-Patin, Y., Carballo-Carbajal, I., Jimenez-Delgado, S., Caig, C., Mora, S., et al. (2012). Disease-specific phenotypes in dopamine neurons from human iPSC-based models of genetic and sporadic Parkinson's disease. *EMBO Mol. Med.* 4, 380–395. doi: 10.1002/emmm.2012.00215
- Saura, J., Andres, N., Andrade, C., Ojuel, J., Eriksson, K., and Mahy, N. (1997). Biphasic and region-specific MAO-B response to aging in normal human brain. *Neurobiol. Aging* 18, 497–507. doi: 10.1016/s0197-4580(97)00113-9
- Smigrodzki, R. M., and Khan, S. M. (2005). Mitochondrial microheteroplasmy and a theory of aging and age-related disease. *Rejuvenation Res.* 8, 172–198. doi: 10.1089/rej.2005.8.172
- Sofroniew, M. V., and Vinters, H. V. (2010). Astrocytes: biology and pathology. *Acta Neuropathol.* 119, 7–35. doi: 10.1007/s00401-009-0619-8
- Sohal, R. S., and Brunk, U. T. (1992). Mitochondrial production of pro-oxidants and cellular senescence. *Mutat. Res.* 275, 295–304. doi: 10.1016/0921-8734(92)90033-1
- Sohal, R. S., and Weindruch, R. (1996). Oxidative stress, caloric restriction and aging. *Science* 273, 59–63. doi: 10.1126/science.273.52.71.59
- Soldner, F., Hockemeyer, D., Beard, C., Gao, Q., Bell, G. W., Cook, E. G., et al. (2009). Parkinson's disease patient-derived induced pluripotent stem cells free of viral reprogramming factors. *Cell* 136, 964–977. doi: 10.1016/j.cell.2009.02.013
- Song, Y. J., Halliday, G. M., Holton, J. L., Lashley, T., O'Sullivan, S. S., Mccann, H., et al. (2009). Degeneration in different parkinsonian syndromes relates to astrocyte type and astrocyte protein expression. *J. Neuropathol. Exp. Neurol.* 68, 1073–1083. doi: 10.1097/NEN.0b013e3181b666f1b
- Stark, A. K., and Pakkenberg, B. (2004). Histological changes of the dopaminergic nigrostriatal system in aging. *Cell Tissue Res.* 318, 81–92. doi: 10.1007/s00441-004-0972-9
- Streit, W. J., Miller, K. R., Lopes, K. O., and Njie, E. (2008). Microglial degeneration in the aging brain—bad news for neurons? *Front. Biosci.* 13, 3423–3438. doi: 10.2741/2937
- Takahashi, K., and Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 126, 663–676. doi: 10.1016/j.cell.2006.07.024
- Toussaint, O., Dumont, P., Dierick, J. F., Pascal, T., Frippiat, C., Chainiaux, F., et al. (2000). Stress-induced premature senescence. Essence of life, evolution, stress and aging. *Ann. N Y Acad. Sci.* 908, 85–98. doi: 10.1111/j.1749-6632.2000.tb06638.x
- Valente, E. M., Abou-Sleiman, P. M., Caputo, V., Muqit, M. M., Harvey, K., Gispert, S., et al. (2004a). Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science* 304, 1158–1160. doi: 10.1126/science.1096284
- Valente, E. M., Salvi, S., Ialongo, T., Marongiu, R., Elia, A. E., Caputo, V., et al. (2004b). PINK1 mutations are associated with sporadic early-onset parkinsonism. *Ann. Neurol.* 56, 336–341. doi: 10.1002/ana.20256
- Vincow, E. S., Merrihew, G., Thomas, R. E., Shulman, N. J., Beyer, R. P., MacCoss, M. J., et al. (2013). The PINK1-Parkin pathway promotes both mitophagy and selective respiratory chain turnover in vivo. *Proc. Natl. Acad. Sci. U S A* 110, 6400–6405. doi: 10.1073/pnas.1221132110
- Wood-Kaczmar, A., Gandhi, S., Yao, Z., Abramov, A. Y., Miljan, E. A., Keen, G., et al. (2008). PINK1 is necessary for long term survival and mitochondrial function in human dopaminergic neurons. *PLoS One* 3:e2455. doi: 10.1371/journal.pone.0002455
- Yu, B. P. (1996). Aging and oxidative stress: modulation by dietary restriction. *Free Radic. Biol. Med.* 21, 651–668. doi: 10.1016/0891-5849(96)00162-1

- Zeevalk, G. D., Razmpour, R., and Bernard, L. P. (2008). Glutathione and Parkinson's disease: is this the elephant in the room? *Biomed. Pharmacother.* 62, 236–249. doi: 10.1016/j.biopha.2008.01.017
- Zhang, W., Wang, T., Pei, Z., Miller, D. S., Wu, X., Block, M. L., et al. (2005). Aggregated alpha-synuclein activates microglia: a process leading to disease progression in Parkinson's disease. *FASEB J.* 19, 533–542. doi: 10.1096/fj.04-2751com
- Zhao, M., and Janson Lang, A. M. (2009). Bromodeoxyuridine infused into the cerebral ventricle of adult mice labels nigral neurons under physiological conditions—a method to detect newborn nerve cells in regions with a low rate of neurogenesis. *J. Neurosci. Methods* 184, 327–331. doi: 10.1016/j.jneumeth.2009.08.007
- Zhao, M., Momma, S., Delfani, K., Carlen, M., Cassidy, R. M., Johansson, C. B., et al. (2003). Evidence for neurogenesis in the adult mammalian substantia nigra. *Proc. Natl. Acad. Sci. U S A* 100, 7925–7930. doi: 10.1073/pnas.1131955100

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 16 June 2014; accepted: 22 July 2014; published online: 07 August 2014.

Citation: Rodriguez M, Morales I, Rodriguez-Sabate C, Sanchez A, Castro R, Brito JM and Sabate M (2014) The degeneration and replacement of dopamine cells in Parkinson's disease: the role of aging. *Front. Neuroanat.* 8:80. doi: 10.3389/fnana.2014.00080 This article was submitted to the journal *Frontiers in Neuroanatomy*.

Copyright © 2014 Rodriguez, Morales, Rodriguez-Sabate, Sanchez, Castro, Brito and Sabate. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.