The brain on time: links between development and neurodegeneration

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SPOTLIGHT

The brain on time: links between development and neurodegeneration

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ABSTRACT

Neurodegenerative diseases are characterized by the progressive loss of structure or function of neurons. In this Spotlight, we explore the idea that genetic forms of neurodegenerative disorders might be rooted in neural development. Focusing on Alzheimer's, Parkinson's and Huntington's disease, we first provide a brief overview of the pathology for these diseases. Although neurodegenerative diseases are generally thought of as late-onset diseases, we discuss recent evidence promoting the notion that they might be considered neurodevelopmental disorders. With this view in mind, we consider the suitability of animal models for studying these diseases, highlighting human-specific features of human brain development. We conclude by proposing that one such feature, human-specific regulation of neurogenic time, might be key to understanding the etiology and pathophysiology of human neurodegenerative disease.

KEY WORDS: Brain development, Neurodegeneration, Temporal mechanisms

Introduction

Neurodegenerative diseases (NDs) are characterized by the progressive loss of structure or function of neurons. They are the second-leading cause of death worldwide and have increased considerably over the past 25 years due to ageing and growing population numbers (Feigin et al., 2019). Here, we propose that genetic forms of neurodegeneration might be rooted in neural development. We explore this idea using Alzheimer's, Parkinson's and Huntington's disease, three well-known examples of NDs that inevitably progress to severe disability and death, as examples.

Brief overview of the genetics of selected neurodegenerative disorders

Alzheimer's disease

Alzheimer's disease (AD) is the leading cause of dementia, accounting for more than 50% of cases. It is characterized by progressive memory loss followed by impairments in executive functions and behavioral disturbances. AD has three pathological hallmarks: senile plaques, neurofibrillary tangles, and hippocampal and cortical neurodegeneration (Jack et al., 2016; Long and Holtzman, 2019). AD can be divided into two forms: early-onset familial AD (fAD; also known as autosomal dominant AD) and late-onset sporadic AD. Late-onset AD is the most common form and begins to manifest after the age of 65, whereas early onset AD symptoms manifest earlier, usually between 45 and 60 years (Cacace et al., 2016). fAD represents, at most, 4-6% of AD cases (Mendez, 2017). Mutations in the amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2) are the key causes of fAD, and the apolipoprotein E4 allele (APOEε4) is a major risk factor for the sporadic form (Carmona et al., 2018). Thus, between fAD causing mutations and the APOEε4 risk factor, heritable genetic alterations clearly play a significant role in AD. APP is a transmembrane protein, the extracellular domain of which is thought to act both as a receptor of extracellular ligands, such as the Wnt family of proteins (Liu et al., 2021), netrin 1 (Lourenço et al., 2009), F-spondin (SPON1; Ho and Südhof, 2004), BRI2 (ITM2B) and BRI3 (Matsuda et al., 2005, 2009), and as a secreted signal via its own processed product, sAPPα (Gralle et al., 2009) and Aβ (Shaked et al., 2006). The APP intracellular domain is thought to act as a transcriptional regulator due to similarities to Notch intracellular domain via interaction with adaptor proteins, such as Fe65 (APBB1) and X11 (MINT; APBA1) (Tamayev et al., 2010). PSEN1 and PSEN2 are part of the enzymatic core of gamma-secretase (γ−sec), a membrane protease required for the cleavage of APP as well as many other transmembrane proteins, notably the Notch receptor, which is required for numerous aspects of normal brain development (Brunkan and Goate, 2005; Güner and Lichtenthaler, 2020). Finally, APOE is a lipid transporter that is involved in distribution of phospholipids and cholesterol throughout the body. It plays an important role in lipid metabolism and neurobiology by mediating binding of lipoproteins to specific cell-surface receptors (Huang and Mahley, 2014; Huang et al., 2004; Raulin et al., 2022).

Parkinson's disease

Parkinson's disease (PD) affects 1% of the population over 60 years of age (Tysnes and Storstein, 2017). It is characterized by two hallmarks: the progressive loss of dopamine (DA) neurons in the substantia nigra pars compacta and the presence of structures called Lewy bodies that are formed by misfolded α-synuclein (Kim et al., 2014; Savitt et al., 2006). PD symptoms include motor symptoms (resting tremor, bradykinesia and rigidity), cognitive decline and behavioral/neuropsychiatry changes (Beitz, 2014; Bloem et al., 2021). The onset of the disease is usually at an age of 65 to 70 years and, in most of the population, 3-5% of cases with PD are monogenic and linked to known PD genes. Mutations in synuclein alpha (*SNCA)* and leucine rich repeat kinase 2 (*LRRK2*) cause autosomal dominant PD, whereas mutations in parkin (*PRKN)*, PTEN-induced kinase 1 (*PINK1*) and parkinsonism associated deglycase (*PARK7*) cause the autosomal recessive form of PD (Cherian and Divya, 2020; Klein and Westenberger, 2012). It has been found that 16-36% of the heritability of PD could be explained by the ∼90 known genetic risk variants (Bloem et al., 2021) and more are continuously being discovered. SNCA is a small intracellular protein, the physiological function of which remain controversial. It has been suggested that it is involved in maintaining neuronal homeostasis by affecting release of neurotransmitters, such

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as DA and serotonin, thus participating in synaptic plasticity, autophagy and vesicle transport (Sulzer and Edwards, 2019; Villar-Piqué et al., 2016). LRRK2 is located in the cytoplasm and its biological function remains unknown, but it is thought to be involved in autophagy and mitochondrial regulation, microtubule dynamics and vesicular trafficking (Cookson, 2016; Krumova et al., 2015; Roosen and Cookson, 2016). Both *PINK1* and *PRKN*, as well as several other PD genes, are thought to play a role in homeostatic mitochondrial quality control in neurons (Lizama and Chu, 2021; Moehlman and Youle, 2020), giving rise to the mitochondrial hypothesis of the etiology of PD.

Huntington's disease

Huntington's disease (HD) is the most common monogenic neurodegenerative disease in the western world, with the prevalence of 5-12 per 100,000 in the UK (Evans et al., 2013). HD is characterized by progressive chorea, neuropsychiatric symptoms and cognitive decline (Stoker et al., 2022). HD is a polyglutamine disease caused by abnormal expansion of CAG repeats in the huntingtin (*HTT*) gene, a highly conserved gene in which the number of CAG repeats increases with phylogenetic proximity to humans. The age of onset of HD is usually between 30 and 50 years of age and correlates strongly with CAG repeat length (Kim et al., 2021). HTT is expressed ubiquitously throughout the body with particularly high levels in the brain, where it is present in both neurons and glia, and testes. *HTT* encodes a large cytosolic protein with an uncertain function, although there is good evidence for its involvement in vesicular trafficking in neurons (Saudou and Humbert, 2016; Trushina et al., 2004). Mutations in HTT (mHTT) are thought to lead to both the gain of toxic protein function and the loss of normal function, the combination of which is thought to be toxic to neurons (Bates et al., 2015; Wanker et al., 2019). Specific neurons are affected in HD, in particular those of the cortex and striatum (Stoker et al., 2022; Tartari et al., 2008).

Developmental origin of susceptibility to neurodegenerative disorders

Although the diagnosis of NDs tends to occur between 40 and 60 years of age, depending on the specific disorder, it is now widely accepted that the clinical manifestations of NDs appear decades after neuronal circuits begin to lose connectivity and cells. Similarly, the loss of connectivity manifests as an earlier failure of protective tissue and cell level mechanisms after the onset of the original imbalances at the molecular scale that occur earlier still. Therefore, a clinical diagnosis at the age of 60 could still mean that the initiating insult or onset may have been experienced in early childhood or even during embryonic development. While this is becoming increasingly acknowledged, today, there is no general conceptual or experimental framework attempting to explicitly understand whether and how brain development is linked to neurodegeneration. However, recent studies have precisely suggested such a link at the genetic and molecular levels, as we discuss below.

Developmental origins of Alzheimer's disease

There is emerging evidence that fAD genes and mutations are required for normal mammalian brain development. For example, the ventricular zone of *Psen1*$^{-/-}$ mice brains is markedly thinner by embryonic day (E)14.5, indicating an impairment in neurogenesis (Shen et al., 1997). Another report suggests that loss of mouse Psen1 causes the loss of Cajal-Retzius cells and cortical hyperplasia (Hartmann et al., 1999). Premature neurogenesis has been observed in early-onset fAD induced pluripotent stem cells (iPSCs) harboring PSEN1 mutations compared with non-isogenic controls using cortical differentiation in 2D and cerebral organoid generation in 3D (Arber et al., 2021). We have also recently shown that loss of APP in two different genetic backgrounds causes significantly accelerated human, but not mouse, cortical neurogenesis (Shabani et al., 2021 preprint). One reason for this species-specific effect of APP might be because mouse cortical neurogenesis is already too rapid to be significantly shortened further by the APP dependent mechanism we unraveled. Thus, APP may play a specific role in protracting the progenitor state of cortical radial glial cells. Consistent with this hypothesis, we did not observe acceleration of neurogenesis due to loss of APP during human motor neuron generation, a process that takes 2-3 weeks (Dady et al., 2022). However, previous studies of mouse neurogenesis suggest that APP may also have a subtle role in mouse cortical neurogenesis, although what that precise role may be is unclear (Bergmans et al., 2010; Hu et al., 2013; Ma et al., 2008; Shariati et al., 2013). The requirement for PSEN1 and PSEN2 in the activation of the Notch receptor and processing of APP itself, strongly implies that these proteins play roles in various brain development steps, from neurogenesis to neuronal migration, and axonal and dendritic arborization (Haass, 2000; Soldano and Hassan, 2014).

Developmental origins of Parkinson's disease

Clinically, rare cases of juvenile PD have been reported. For example, juvenile PD has been reported in a 16 year old with tremors and walking difficulty carrying an autosomal recessive mutation in ATPase cation transporting 13A2 (*ATP13A2*) (Anwar et al., 2019). In another case, a patient with young onset of Parkinsonism carrying a homozygous mutation (c.G859A) in *PRKN* has been reported (Magistrelli et al., 2022). The patient developed difficulty in walking at the age of nine, due to left leg 'stiffness', followed by bradykinesia and rigidity, which progressively worsened and left the patient severely disabled. Eleven other patients carrying mutations in *PRKN* with an age at onset of between 3-8 years have been listed within the same paper (Magistrelli et al., 2022). Furthermore, even in adult-onset PD, there is evidence for developmental consequences of PD mutations. For example, neuroepithelial stem cells derived from the iPSCs of a person with PD carrying the LRRK2-G2019S mutation recapitulate key mitochondrial defects shown only in differentiated dopaminergic neurons, suggesting a developmental element to this form of PD (Walter et al., 2019). The LRRK2-G2019S mutation is an autosomal-dominant genomic mutation in the *LRRK2* gene (c.6055 G>A), results in an amino acid substitution (p.G2019S) and it is the most prevalent genetic risk factor for PD (Funayama et al., 2002; Paisán-Ruíz et al., 2004). Interestingly, very recent work suggests a role for mitochondrial homeostasis in early human neurogenesis (Iwata et al., 2020, 2023). It is thus not unreasonable to speculate that PD mutations that impair mitochondrial function might also affect brain development.

Developmental origins of Huntington's disease

Juvenile HD has been reported by different studies including in seven patients manifesting symptoms between the age of 1.5 to 7 years old (Jongen et al., 1980) and 29 cases below the age 20 (Ribaï et al., 2007). Moreover, patients at ages of 8 (Choudhary et al., 2017), 13, 16 (Lesinskien et al., 2020) and 17 (Luciana de Andrade et al., 2019) have been reported. Finally, in landmark studies on HD, there are clear abnormalities in cortex development, including mislocalization of mHTT and junctional complex

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proteins, defects in neural progenitor cell polarity and differentiation, changes in mitosis and cell cycle progression (Barnat et al., 2020). This may explain why a longitudinal HD study comparing 366 individuals including control, pre-HD and early HD patients, revealed the appearance of MRI defects well before clinical manifestation (Tabrizi et al., 2009). Moreover, mouse mHTT impairs cell division of neural progenitors, neuronal migration and maturation, leading to a thinner cortex in HD mice (Godin et al., 2010; McKinstry et al., 2014; Molina-Calavita et al., 2014). Expression of either mHTT or hypomorphic HTT alone during early life is enough to induce HD features in adult mice, strongly suggesting there is a developmental component to the disease (Arteaga-Bracho et al., 2016; Molero et al., 2016). A study investigating the physiological function and evolution of the CAG tract in the *HTT* gene suggests that small variations in HTT poly-glutamine (polyQ) lengths significantly correlate with neurogenic potential of the cells and changes in the gene transcription network involved in neuronal function, where both could potentially contribute to development of a more complex nervous system (Iennaco et al., 2022). Studies on human neurons generated from the iPSCs of people with HD have shown changes in gene expression pattern, which support an altered developmental program. For example, HTT CAG length-dependent impairment of germ layer patterning has been reported in a human embryonic stem cell-derived *in vitro* model of gastrulation with a reduction in the extension of the ectodermal compartment (Galgoczi et al., 2021). In addition, mHTT changes neuronal identity in cortical populations of HD brain organoids (Conforti et al., 2018; Lim et al., 2017). Thus, a clear link is emerging between brain development and HD.

A developmental perspective of neurodegenerative disorders

When considered together, the clinical cases and mechanistic studies in mouse and human models suggest that it is highly possible that NDs have a developmental component. One way to frame this would be to suggest that ND-causing mutations lead to the development of what might be referred to as an 'at-risk normal brain' that functions normally after birth but is susceptible to the lifelong stresses both intrinsic (somatic mutations, excitotoxicity, vascular and inflammatory reactions, etc.) and extrinsic (environmental toxins, lifestyle, injury, etc.). This hypothesis considers the possibility of developmental trajectories for NDs in which mutations in specific genes (familial cases), or a genetic background with multigenic risk factors (sporadic cases), selectively renders as vulnerable to lifelong stress different subtypes of neurons and glia. Interestingly, some patients carrying risk factor genes do not develop these diseases, pointing to the protective/compensatory factors against the pathophysiological mechanism present during development. The late onset of clinical phenotypes would reflect the fact that the developmental 'heritage' of the postnatal brain was mild enough not to affect brain function for most of adult life due to the redundancy and robustness inherent to the way the brain forms and functions. In other words, it is the clinical phenotype of NDs that is ageing dependent, not the pathophysiological mechanism itself. From this perspective, NDs could be seen as late onset neurodevelopmental disorders.

Challenges in modeling neurodegenerative disorders in animal models

The proposal that NDs might be developmental disorder revolutionizes the tools (animal models) that are currently widely used in the research field. Although animal models are valuable for studying neurodevelopment and have increased our understanding of NDs, they do not fully recapitulate the human disease. One reason that animal models do not fully recapitulate ND is thought to be lifespan, particularly for late onset disease – or more accurately, late diagnosis NDs. For example, although AD is prevalent in humans, non-human-primates develop only a partial form of the disease and it rarely occurs in non-primate mammals (Nitsche et al., 2021). Therefore, it has been suggested that AD-like neurodegeneration requires a long lifespan (Sherwood et al., 2011). In addition to lifespan, animal models may not fully capture molecular and cellular pathophysiological mechanisms of neurodegeneration due to the evolution of human-specific genetic loci, such as human accelerated regions of the genome (HARs) (Doan et al., 2016). Furthermore, most animal models used in research are inbred populations that do not reflect the genetic diversity of human populations. Finally, the genomic and evolutionary differences between human and other mammals makes modeling human ND challenging. It is, therefore, reasonable to suggest that human-specific aspects of brain development play a role in human ND, which will not be possible to model in traditional animal models.

Human enriched features of brain development

Human-specific features of brain structure, surface, cellular diversity and duration of neurogenesis are under increasingly broad study (Azevedo et al., 2009; Florio and Huttner, 2014; Herculano-Houzel, 2009; Herculano-Houzel et al., 2007). Recent studies have revealed the possibility of human-specific progenitor subtypes (Kalebic et al., 2019), as well as human-specific genes associated with brain development (Florio et al., 2017; Heide et al., 2020; Suzuki et al., 2018) and HARs, which might contribute to unique features and evolution of the human brain.

Another human-specific feature of brain development is the duration of neurogenesis. Humans have a prolonged duration of neurogenesis during brain development compared with other mammals and this lengthening of the neurogenic period appears to play a key role in determining the number of neurons and glia, and thus the expansion of the neocortex (Stepien et al., 2020, 2021). Interestingly, comparing the gyrencephaly index (GI), physiological and life history data for 102 mammalian species has shown that the length of the neurogenic phase alone, rather than any novel neurogenic progenitor lineage, is sufficient to explain differences in the number of neurons and neocortical size between species within the same principal group (Lewitus et al., 2014). For example, the differentiation of neuroepithelial cells to apical radial glia (aRG) is protracted in human-derived organoids when compared with organoids derived from gorilla cells (Benito-Kwiecinski et al., 2021). Similarly, the transition from a proliferating to neurogenic state of aRG is slower in human cerebral organoids than in chimpanzee organoids, possibly because human apical progenitors have a longer S-phase that, in turn, correlates with a higher proliferative potential (Arai et al., 2011; Kornack and Rakic, 1995). We have recently shown that human APP slows the onset of the neurogenic phase during human cortical neurogenesis (Shabani et al., 2021 preprint), potentially providing a direct genetic link between human-specific temporal features of cortical development and neurodegeneration. It is important to note that current organoid models do not recapitulate the full maturation and ageing of the human brain. As such, they are excellent models for revealing and analyzing developmental deficits potentially associated with NDs, but do not account for maturation- and ageing-dependent phenotypes.

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Considerations on the link between developmental timing and neurodegeneration

Perhaps one of the most puzzling aspects of brain disorders in general, and NDs in particular, is the high degree of specificity of the initial brain regions and type of neurons affected in each ND. This is surprising because both the genetic mutations and the environmental factors do not appear to have specificity. Most, if not all, genetic forms of ND arise from mutations in genes that are ubiquitously expressed and involved in basic cell biological functions. Why mutations in *APP*, *PINK1* or *HTT* should preferentially affect cortical, dopaminergic or striatal neurons, respectively, is not entirely obvious.

Current ideas for explaining selective vulnerability of different neuronal and glial subtypes and different brain areas to NDs consider spatial and functional characteristics, such as size, firing rate and neurotransmitter subtypes, as potential sources of such vulnerability. In addition, we suggest that it may be worth exploring the notion that different temporal developmental trajectories of different neuronal subtypes make them selectively susceptible to different types of insults. It should be noted that different functional subtypes of neurons develop at different times and, at least in models such as *Drosophila* and the mouse neocortex, there is a causal link between timing of neuronal birth and functional identity. Thus, these two aspects of neuronal characteristics are not fully independent. Furthermore, it is well established that the peak of neurogenesis is different in different regions of brain. Whereas generation of DA neurons (targeted in PD) occurs between gestational week (GW)6 and GW11 (La Manno et al., 2016), cortical neurogenesis (targeted in AD) happens between GW6 and GW28, with a peak at GW18 (Polioudakis et al., 2019). Perhaps different ND genes have different temporal profiles of expression or activity, or crucial periods during which their functions are non-redundant, such that mutations in these genes lead to differential effects on neurons depending on when these neurons are generated or maturing, forming circuits or undergoing a crucial period of plasticity. These temporal profiles of brain development differ across brain areas and cell types and – we suggest – may play a role in differential vulnerabilities in NDs. The same would be true for perinatal infections, stress, poor nutrition, trauma, pesticides and metal exposure that may contribute to different diseases depending on the time of exposure. Of note, and as discussed above, these temporal differences in brain development have an evolutionary origin (Florio et al., 2018; Suzuki et al., 2018) and thus may simultaneously help explain differential phenotypes of different NDs and the particular vulnerability of the human brain to these diseases. To illustrate this idea, the brain regions that display the earliest signs of AD are the same regions that have longest maturation during childhood and adolescence (Moceri et al., 2000). For example, the association areas of the human neocortex are regions with most significant differences in gene expression between human and non-human primates (Cáceres et al., 2003, 2007). These regions underwent significant expansion during evolution and interestingly they are most early and consistently affected in AD (Arendt et al., 2017; Braak and Braak, 1991). Expansion of these regions requires a developmental deceleration and a prolonged period of high neuronal plasticity into adulthood which may make them more vulnerable to the factors that lead to the development of AD (Arendt, 2001; Somel et al., 2009). Future studies carefully analyzing whether ND mutations affect the brain's developmental timing are essential. In addition, manipulating the timing of birth and maturation of various neuronal populations under conditions of ND susceptibility are needed to confirm or reject this hypothesis.

Conclusions and future perspectives

In this Spotlight, we advance the notion that understanding the temporal mechanisms of brain development, especially from an evolutionary perspective, may be a – if not the – key to understand the etiology and pathophysiology of human ND and therefore to develop better models and eventually efficient therapies. To begin to test this idea, significant and concerted effort needs to be put into comparative analysis of the developmental effects of ND-causing genes, genomes and environmental factors in human versus non-human models of brain development.

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Competing interests

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