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REVIEW ARTICLE

Developmental neuroplasticity and the origin of neurodegenerative diseases

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Abstract

Objectives. Neurodegenerative diseases like Alzheimer's and Parkinson's Disease, marked by characteristic protein aggregations, are more and more accepted to be synaptic disorders and to arise from a combination of genetic and environmental factors. In this review we propose our concept that neuroplasticity might constitute a link between early life challenges and neurodegeneration. *Methods.* After introducing the general principles of neuroplasticity, we show how adverse environmental stimuli during development impact adult neuroplasticity and might lead to neurodegenerative processes. *Results.* There are significant overlaps between neurodevelopmental and neurodegenerative processes. Proteins that represent hallmarks of neurodegeneration are involved in plastic processes under physiological conditions. Brain regions – particularly the hippocampus – that retain life-long plastic capacities are the key targets of neurodegeneration. Neuroplasticity is highest in young age making the brain more susceptible to external influences than later in life. Impacts during critical periods have life-long consequences on neuroplasticity and structural self-organization and are known to be common risk factors for neurodegenerative diseases. *Conclusions.* Several lines of evidence support a link between developmental neuroplasticity and neurodegenerative processes later in life. A deeper insight into these processes is necessary to design strategies to mitigate or even prevent neurodegenerative pathologies.

Key words: *Neurodegenerative diseases; brain development; Alzheimer's disease; Parkinson's disease; neuroplasticity*

Introduction

Neurodegenerative diseases like Alzheimer's (AD) or Parkinson's disease (PD) produce specific protein-aggregation patterns in different types of neurons leading to characteristic pathological symptoms. While AD is characterized by extracellular aggregation of amyloid-precursor proteins leading to Aβ plaques and intracellular fibrillation of tau-protein forming tangles (Khairallah et al. 2001; Tiraboschi et al. 2004), PD involves the fibrillation of α-synuclein to form intracellular inclusions called Lewy-bodies (Lewy 1912; Koller 1992; Braak et al. 2004). However, many of the pathological mechanisms overlap: most cases of neurodegeneration are assumed to arise through interactions of genetic and environmental factors (Allam et al. 2005; Landrigan et al. 2005), with age being the most important risk factor for the sporadic incidence (Brookmeyer and Gray 2000; Muangpaisan et al. 2011; Wirdefeldt et al. 2011). Although there are specific symptoms when the illness becomes clinically manifest, neurodegenerative diseases are multisystem disorders involving pathology in several different brain areas (Braak et al. 2006; Ferrer et al. 2011).

While in PD clinical symptoms become manifest when severe changes occur in the substantia nigra, leading to dopaminergic hypoinnervation of the striatum, the pathology starts much earlier by affecting the medulla oblongata, pontine tegmentum and anterior olfactory structures (Braak et al. 2004, 2006). Many non-motor symptoms like depression, anxiety, constipation and REM sleep disturbances precede the motor symptoms and persist in the course of the disease (Harding et al. 2002; Przuntek et al. 2004; Zesiewicz et al. 2006; Ravina et al. 2007). These symptoms seem to have their anatomical and physiological correlate in axonal pathology in limbic and thalamic structures. Post-mortem analyses of PD patients' brains revealed α-synuclein aggregation in hippocampal and amygdalar structures

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accompanied by presynaptic axonal degeneration (Bertrand et al. 2003). Similar pathology was also found in thalamic nuclei assigned to limbic circuits (Rüb et al. 2002).

In AD, cognitive symptoms prevail. However, non-cognitive symptoms, i.e. behavioural and psychological symptoms, are often underestimated, although they often occur before the onset of cognitive symptoms (Rubin and Kinscherf 1989), increase with dementia severity (Petry et al. 1988; Artaso-Irigoyen et al. 2004; Frenández et al. 2010) and worsen patients' quality of life (Gonzalez-Salvador et al. 2000; Mok et al. 2004).

As pathological alterations occur long before symptoms' manifestation and as neurodegeneration is also an aspect of healthy aging (Dickson et al. 1992; Thal et al. 2004), it is still unknown when and where the disease processes really start and how long the pathobiochemical processes take to develop (Koller 1992; Lahiri et al. 2008). Moreover, the interactions of genes and environment in the development of neurodegenerative diseases are still poorly understood.

The idea that plasticity is involved in the development of neurodegenerative diseases has already been proposed by some authors, who, however, examined merely the interaction of synaptic plasticity and protein aggregation on the molecular level and at the direct onset of the disease (Arendt et al. 1998, 2001a,b, 2004; Stéphan et al. 2002; Tampellini et al. 2009; Picconi et al. 2012). In contrast, we want to take a step further and consider neuroplasticity also systemically as the link between genes and environment as well as between early life events and neurodegeneration in old age. For psychoses like schizophrenia – which is by the way often assumed to be a neurodegenerative disorder as well (review in Rund 2009; Archer 2010) – it is widely accepted that they have their origin in adverse early-life events destabilizing prefrontal-hippocampal networks and plasticity, while it is often a second challenge later in life that leads to the onset of the disorder (Dawirs and Teuchert-Noodt 2001; Cannon et al. 2003; Archer 2010).

Our group has been working for over 20 years on developmental neuroplasticity in the prefrontal-limbic system, and early-infantile induced vulnerability for psychiatric and neurological disorders. In this article we now review our concept that neurodegenerative diseases like AD and PD also have their seeds in early-life challenges that induce vulnerability for structural maladaptations and neurodegeneration later in life. To support this hypothesis we will first review the main principles of neuroplasticity before the link to neurodegenerative processes will be shown.

Neuroplasticity during development and normal aging

General principles of neuroplasticity

Neuronal connections are – even in adulthood – not fixed and invariable. They can change in response to intrinsic and extrinsic stimulation. This plasticity enables the brain to compensate for injury and disease and to adapt to new situations in the environment, i.e. to learning processes and memory formation. Hence, it is the prerequisite for a lifelong adaptive structural development (Wolff and Wagner 1983; Wolff et al. 1989). It connects structure to function or – in other words – genetically determined hardware to environmental requirements.

Neuroplasticity involves several levels. Functional plasticity on the level of the synapse involves changes in the quantity of transmitter release or receptor densities. Structural changes lead to an enlargement or reduction of the synaptic contact area, the remodelling of whole synapses or even the retraction or extension of spines, branches, dendrites or axons. Last but not least, lifelong neurogenesis and synaptogenesis in the hippocampal dentate gyrus constitute the most extraordinary forms of neuroplasticity.

In the face of these plastic challenges, neural circuits, nevertheless, must maintain stable function and a balance between excitatory and inhibitory activities. Destabilizing plasticity is, hence, counterbalanced by homeostatic plasticity mechanisms (Turrigiano and Nelson 2000; Turrigiano 2012). The alternation of destabilizing and stabilizing plastic events is like an upwards rotating helix: a specific neuronal state is held only transiently before the next level is reached, leading to lifelong self-organization and self-optimization of neuronal networks, synaptic and transmitter function (Wolff and Wagner 1983; Birkmayer and Riederer 1986; Wolff et al. 1989; Teuchert-Noodt 2000; Arendt 2001a)

All these structural conformations depend both on synthesis and degradation of proteins and cell organelles. Hence, processes like proteolysis and protein clearance as well as lysosomatic processes of organelle and membrane turnover are not only hallmarks of degenerative processes but also of natural occurring neuroplasticity (Bingol and Sheng 2011).

Neuroplasticity during development

Structural plasticity is highest early in life. One year after birth, the child brain contains twice as many synapses as the adult one. This overproduction is followed by a phase of synapse elimination, while different brain regions with different functions develop on different time courses (Huttenlocher

1979; Huttenlocher and Dabholkar 1997). These time courses are guided by maturing neurotransmitter systems, receptor fields, hormones and other trophic factors (Wolff 1981; Seeman et al. 1987; Andersen 2003; Ruediger and Bolz 2007) that challenge the networks and enforce reorganization.

For example, it has recently been shown by live imaging that GABA regulates the activity-dependent inhibitory synapse formation by co-ordinately eliminating certain nascent synaptic contacts and promoting the maturation of others (Wu et al. 2012). As demonstrated in rodents, the GABAergic innervation pattern reaches mature levels very early in life and remains at a rather constant level in adulthood (Brummelte et al. 2007). In contrast, fibre systems of the modulating transmitter dopamine show a prolonged maturation in rodents (Kalsbeek et al. 1988; Dawirs et al. 1993) as well in primates (Goldman-Rakic and Brown 1982; Lidow and Rakic 1992), rendering dopamine especially interesting for neuroplastic processes. Moreover, dopaminergic fibres are – in contrast to serotonin or norepinephrine – confined to specific pathways that link brainstem, striatum, limbic system and prefrontal cortex. The maturation of dopaminergic fibre systems proceeds from caudal to rostral fields. There is first an excess of dopamine in motoric and limbic areas which is later reduced in favour of a higher dopaminergic innervation of the prefrontal cortex (Dawirs et al. 1993; Busche et al. 2004; Brummelte and Teuchert-Noodt 2006, 2007). Full maturation of the prefrontal cortex is not reached until young adulthood (Kalsbeek et al. 1988; Witte et al. 2007a) and not till then a balance between the plastic events on the levels of the brainstem, striatum, limbic system and cortex is reached. The different maturation phases of the specific brain regions lead to critical periods, in which the respective regions are especially susceptible to external influences. Appropriate influences and stimuli during these periods are necessary for normal maturation, while inappropriate ones can cause abnormal development (Hubel and Wiesel 1970; Wolff and Missler 1992; review in Michel and Tyler 2005; Thomas and Johnson 2008).

Last but not least, also the production of new neurons in the hippocampus – one of the most important brain regions for learning and memory consolidation – is highest early in life with a hyperbolic decline to adulthood and aging (Dawirs et al. 2000; Bizon and Gallagher 2003). Neurogenesis is not only itself a form of structural plasticity, but also induces further structural adaptation processes, as the newborn neurons demand integration (Lehmann et al. 2005; Leuner and Gould 2010; Mongiat and Schinder 2011). This corresponds to the finding of highest synaptic turnover rates in the dentate gyrus in the first quarter of life (Dawirs et al. 2000).

Neuroplasticity in adulthood and during normal aging

Although there is a considerable decline in hippocampal neurogenesis during adulthood and aging, it still can be detected in old age in rodents as well as in humans (Eriksson et al. 1998; Cameron and Kay 1999; Dawirs et al. 2000; Bizon and Gallagher 2003). Hence, within the hippocampal system, there still remains a store of high structural plasticity even in adulthood. In contrast, the cortex contains high dynamics only until neurotransmitter maturation is completed in young adulthood. Then, a balance of activities is reached and plastic reconstruction only takes place slowly (Grutzendler et al. 2002; Trachtenberg et al. 2002; Neufeld et al. 2009). This is in favour of a higher stability of shaped networks and a stable treasure trove of experience.

Also during normal and physiological aging, plastic processes in hippocampal and cortical circuits continue to decline (Dawirs et al. 2000; Hof and Morrison 2004). The number of synapses decreases and the morphology of synaptic contacts changes (Hof and Morrison et al. 2004; Morrison and Baxter 2012). Lastly, recent studies showed a reduction in synthesis, receptor densities and binding sites of several neurotransmitters including dopamine, serotonin, GABA and glutamate (Seeman et al. 1987; Miettinen et al. 1993; Bu et al. 2003; Kaiser et al. 2005; Ota et al. 2006; Brummelte and Teuchert-Noodt 2007; Hof and Mobbs 2009).

Neuroplasticity – chance and risk for the brain

Neuroplasticity enables the brain to become wired in response to the needs of the environment. Changes in neurotransmitter levels induce critical periods of development in selective brain regions. During these periods the respective brain regions are especially susceptible to extrinsic stimulation. This high susceptibility is at the same time a chance and a risk, because neuroplastic processes are not only induced by beneficial stimuli but also by harmful ones like traumata, drugs and environmental toxins. Insults during these sensitive periods have a significantly greater impact on the brain than the same event later in life (Purves et al. 1988).

While the immature brain adapts by incorporating environmental information permanently into existing networks, the mature one tries to compensate changes in the environment (Andersen 2003). During juvenile development the whole brain is highly susceptible and at the same time vulnerable to external influences with life-long consequences on

structure and function. In contrast, in adulthood, detrimental impacts may primarily affect the brain via the still highly plastic hippocampal system, as dentate neurogenesis and synaptogenesis are still extremely susceptible to pharmacological (Dawirs et al. 1998; Teuchert-Noodt 2000; Malberg and Schechter 2005) and environmental perturbations (van Praag et al. 1999; Mirescu and Gould 2006; Iso et al. 2007). The hippocampus constitutes a bottleneck, in which a huge amount of information converges, and whose output reaches widespread regions of the nervous system (Amaral and Witter 1995; Insausti et al. 1997; Amaral and Lavanex 2006). Thus, it is conceivable that plastic maladaptations in this bottleneck induced by detrimental impacts early in life produce a vulnerability for additional challenges in adulthood and that pathological processes could be spread from there over various regions of the brain.

Drugs and psychotropics. Exposure to drugs or psychotropics early in life has long-lasting consequences on brain maturation and function. Even a single exposure to psychostimulants like methamphetamine (also known as ecstasy/XTC) early in life disturbs the maturation of dopaminergic and serotoninergic innervation of the prefrontal cortex (Teuchert-Noodt and Dawirs 1991; Dawirs et al. 1994; Neddens et al. 2003) with consequences on the maturation of prefrontal pyramids (Blaesing et al. 2001; Bagorda et al. 2006) and interneurons (Brummelte et al. 2007). The same exposure later in life has minor impact on dopaminergic fibre densities (Brummelte et al. 2006) and behaviour (Good and Radcliffe 2011).

In contrast, numerous antipsychotic drugs like haloperidol or risperidone (Dawirs et al. 1998; Hildebrandt et al. 1999; Keilhoff et al. 2010) as well as antidepressants impact the regulation of hippocampal neurogenesis and plasticity even acutely in adulthood. Thereby, the effect depends on gender and on age (Malberg et al. 2000; Hodes et al. 2009, 2010). Moreover, we could demonstrate that the decrease of newborn cells in the hippocampal dentate gyrus in response to methamphetamine administration as well as the increase after haloperidol administration (Dawirs et al. 1998; Hildebrandt et al. 1999; Teuchert-Noodt et al. 2000) are accompanied by severe alterations in synaptic plasticity as well (Butz et al. 2008) demonstrating the far-reaching and long-term effects of these pharmacological interventions (cf. Table I).

Metals and environmental toxins. Environmental toxins, especially heavy metals, impact neuroplastic processes. Chronic lead exposure during development leads to reduced rates of neurogenesis in adulthood (Gilbert et al. 2005; Verina et al. 2007). Developmental exposure to manganese chloride induces sustained aberration of adult neurogenesis (Wang et al. 2012). Mercury exposure during brain maturation causes acute cell death and reduction in neurogenesis (Falluel-Morel et al. 2007). These findings demonstrate that developmental exposure to these metals does not only have acute effects but impacts the regulation of hippocampal neurogenesis and plasticity for life.

In contrast, essential trace elements exist that are pivotal for plastic processes. Iron deficiency in early development reduces neurotrophic factors and impacts neuroplastic processes (Tran et al. 2008, 2012). The same holds true for zinc which has a key role in the control of developmental and adult neurogenesis (Suh et al. 2009; Levenson and Morris 2011).

The environment and adverse life events. Drugs and toxins constitute inappropriate stimuli for brain maturation. Normal brain development, however, depends not only on the absence of insults but also on an appropriate stimulation during the respective critical periods (Andersen 2003). Hence, it depends on an environment that is rich in physical structure and populated with conspecifics. Deprivation of such an environment has detrimental consequences for animals as well as for humans.

Rearing rodents (*Meriones unguiculatus*) under deprivation of natural environmental stimulation causes deficits in the dopaminergic innervation of the prefrontal cortex (Winterfeld et al. 1998; Neddens et al. 2001) as well as in the GABAergic network (Brummelte et al. 2007). This leads to an aberrant maturation of prefrontal efferences to ipsi- and contralateral parietal and limbic areas (Bagorda et al. 2006; Witte et al. 2007b) as well as behavioural abnormalities (Winterfeld et al. 1998). In contrast to the hypoinnervation of the prefrontal cortex, dopaminergic, cholinergic and serotoninergic innervation of subcortical and limbic structures is enhanced (Busche et al. 2002, 2004, 2006).

These imbalances impact the regulation of neurogenesis in the hippocampal dentate gyrus. In *Meriones unguiculatus*, cell proliferation rates are chronically enhanced after isolated and deprived rearing (Keller et al. 2000), while synaptic turnover rates are reduced (Dawirs et al. 2000), indicating that hippocampal capacities depend on a balance between new neurons and their synaptic integration (Butz et al. 2008; Epp and Galea 2009).

Another recent study in mice confirmed that deprivation of appropriate environmental stimulation during development not only leads to short-term consequences on neural plasticity but alters the responsiveness of cell proliferation and synaptic remodelling rates to external stimulation even in

Table I. Overview of interventions in child- and adulthood that have been shown to have chronic effects on neurophysiology, -anatomy and -plasticity.

Intervention		
In childhood	In adulthood	Effects in adulthood
Drugs and psychotropics		
Methamphetamine (gerbils)	Dopaminergic fibres in PFC ⇩	Teuchert-Noodt and Dawirs, 1991; Dawirs et al. 1994
	Serotoninergic fibres in PFC ⇧	Neddens et al. 2003
	GABAergic fibres ⇧/GABAergic boutons ⇩ in PFC	Brummelte et al. 2007
	Branching and spine densities of PFC pyramids ⇧	Blaesing et al. 2001
	Miswiring of PFC efferences	Bagorda et al. 2006
Metamphetamine (gerbils)	Dendritic spines of PFC pyramids ⇩	Dawirs et al. 1991
	Dopamine in PFC and limbic areas ⇔	Brummelte et al. 2006
Haloperidol (gerbils, rats)	Neurogenesis ⇧	Dawirs et al. 1998; Hildebrandt et al. 1999; Keilhoff et al. 2010
Risperidone (rats)	Neurogenesis ⇧	Keilhoff et al. 2010
Metals and environmental toxins		
Chronic lead (rats)	Neurogenesis ⇩	Gilbert et al. 2005; Verina et al. 2007
	Mossy fibre density ⇩	Verina et al. 2007
Chronic manganese (mice)	Neurogenesis ⇩	Wang et al. 2012
Mercury (rats)	Cell death with lifelong consequences on hippocampus	Falluel-Morel et al. 2007
Iron deficiency (rats)	Neurotrophic factors ⇩	Tran et al. 2008, 2012
	Neurogenesis ⇩	
Zinc deficiency (mice, rats)	Neurogenesis ⇩	Suh et al. 2009; rev. in Levenson and Morris 2011
Environment and adverse life events		
Rearing under deprivation (gerbils, mice)	Dopamine in PFC ⇩	Winterfeld et al. 1998; Neddens et al. 2001
	GABAergic boutons in PFC ⇩	Brummelte et al. 2007
	Miswiring of PFC efferences	Bagorda et al. 2006; Witte et al. 2007b
	Serotonin in hippocampus ⇧	Busche et al. 2002
	Dopamine in amygdala, EC ⇧	Busche et al. 2004
	Acetylcholine in hippocampus ⇧	Busche et al. 2006
	Hippocampal cell proliferation in gerbils ⇧	Keller et al. 2000
	Synaptic remodeling ⇩	Dawirs et al. 2000
	Responsiveness of cell proliferation and Synaptic rewiring to additional stimuli ⇧	Schaefers et al. 2010; Schaefers 2012
High levels of pup licking and grooming (rats)	NMDAR, BDNF, synaptogenesis in hippocampus ⇧	Liu et al. 2000
	GABA receptors in PFC, hippocampus, amygdala ⇧	Caldji et al. 2003
	PFC dependent cognitive abilities ⇩, exaggerated synaptic plasticity	Baudin et al. 2012
	Altered dendritic morphology in PFC, hippocampus, NAcc	Monroy et al. 2010
Childhood adversities in humans		
Social deprivation and misfortune	Risk of physical illness and psychiatric disorders ⇧	Patterson et al. 1992; Bidzan 2006
Adversities and maltreatment	Morning cortisol levels ⇩	Power et al. 2012
• pre-/postnatally and during ages 6–11	Cortisol response ⇧	Bosch et al. 2012
• during ages 12–15	Cortisol response ⇩	
	Telemore length ⇩	Kananen et al. 2010
	Gray matter volumes in hippocampus, insula, orbitofrontal cortex, anterior cingulate gyrus, and caudate ⇩	Teicher et al. 2012; Dannlowski et al. 2012

PFC, prefrontal cortex; EC, entorhinal cortex; NAcc, nucleus accumbens; NMDAR, *N*-methyl-D-aspartate receptors; BDNF, brain-derived neurotrophic factor.

adulthood (Schaefers et al. 2010; Schaefers 2012). These findings emphasize the significance of early-life impacts making the brain vulnerable to maladaptive responses to additional challenges in adulthood.

Similar results were shown for maternal nursing. Maternal care influences hippocampal synaptogenesis (Liu et al. 2000) and GABA receptor expression (Caldji et al. 2003), prefrontal synaptic plasticity (Baudin et al. 2012) and dendritic branching (Monroy et al. 2010). Moreover, maternal care is essential for cognitive development (Liu et al. 2000; Niwa et al. 2011; Baudin et al. 2012).

That adverse life events exert most detrimental effects in childhood has also been demonstrated in humans. Social deprivation and misfortune in young age increase the risk of physical illness and psychiatric disorders in adulthood (Patterson et al. 1992; Bidzan 2006). Furthermore, childhood adversities cause chemical and structural changes in adult age, like altered levels of cortisol (Power et al. 2012; Bosch et al. 2012), shorter telomere length (Kananen et al. 2010) and reduced gray matter volumes in several prefrontal-limbic areas including the hippocampus and the orbitofrontal cortex (Teicher et al. 2012; Dannlowski et al. 2012). It is feasible that these alterations predispose the brain to develop neurodegeneration after a potential second challenge in adulthood (cf. Table I).

Neuroplasticity and neurodegenerative diseases

The role of neuroplasticity in the development and course of neurodegenerative diseases like AD and PD is often underestimated. However, the hallmarks of these diseases like β-amyloid and neurofibrillary tangles in AD or α-synuclein aggregation in PD are tightly linked to neuroplasticity.

β-*Amyloid, neurofibrillary tangles and neuroplasticity*

The hallmarks of AD are extracellular aggregation of amyloid-precursor protein leading to β-amyloid plaques and intracellular fibrillation of tau-protein forming neurofibrillary tangles (Tiraboschi et al. 2004; Khairallah et al. 2011).

However, both the amyloid-precursor protein (APP) and β-amyloid play pivotal roles in normal functioning. Endogenous β-amyloid has been demonstrated to be necessary for hippocampal synaptic plasticity and memory (Puzzo et al. 2011). Moreover, APP as well as components of the APP-processing pathway are involved in synaptic transmission and plasticity (Turner et al. 2003; Gralle and Ferreira 2007; Randall et al. 2010). Thereby, it mainly interacts with glutamate (Lesné et al. 2005) – especially glutamatergic NMDA receptors (Hoe et al. 2009) – and acetylcholine receptors (review in Parri and Dineley 2010), those neurotransmitters which are also the key targets of β-amyloid pathology. In turn, synaptic activity increases APP (Stéphan et al. 2002; Kamenetz et al. 2003) and extracellular β-amyloid, while it reduces intraneuronal β-amyloid and protects against β-amyloid-related synaptic alterations (Tampellini et al. 2009). Thereby, β-amyloid deposition occurs preferentially in multimodal brain regions like the hippocampus which show continuous levels of heightened activation and plasticity across the lifespan (Jagust and Mormino 2011).

Also the distribution of neurofibrillary tangles matches the pattern of neurons that retain their capacity of plastic remodelling in adulthood, namely those involved in higher brain functions like the regulation of memory, learning, perception, self-awareness and consciousness (Arendt 2004). Arendt et al. (1998) demonstrated that regional differences in the changes in dendritic length and arborization follow the same pattern as the regional densities in tangle formation. These results indicate that a high degree of structural neuronal plasticity might even predispose neurons to tangle formation (Arendt et al. 1998).

In the developing brain, phosphorylation of microtubule-associated protein tau is a physiological way of destabilizing axons and promoting synaptic plasticity. Hence, newborn infants show extremely high levels of phosphorylated tau (Mattsson et al. 2010). Recent studies with a hibernation model demonstrated that the repeated formation and degradation of phosphorylated tau represents a physiological mechanism necessary for structural neuroplasticity (Arendt et al. 2003; Arendt 2004; Stieler et al. 2011). These findings spotlight the hippocampus with its life-long neuroplastic capacity to be crucial in the onset of the pathological process cascade of AD.

Last but not least, both nicotinic and muscarinic acetylcholine receptors are involved in tau phosphorylation either in a direct way or through the interaction with β-amyloid (Rubio et al. 2006).

α-*Synuclein and neuroplasticity*

The fibrillation of α-synuclein forming intracellular inclusions called Lewy bodies is implicated in several neurodegenerative diseases like AD, PD and dementia with Lewy bodies, collectively known as synucleinopathies (Braak et al. 2004; Cheng et al. 2011).

However, α-synuclein is a ubiquitously expressed protein, which is enriched in the presynaptic terminals of almost all types of neurons in the central nervous system (Bellani et al. 2010). Several studies document its pivotal role in neurotransmitter synthesis and release, synaptic efficiency, function and plasticity (Di Rosa et al. 2003; Uversky 2008; Bellani et al. 2010; Cheng et al. 2011). This applies especially to dopamine: α-synuclein is involved in dopamine synthesis, storage, release and uptake (Yu et al. 2005; Al-Wandi et al. 2010) and, in turn, dopamine promotes the formation and secretion of α-synuclein (Leong et al. 2009; Lee et al. 2011). This interaction may account for the specific vulnerability of the dopaminergic system to α-synuclein fibrillation (Lee et al. 2011) leading to severe functional motor deficits. However, α-synuclein is also involved in glutamate release in the hippocampus (Gureviciene et al. 2007) and in structural plasticity and learning, as it is responsible for localized experience-dependent turnover of synaptic membranes ("synaptic tagging"), that provides a basis for learning and memory formation (Clayton and George 1998, 1999; Ma et al. 2003). Moreover, it also interferes with adult hippocampal neurogenesis (Desplats et al. 2012). These findings of the role of α-synuclein in health and disease led to the recent published hypothesis of PD as a disorder of synaptic dysfunction (Bagetta et al. 2010; Picconi et al. 2012). Nevertheless, to date, it remains still unclear where the pathological processes start to develop and why α-synuclein is deposited. The role of α-synuclein in functional and structural plasticity, learning and memory, however, suggests that similar mechanisms might apply for α-synuclein-fibrillation as for β-amyloid and tau deposition and that pathological mechanisms of neurodegeneration in PD and AD might be more similar than widely supposed.

The link between neurodevelopmental processes and neurodegenerative diseases

Taking the aforementioned findings into consideration, there are several lines of evidence for the hypothesis that neuroplasticity not only interferes with pathological protein-processing cascades during neurodegenerative processes, but even constitutes the link between early-life events and late-life pathology manifestation.

First, AD and PD are synaptic disorders, as they are associated with aberrant synaptic function and plasticity (Arendt 2001a,b; Scheff 2003; Bagetta et al. 2010; Picconi et al. 2012).

Secondly, there are significant overlaps between neurodevelopmental processes and the development of neurodegenerative diseases. The distribution of the AD pathology matches the pattern of brain regions that take the longest to mature during childhood and adolescence (Moceri et al. 2000) and retain their plastic capacities in adulthood (Arendt et al. 1998), namely the hippocampal formation and specific laminae in associative prefrontal and limbic cortices (Neufeld et al. 2009).

In a way, this holds also true for PD. Meanwhile, it is commonly accepted that PD is not only a disease of the substantia nigra and the nigrostriatal dopamine pathway, but a multisystem neurodegenerative disorder involving several non-motor symptoms (Jellinger 2011, 2012). Staging procedures demonstrated that the Lewy pathology does not primarily start in the substantia nigra, but much earlier in the medulla oblongata and pontine tegmentum (Braak et al. 2006), from where serotoninergic pathways modulate dopamine release to the striatum, limbic system and prefrontal cortex (Alex et al. 2005; Di Matteo et al. 2008). In the course of the disease, the synucleinopathy also spreads to limbic areas like the hippocampus and amygdala, the thalamus and, lastly, also to the neocortex (Rüb et al. 2002; Bertrand et al. 2003; Braak et al. 2006). Recently, the connection of hippocampal pathology with dementive and depressive symptoms of PD could be clinically demonstrated by diffusion tensor imaging analysis (Carlesimo et al. 2012). Hence, in PD as in AD, the development of protein aggregation and neurodegeneration follows the same pattern as neuroplasticity during brain development, namely from caudal to rostral areas (Nelson 2005; Arendt 2001a). Moreover, the lateralisation of PD with the early onset of degeneration in one hemsiphere (review in Riederer and Sian-Hülsmann 2012) – corresponding to findings that hippocampal neurogenesis and synaptogenesis also respond asymmetrically to pharmacological interventions (Dawirs et al. 1998; Teuchert-Noodt et al. 2000) – also points to a developmental and systemic causality.

Taking our own findings into consideration, it is likely that the disturbed hippocampal neuroplasticity – impacted by early life challenges – is of great importance for a second insult leading to the final pathological process cascade.

Lastly, the same insults that impact neuroplastic processes constitute the main risk factors for developing neurodegeneration. The sporadic nature of most cases of neurodegenerative disorders, the late onset, the different susceptibility to and course of neurodegeneration suggest that genetic as well as epigenetic and environmental influences play a role in the development and course of the diseases. Indeed, it has been shown that a low cognitive and physical engagement has a significant correlation with the risk of developing AD or PD (Friedland

et al. 2001; Wilson et al. 2002; Chen et al. 2005; Xu et al. 2010). Moreover, in the last years evidence has accumulated that even early-life events and insults may contribute to the diseases' onset including perinatal infections (Miller and O'Callaghan 2008; review in Logroscino 2005), poorly structured environment and social isolation (Moceri et al. 2000; Borenstein et al. 2006; Herring et al. 2011), stress (Miller and O'Callaghan 2008), poor nutrition (Miller and O'Callaghan 2008), traumata (Campdelacreu 2012; review in Logroscino 2005), pesticides (Uversky et al. 2001a; Landrigan et al. 2005; Campdelacreu 2012) and metal exposure (Uversky et al. 2001b; Landrigan et al. 2005; Lahiri et al. 2008; Sian-Hülsmann et al. 2011; Campdelacreu 2012). Although neurodegenerative diseases have characteristic pathological patterns, there is an obvious overlap of early-life risk factors. Moreover, as shown before, all these risk factors are life events that interfere with the neuroplastic development in childhood and adolescence. They place an additional burden on the plastic capacity of the developing neuronal system and may lead to the disturbance of structural brain self-organization (Arendt 2001a). It is feasible that a second challenge later in life, then, leads to the final onset of neurodegeneration and even might be decisive as to whether the one or the other disorder becomes manifest. Neuroplasticity in the developing nervous system is more susceptible to insults than the adult brain (Andersen 2003; Giordano and Costa 2012), but it is the hippocampal neuroplasticity that ensures life-long adaptation and learning capacities on one hand, while it causes life-long vulnerability on the other hand.

Conclusion

The delicate balance between destabilization and homeostatic stabilization during critical and sensitive periods of development is highly susceptible to external influences as well as external perturbations. Insults imprint on the final adult structure and affect neuroplasticity and structural self-organization, but may induce pathological symptoms not before dynamics of neuroplasticity decline in higher ages.

It is a hallmark of neurodegenerative diseases like AD and PD that the pathological processes start much earlier than the symptoms become manifest. Moreover, they are strongly linked to neuroplasticity especially in the hippocampal system which constitutes a bottleneck for incoming influences as well as insults. Deprivation of natural external stimulation as well as perturbations that influence neuroplasticity during early development are also known as common risk factors for the development of neurodegenerative diseases like AD and PD. A second challenge in adulthood might impact the brain most potently via the hippocampal system that retains life-long plastic capacities, and might not be able to be compensated in a predisposed brain.

A deeper understanding of the link between developmental neuroplasticity and neurodegeneration later in life will help to design strategies to mitigate or prevent pathological outcomes of adverse life events.

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Statement of Interest

The authors declare no competing interests.

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