Paleoneurology: Neurodegenerative diseases are age-related diseases of specific brain regions recently developed by homo sapiens

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Understanding of the genetic mechanisms underlying the evolution of these recent human brain regions and paleoneurology may be the key to the focal, asymmetrical or systemic character of neurodegeneration, the pathologic heterogeneity/overlap of syndromic presentations associating gait, hand, language, cognition, mood and behaviour disorders.

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Introduction/background

Clinical presentations of functional deficits in neurodegenerative diseases, that may be focal, asymmetrical or lumped into multisystem atrophies along functional networks is puzzling to both the clinician and the neuroscientist. Age-relation seems to be the major risk factor, but the "functional dissection" that prevails in these diseases may rely on another logic, that may look for a reappraisal from a darwinian perspective.

Rapoport [1–3] was the first to think of Alzheimer’s disease as a phyllogenic disease, using the concept of phyllogenic regression [4–8], that compares brain aging involution to the reversed phenomenon of darwininan evolution. Recently, Seeley et al. [9] reported that early frontotemporal dementia targets von Economo neurons unique to apes and humans. Gene action, changes in signal transduction pathways and many other changes are known to occur in the aging brain [10]. They may explain the premature aging of phylogenetically recent cortical areas [11], more prone to apoptosis [12], mutations [13] or loss of differentiation [14], because of more plasticity due to more rapid evolution and wider connections as secondary or integrative cortical areas, and may be to other mechanisms that start in the embryo. Paleoneurology [15–20] may then be the new way of thinking dementia and neurodegenerative disorders in general.

The aim of this paper is to re-understand neurodegenerative diseases as specific entities to homo sapiens, to re-evaluate clinical presentations from a darwininan perspective, and to ask neuroscience to understand their underlying mechanisms at the level of those 20,000 genes, transcriptional factors, non expressed DNA and proteomes that differentiate homo sapiens from his nearest living cousin, sharing 99% of his genome, the chimpanzee [21].

The hypothesis/theory

A. Development of the human brain

In the 5 millions of years of evolution of hominoids through the Miocene, Pliocene and Pleistocene, prehuman primates operated a cladic separation from the chimpanzee–bonobo branch (panides) that ended up in the present homo sapiens sapiens. In the 3 billion base-pair of the human genome, only 1% differed from the chimpanzee [20]; however, changes in brain anatomy and consecutive new cognitive capacities, perception and regulation of self and adaptation environment are much more significant [22,23].

Bipedal locomotion and posture, or bipedalism [24–27] seems to start with samburupithecus sahelanthropus. Derived from tree climbing and/or knuckle-walking, it was acquired by oreopithecus babolii, some 8 millions of year ago, but forgotten until it recovered and became the main locomotor pattern for Sahelanthropus tchadensis (Tumai), 7 millions of years ago. It became the exclusive mode of locomotion and reached motor maturity withrrorin tugunensis 5–6 millions of years ago, probably imposed by changes in climate and new energetic needs induced by the Ethiopian rift [28–36]. Prehumans had to quit their trees and change habits in order to survive. The acquisition of full skills in bipedal locomotion induced major changes in both the locomotor apparatus and brain, which ended up in an increase in volume of the latter due to new cortical areas and increased interconnections [37]. From homo abilis (550–690 cm$^3$) about 2 billions of year ago, the brain volume increased in the 3–4 branches in evolution, homo georgicus (700–800 cm$^3$), homo florensis (only 380 cm$^3$) and homo neandertalis (1750 cm$^3$) (all disappeared). Finally homo ergaster-erectus evolved into the present homo sapiens sapiens (1350–2650 cm$^3$) with gracious bipedal walk, fine hand manipulation, new cognitive functions, self perception, new social rules and better capacities to adapt to a complex environment [38], allowing him to conquer the planet and domesticate the environment.

In order to improve bipedal standing and locomotion, anatomical modifications occurred at the mechanical level in the pelvis [39], hip (femoral neck angle and adduction), knee, ankle joint, arms and feet [40,41]. Displacement of the occipital hole [25] and shortening of the arms with lengthening of legs and lumbar lordosis [40,41] also improved bipedal posture. New cortical areas
appeared in medial and lateral prefrontal cortex, basal ganglia, parietal lobe, brainstem, cerebellum and spinal cord locomotor centers [42–50], in order to adapt and coordinate the new bipedal posture and stabilize it during locomotion in a complex environment. Old pace-makers and automatisms of the spinal cord and reticular formation that regulated quadrupod locomotion were modified and controlled by new medial and lateral prefrontal cortical areas, with changes and evolution of the function of locomotor centers of brainstem pons, medulla, mesencephalon, diencephalon and cerebellum [for a review see [43]]. This allowed executive context-modulation of bipedal gait, upgrading of the vestibular, proprioceptive, visual and cerebellar functions to new locomotor patterns [45–50]. A bimodal new control of substantia nigra/ventral tegmental area and subthalamic nucleus on speed of automatic procedures of gait, fine motility of hand, larynx, vertical bipedal gaze orientation and motivation to cognition also developed, the anterior striatum increased in volume [51–52]. New reticular formation nuclei for righting reactions (standing, sitting, lying) also appeared in the pons and medulla [43]. Oculomotor supranuclear control also adapted to upright posture, especially vertical gaze and eyelid synkinesias in the upper brainstem and basal ganglia [52]. Changes in autonomic control for upright bipedal posture and new environmental demands also occurred, with development of insular, diencephalic and brainstem centers of regulation of autonomic peripheral nervous system [53–54].

The hand acquired fine fractionated movements of the fingers, pinch grip from thumb abduction, precision grasp and manipulation [55–60] processed by the development of the pyramidal tract, modulated by nigrostriatal connections for speed of movement. Ventroegumento-limbic dopaminergic system [51] allowed connection of emotion to motor control (motivation). Secondary sensori-motor cortical areas [61,62] developed, together with pontine nuclei, in order to assist the new fine motility patterns of hand and larynx and interconnected them to all other new cortical areas, linking manipulation of objects to new conceptual forming areas for tool manufacture [63–66], drawing, writing, gestural and verbal communication and creativity [67] and to emotion, giving way to music, poetry, painting, i.e. and art and culture [67–68].

Facial changes [69] with reduction of face projection [70], angulation of the mandible [71], caudal displacement of the larynx and hyoid bone [72], and increased thickness of enamel allowed fine modulation of laryngeal sounds [73] to better communicate within the group. The fine facial muscles become innervated by new cranial nerve efferent, corticobulbar tracts and brainstem motoneurones pathway [74–79], for fine tuning of speech, singing, whistling (Sherwood et al. [80]), helped by the speech automatic speed processing of basal ganglia and substantia nigra. Finally language, processed by the new perisylvian anterior praxic/expressive (frontoinsular) and posterior receptive (temporal) cortical areas [16,80–95] developed from fine laryngeal motility, with hemispheric dominance [96–108]. In the brainstem, new pathways for facial social emotional expression (laughing and crying, singing, vocal and facial prosody, subtle mimics...) also developed together with more facial muscles to express them [75,78,79]. Fine motility of hand and larynx were also connected with new posterior cortical and temporal areas, allowing coordination of eye, hand and vision to cognition [109–113]. New secondary associative areas appeared in the prefrontal cortex, parietal angular gyrus and planum temporal that allowed writing, reading, calculation (from parietal digit knowledge), musical and rhythmic cognition [101–108].

Working memory allowed cognition by on-line synthesis of multiple processing [114–115]. New thalamic nuclei supplied the new cortical areas [116]. In order to improve from the old implicit/procedural memory function, heavily relying on errors for learning, archives of the past events could be translated into language (explicit) and abstract concepts (knowledge, semantic), in order to be re-used in the future. This allowed better prediction and survival in a complex environment, social interactions and translation of experience to further generations. Explicit episodic and semantic storage and retrieval developed from an enlargement in hippocampal, parahippocampal and entorhinal cortices [117–121] and expansion of the lateral temporal lobes. Some increase in anterior and laterodorsalis limbic thalamus and medial mammillary body occurred. In the hippocampus, CA1 pyramidal cells spread over the whole stratum oriens, reaching the alveus and entorhinal cortex which underwent structural enlargement and differentiation [122–129]. The limbic lobe remained otherwise largely preserved [125–129], except that the olfactory lobe lost his prominent role [124] and some changes also occurred in the amygdala [125–128] with interactions with hippocampal explicit memory structures, allowing association of explicit to affective memory, i.e. the detection of relevance of memories by the amygdala and insular cortex [128], classification of positive and negative experiences. Oral transmission, culture, anticipa-
tion and intergenerational transfer were possible [129–130].

Visuospatial posterior temporal and posterior parietal cortices also expanded widely [131–135], establishing connections with the new somatosensory cortical areas, processing the where and what [135] in respectively parietal and temporal cortices. From the 20–25 visual cortical areas of the monkeys, it evolved to an estimated 200 in humans, associated with changes in the pulvinar nucleus of thalamus [136], allowing high level analysis of symbols, faces and uniqueness, necessary for social interactions [137]. Improvement in peripheral perception of complex symbols by the macula of retina also allowed reading and writing. The role of visual perception was major in the evolution of the whole brain [138–141].

By far the major new development in the brain of Homo occurred in the prefrontal cortex [140–153], with disproportionately large white matter volume [153]. It allowed to adapt to and anticipate the more and more complex and unexpected events of the environment (executive functions) with flexibility, in order to deal with both social and environmental needs, i.e. social intelligence and behaviour, theory of mind, group interaction for selling (motivation), hunting, fighting or empathy and solidarity [142–173] and recently, neuroecology [146]. The prefrontal cortex, language and mirror neurons also allowed self consciousness [154,174–182], abstract judgments, generation of concepts [163], domestication of the environment: fire, animals, hunting and fighting strategies, conception of sophisticated arms and tools [155]. The new medial cingulate areas, orbitofrontal cortex and ventral striatum allowed Homo to monitor and regulate the self to superior needs (internal or social), to connect cognition with emotion [162] (social interaction, art), but also self perception, self monitoring and regulation of personal and social behaviours [154,174–187], inhibition of old automatisms (mother-dependent archaic reflexes, older locomotor modes, nociceptive reflexes), repression of environment-echoing-driven responses to stimuli, modulation of mirror neurons for social behaviour and cognitive learning, modulation of internal pulsions and emotional behaviours, knowledge of well and bad [160,175–187], perception and communication of emotions and intentions [166,169–170]. In short, the prefrontal lobe development allowed humans to adapt to the self to unexpected and complex situations and superior need, and even to anticipate, make concepts and perform abstract reasoning, what we call now intelligence [166,167,173], but also social and affective intelligence [158]. It also allowed cognition of cognition (metacognition), with perception of one’s own brain capacities, knowledge of time (chronologic memory, past present and future, durations), self consciousness [148,174–182], self determination, perception of the limits of senses, reality testing (lost in hallucinations, delusions, confabulations), knowledge of death, with resulting spirituality [182], burial of bodies, beliefs (magic, mystic thinking), ritualistic behaviours that translated into religion, knowledge of well and bad or morale, capital sins [183], sense of responsibility, altruism, forgiving, empathy and intuition [161,171,183,185,186].

Dysfunction of medial and orbitofrontal cortex result in psychiatric disorders: behavioural changes, hysteria, psychosis (delusions, hallucinations, disorders of formal thinking), schizophrenia, personality disorders, obsessive—compulsive/impulsive behaviours and mood disorders [187–193]. This results from the loss of fine-tuning of hierarchical ordering of mood, needs, cognition and behavior to the context.

As a result, production economy started to arise 10,000 BC, 800 AD schools improved knowledge transmission, 200 years ago industry with machines and economic theories further expanded the complexity of interactions, and only since 20 years, ecologic concerns appear, i.e. much larger perception of his restricted environment. Cognition of the future is probably now in evolution, that started with weather forecast and economic and military prediction, now directed thank to computers towards daily living, science, history and even art. Signs of further evolution in the brain have been observed [193–199], may be for the perception and prediction of future (cognition of future).

Evolution of sleep—wake cycle and behaviour [200–204] is less well studied, but also adapt to the new cognitive functions, context and environment.

B. Systems that degenerate in so called neurodegenerative disorders

From a clinical point of view, neurodegenerative diseases align along 16 recognisable clinical syndromes, translating the dysfunction of the most recent brain functions of Homo sapiens:

1. Parkinsonism: it results from the loss of function of the nigrostriatal/ventral tegmental—olfactory—limbic—frontal network for rapid execution of fine distal and laryngeal motility and bipedal posture and gait. The restricted syndrome is pre-synaptic nigrostriatal classical dopa-sensitive parkinsonism; extended parkinsonism includes involvement of the cerebellum dentate and cortex, pons, oculomotor, corticospinal, corticobulbar, pre and postsynaptic nigrostriatal, autonomic, prefrontal cortex: “Parkinson plus” “multiple system
atrophy', 'parkinsonism', 'pallidopontonigral', 'pallidopyramidal', 'progressive supranuclear palsy syndrome', 'dentatoriballidousian atrophy', 'olivopontocerebellar atrophy', 'basal ganglia and dentate calcifications'. Generalized slowness of fast movements of hand and larynx and 'simian hand gait and posture' occurs together with the release of an old primate subroutine, tremor, probably translating reemergence of simian scratching—grooming behaviour of the hand.

(2) Bipedal gait and postural executive and procedural syndromes: highest level gait syndromes, frontal gait disorders, gait apraxia or lower body parkinsonism [for review [205]]: gait ignition failure, primary freezing of gait, frontal gait disorder) and postural disorders (subcortical and frontal disequilibrium, astasia—abasia): including vertical gaze (especially downgaze for upright progression) translates the loss of executive control of bipedal posture and gait, defective adaptation to the context, apraxia of bipedal posture and gait, emergence of older locomotor and postural patterns (retropulsion).

(3) Ataxia: limb kinetic and postural-axial ataxic syndromes (neocortex—dentate nucleus): spinocerebellar, olivopontocerebellar, cortical cerebellar, olivocerebellar atrophias. It translates the loss of medium level coordination of synergies for bipedal gait and fine motility of hand and larynx.

(4) Dyskinesia: chorea, dystonia, myoclonus, represent the intrusion of disinhibited basal ganglia subroutines of older sensori-motor distal simian hyperactivity (chorea) or postural routines (simian hand prehension, wrist knuckle gait, tree climbing postures of the legs) or limbic-associated emotional motor routines (tics) or locomotor patterns (restless legs). Huntington's chorea translates selective involvement of recent motor, limbic, anterior and caudal cognitive striatum.

(5) Motoneuron diseases: amyotrophic lateral sclerosis, lateral sclerosis, bulbar form of ALS, Kennedy bulbospinal amyotrophy. They translate the degenerescence of the recent central motoneuron of pyramidal and corticobulbar pathways for fine motility of hand and bulbar muscles and new peripheral pool of bulbar and proximo-distal motoneurone pools of anterior horn, preserving older muscles such as oculomotor and abdominal pools.

(6) Archaic (primitive) reflexes: perioral reflexes, grasping, prehension, mastication, gegenhalten... They translate the loss of frontal inhibition on brainstem—spinal primitive mother-and tree-climbing oriented reflexes (grasping—prehension, sucking, mastication, Babinski/triple retraction, gegenhalten), social alarm reflexes (laughter, crying, yawning, grunting, whistling, startle), social and nociceptive grooming (tremor = scratching), and environmental protective nociceptive reflexes (triple retraction, nasopalpebral, palmoental, coughing, sneezing, clearing throat, spitting, scratching ...) and reemergence of old pace-makers (branchial myolconus).

(7) Dysautonomia: it translates the loss of regulation of autonomic functions for bipedal gait (orthostatism)' recent' voluntary control of autonomic functions in relation to the context.

(8) REM sleep disorders: they translate the loss of inhibition of recent brain functions during REM sleep rehearsal, manifesting as REM sleep behaviour disorders, parasomnias, periodic leg movements of sleep.

(9) Corticobasal syndrome: progressive limb kinetic fine motility of hand prehension-manipulation and language expression. It translates the loss of parieto-frontal and basal ganglia sensorimotor melokinetic praxes of fine motility of hand, leg and language with a mixture of melokinetic apraxia, procedural memory loss and dyskinesia, giving to the limb the appearance of older prehension and posture of hand or a climbing leg (simian-like) with akinetic—rigid—dystono—myoclonic simian parasitic motor subroutines, progressive aphasia (apraxia and melokinetic language apraxia), and complex associative parietal sensory deficit.

(10) Frontal/temporal lobe degeneration: Frontal/behavioural variant, anterior cingulate apathetic, mesial-orbitofrontal disinhibited and stereotyped variants, dorsolateral dysexecutive variant and primary progressive non-fluent aphasia; temporal variant semantic dementia and progressive fluent aphasia. They translate the loss of prefrontal lobe effect of adequation to the context. Frontal variant: medial/orbitofrontal/insular/ orbitofrontal-ventral striatal variant: inadequation to self monitoring and internal needs and pulsions (apathy, akinetic mutism, loss of personal hygiene, impulsive and obsessive behaviours), inadequation to social context (disinhibition, loss of concern and empathy, loss of social regulation, loss of fear for danger or consequences of acts, environment-driven behaviours ...); loss of metacognition, anticipation, abstract reasoning. Dorsolateral prefrontal variant: inadequation to the context of action: dysexecutive syndrome: inadequation to goal, strategy, changes in context; progressive nonfluent aphasia: dysexecutive and loss of newly acquired language expression (more focal syndromes: progressive dysarthria, progressive aphemia...); temporal variant: temporopolar semantic dementia: loss of concepts and perception of uniqueness (restrictive social/familial-personal field), changes in art expression; lateral: lateroposterior variant: progressive fluent aphasia/progressive apraxia.
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(12) Focal posterior degeneration (Benson syndrome, focal progressive apraxia, agnosia, alexia, agraphia, prosopagnosia, Balint syndrome...): progressive visuoperceptual and spatial explicit/implicit cognition. It translates the loss of human visuospatial treatment of what and where by respectively the posterior parietal and temporal lobes.

(13) Macular degeneration: It translates the loss of function of specialized new retinal “spot” for perception of symbols for explicit cognition: letters, details of face and objects...

(14) "Psychiatric syndromes": psychosis, schizofrenia, autism, Asperger and personality disorders. It translates the loss of metacognitive-self perception monitoring and hierarchic regulation of cognition (hallucinations, delusions, magic and mystic logic), behaviour (cf frontotemporal dementia), personality (personality disorders) and drive (disorders of impulse control, obsessive–compulsive disorders, psychic tics, stereotypy, catatonia): disorders of heteronoietic social monitoring, cognition and behaviour: theory of mind, autism, Asperger.

(15) Mood disorders: they translate the loss of control on emotion: depression anxiety, biopolar disorders, mania, sense of humor, moria, emotionalism, laughter and crying (pseubulbar lability syndrome), fourire, forced laughter...

(16) Musculoskeletal dysfunction: Paget and inclusion body myositis. They translate the involvement of bipedal gait muscles and fine motility of hand and pharynx (inclusion body myositis) and Paget’s disease the involvement of bones that were modified for bipedal gait: pelvis, hip, femur, tibia, face... It is possible that atrial fibrillation represents a similar mechanism in new pace-maker and electrical cardiac fibres, and constipation the degenerescence of autonomic relays and gut muscles.

Overlapping syndromes are additions of above-mentioned syndromes (multisystem atrophies, frontotemporal dementia-motoneurone, parkinsonism-dementia syndromes, Paget-inclusion body—frontotemporal etc... ) or finally converging generalized involvement of the aphaso—amneso—apracto—agnostico—akinetic states.

What happens in dementia and other neurodegenerative diseases is therefore just the opposite of development in those precise areas of brain that are new to homo. Demented people retrograde in the evolution just in the opposite way of fœtuses and infants follow darwinian evolution. Generally, neurodegeneration chose one of the above-mentioned 16 subsystems of phylogenetically recent neuronal pathways, with more or less respect in borders, to end up, if long enough, in a generalized involvement of all 16 subsystems. For example, in Alzheimer’s disease, psychomotor disintegration starts with explicit and prospective memory (entorhinal cortex and hippocampus), to progress to new limbic and paralimbic cortices, secondary neocortical areas in parietotemporal, frontal and occipital lobes, ending up with motor structures of bipedal gait. In Parkinson’s disease, it is just the opposite, the disease starts with olfaction, then fine hand motility and bipedal gait (simian posture and gait) to finally reach limbic, frontal then generalized cortical areas.

At this point of the reasoning, it seems logical to redirect basic science of neurodegenerative disorders to look at the instable survival of these new brain regions of humans. Studying the mechanisms of the 1% of the genome, non expressed DNA or the transcriptional factors that have differentiated the homo central nervous system from the on the chimpanzee–bonobo prehuman primates would allow to explain why some neurodegenerative diseases are focal in the brain (primary progressive aphasia, progressive pure alexia...), why some are linked to neuronal systems (spinocerebellar atrophies, parkinsonism), and others more generalized (Alzheimer’s disease). Genes or transcriptional factors specific of neuronal populations or functions of brain structures are probably the specific targets that determine focal apoptosis [9]. Looking at developmental genes would allow to understand how these regions are armed for survival in respect to aging.

Evaluation of the hypothesis/idea

Empirical data

It is known from the revision of the literature [121,206–243], that positive selection [218,223] of genes (morphogens) [220] was instrumental in the shift of humans from the chimpanzee–bonobo branch, new genes specific for size of brain [212],
language and mental activities [231–244], brain asymmetry [240], or activations and silencing of present genes [205], segmental duplications [236], rearrangements [214], variation in expression [207, 212, 214, 219], changes in micro RNA and cDNA, transcriptomes [213], promoters [227, 229], length of tandem repeats [230], non-expressed DNA segments, epigenesis [240] and other mechanisms participated in the hominization of the primate brain. The famous 1% difference seems therefore not to be the only actor for the global complexity of evolutionary biology [232] and paleoneurology [15–19]. The hunt for what makes us humans is a trendy topic [230, 233]. Genes specific to cortical functions and regions such as language for example have been recently stressed in family with genetic speech and praxic disorders (FOXP2, SPC1, SRPX2) [231–244], but seems also to play a role in mirror neurons [239], schizophrenia [243] and many are to be found and gene-structure interaction is still in the early phase of evaluation. The effect of age in gene expression has just started [245]. Amyloid beta 40 deposition has been demonstrated in aged monkeys [246], MAPT sequences (tau protein) vary among primates [247], but links between species differences and diseases have been considered. The more than 1000 fold increase in cortical surface without an increase in thickness during mammalian evolution was further refined by changes in structure, connectivity, redeployment of brain areas [126, 144, 248–255]. Specific human glial cells, astrocytic complexity and specific glia-neuron ratio have been reported [256–258]. Finally a specific evolution of connectivity [259–260] has also played a major role in brain evolution of humans. This sets a new neurology, rapidly developing into paleoneurology [15–18, 191, 192, 261–273]. As already mentioned, Alzheimer’s disease has been considered as a phylogenetic disease [1] or an antagonistic pleiotropy [261], i.e. a loss of differentiation control in a subset of neurons that retain immature features in the adult brain [271]. Some similar approach has been considered for Parkinson’s disease [262], gait disorders [263–265] and schizophrenia [190–192]. Summarizing the topographical localization of all neuopathologic and musculoskeletal lesions of degenerative diseases just delineates the new developed brain and body changes that occurred in hominoids and later homo sapiens.

From the clinical analysis of the 16 above-mentioned clinical syndromes, one can infer that all of the symptoms encountered in these syndromes translate a dysfunction of these new secondary cortical areas or newly wired brainstem and diencephalic structures for bipedal locomotion and brain functions indirectly derived from acquisition of fine motility of pharynx and hand, i.e. cognition and mind, often involved together with bipedal gait. Furthermore, even though there is a parkinsonism in the monkey, it is fairly different from the one seen in humans, just because the monkey lacks the main brain networks that allow the human symptoms and signs of the human parkinsonian syndrome. Similarly, highest level gait disorders as summarized by Nutt [205] and seen in hydrocephalus are just a return toward more primate locomotion patterns, simian-like gait and posture or apraxia of standing and bipedal locomotion [267], i.e. the re-emergence of old automatism of prehuman gait or even quadrupodal locomotion which is at his nadir with the Uner Tan syndrome [265].

Consequences of the hypotheses and discussion

This new way of seeing clinical signs in neurodegenerative diseases allows us to lump them as diseases involving new brain areas specific to human primates (homo sapiens sapiens) and to consider the clinical features from a neuroevolutionary (paleoneurological) standpoint specific to Homo and aging [15–18, 189, 190, 268, 269] and build a new chapter in clinical neurology: paleoneurology. It allows us to understand why functional systems are focally involved, to class highest level bipedal gait disorders into the cognitive functions, as highest level control of hand and laryngeal fine processing (oral and written language) and analyse clinical syndromes as the regression of function toward the paleoneurology of prehuman primates. In a way, a demented patient with language dysfunction returns to the level of thinking and communication of an early primate, like the Uner Tan syndrome walks like a primate quadruped with curved fingers during wrist walking with arm and leg ratios of human-like apes and possess primitive language and mental abilities [265]. It also allows to understand the focal (frontotemporal), restricted (semantic dementia, progressive prosopagnosia...) or asymmetrical nature of the syndromes as involved by (a) specific gene(s) or transcription factor(s) sensitive for a functional system, cortical areas or brain dominance. It would also allow us to understand the heterogeneous neuropathology of corticobasal syndrome, progressive supranuclear palsy syndrome and even Parkinson syndrome, frontotemporal dementia or cortical dementias that are homo-specific syndromic presentations rather than patho-specific diseases. It shed lights on the con-
connection between hand and language dysfunction in neurodegenerative syndromes such as corticobasal degeneration syndrome or frontotemporal dementias, and even unexpected associations such as macular degeneration [268], Paget’s disease, inclusion body myositis [109,110,268–274]. It also allows to understand why progressive aphasia cannot compensate with pantomimes of words [266] even in the absence of ideomotor apraxia, why language, speech, fine motility and gait are involved in parkinsonian syndromes, Alzheimer’s disease and frontotemporal dementia [264,267].

What is the role of age in sporadic neurodegenerative diseases? Well, extension of life of humans by about 50 years in the last century has brought up diseases normally not occurring in chimpanzees (maximum age of 50 years) or wild forests inhabitants. Selection of longevity may have resulted from the fact that survival was better in families with grand parents taking care of the children [270,271], selecting longevity genes. Brain aging can be seen in an involutionary process compared to general Darwinian evolution [5] and gene action is known to occur in the aging brain [7–9]. Premature aging of new cortical areas [10] may be possibly due to a still evolving and not fixed genome in newly appeared cortical networks, with a specific sensitivity to age and apoptosis [11], mutations [12] or loss of differentiation [271] because of more plasticity, more rapid evolution and wider connections than primary cortical areas. It may perhaps also explain other systemic diseases such as basal ganglia calcifications, Rett syndrome, vascu lar dementia, Werner’s syndrome [273], perhaps other such as channelopathies, vascular topography of microangiopathic vascular dementia and perhaps arteriosclerosis, boldness of aging, atrial fibrillation and constipation among many other entities linked to ageing. Psychiatric diseases may result from the same unstable mechanisms in these extremely plastic new cerebral areas that perform context-dependent hierarchical soft processing of all these new sophistication brain functions of homo sapiens (mood, needs, behavior, cognition and metacognition).

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