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

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Summary Bipedal locomotion and fine motility of hand and larynx of humans introduced msculoskeletal adaptations, new pyramidal, corticostriatal, corticobulbar, nigrostriatal, and cerebellar pathways and expansions of prefrontal, cingular, parieto-temporal and occipital cortices with derived new brain capabilities. All selectively degenerate in aged homo sapiens following 16 syndromic presentations: (1) Parkinsonism: nigrostriatal control for fast automatic movements of hand, larynx, bipedal posture and gait (''simian gait and hand''). (2) Frontal (highest level) gait disorders (lower body parkinsonism, gait apraxia, retropulsion): prefrontostriatal executive control of bipedal locomotion. (3) ataxia: new synergistic coordination of bipedal gait and fine motility. (4) Dyskinesias (chorea, dystonia, tremor...): intrusions of simian basal ganglia motor subroutines. (5) motoneuron diseases: new proximo-distal and bulbar motoneurones, preserving older ones (oculomotor, abdominal...). (6) Archaic reflexes: prefrontal disinhibition of old mother/tree-climbing-oriented reflexes (sucking, grasping, Babinski/triple retraction, gegenhalten), group alarms (laughter, crying, yawning, grunting...) or grooming (tremor = scratching). (7) Dysautonomia: contextual regulation (orthostatism...). (8) REM sleep disorders of new cortical functions. (9) Corticobasal syndrome: melokinetic control of hand prehension–manipulation and language (retrocession to simian patterns). (10) Frontal/temporal lobe degeneration: medial-orbitofrontal behavioural variant: self monitoring of internal needs and social context: apathy, loss of personal hygiene, stereotypia, disinhibition, loss of concern for consequences of acts, social rules, danger and empathy; dorsolateral executive variant: inadequacy to the context of action (goal, environmental changes...); progressive non-fluent aphasia: executive and praxic processing of speech; temporal variant: abstract concepts for speech, gestures and vision (semantic dementia, progressive nonfluent aphasia) (11) Temporomesial–limbic–paralimbic–associative cortical dementias (Alzheimer's disease, Lewy body, progressive amnesia): processing of explicit cognition: amnesic syndrome, processing of hand, larynx and eye: disorientation, ideomotor apraxia, agnosia, visuospatial processing, transcortical aphasia. (12) Focal posterior atrophy (Benson, progressive apraxia): visuomotor processing of what and where. (13) Macular degeneration: retinal ''spot'' for explicit symbols. (14) ''Psychiatric syndromes'': metacognition, self monitoring and regulation of hierarchical processing of metacognition: hallucinations, delusions, magic and mystic logic, delusions, confabulations; drive: impulsivity, obsessive–compulsive disorders, mental automatisms; social interactions: theory of mind, autism, Asperger. (15) Mood disorders: control on emotions: anxio-depressive and bipolar disorders, moria, emotional lability. (16) Musculoskeletal: inclusion body myositis: muscles for bipedal gait and fine motility. Paget's disease: bones for bipedal gait and cranium.

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Understanding of the genetic mechanisms underlying the evolution of these recent human brain regions and paleoneurology my 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.

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 phyllogenetically 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 form 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 samburupitecus sahelantropus. 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 with orrorin 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 quadripodal 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 rightning 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. Ventrotegmento-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 susbtantia 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 (laughter 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 mamillary 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 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 presynaptic 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'', ''dentatoribropallidouysian 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 nocicpetive reflexes (triple retraction, nasopalpebral, palmomental, caughing, 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 praxias 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 apapathetic, 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 dysathria, 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.

(11) Temporomesial-limbic-paralimbic-associative cortical dementias: Alzheimer's disease, Lewy body disease, progressive amnesia: explicit memory and cognition of new human specific cortical areas. They translate the loss of new hippocampal function for sampling of explicit memory episodes with linking to associative secondary cortical and paralimbic areas processing explicit cognition and memory: explicit amnesic syndrome, explicit hand and larynx and eye-derived treatment of information: ideomotor apraxia, visuospatial deficit, agnosia, transcortical aphasia.

(12) Focal posterior degeneration (Benson syndrome, focal progressive apraxia, agnosia, alexia, agraphia, prosopoagnosia, 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, schizophrenia, 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, austism, 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 foetuses and infants follow darwinian evolution. Generally, neurodegeneration chose one of the above-mentioned 16 susbsystems of phyllogentically 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 (spinocerebllar 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, SPCH1, 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 paleoneurologogy [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 neuropathologic and musculoskeletal lesions of degenerative diseases just delineates the new developed brain and body changes that occurred in hominoïds 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], ie the re-emergence of old automatism of prehuman gait or even quadripodal 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 prospoagnosia...) 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-

nection 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, vascular 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 sophisticated brain functions of homo sapiens (mood, needs, behavior, cognition and metacognition).

References

[1] Rapoport SI. Brain evolution and Alzheimer's disease. Rev Neurol 1988;144(2):7990.

[2] Rapoport SI. Hypothesis: Alzheimer's disease is a phyllogenetic disease. Med Hypotheses 1989;29(3):147—50.

[3] Rapoport SI. Integrated phylogeny of the primate brain, with special reference to humans and their disease. Brain Res Brain Res Rev 1990;15(3):267—94.

[4] Bayle KG. The concept of phyllogenic regression. J Am Acad Psychoanal 1978;6(1):5—35.

[5] Hofman MA. From here to eternity: brain aging in an evolutionary perspective. Neurobiol Aging 1991;12(4): 338—40.

[6] Calvin WH. The emergence of intelligence. Sci Am 1994;371(4):100—7;
Calvin WH. The brain as a Darwin machine. Nature 1987;330(6143):33—4.

[7] Parent A. The brain in evolution and involution. Biochem Cell Biol 1997;75(6):651—67.

[8] Martin GM. Gene action in the aging brain: an evolutionary biological perspective. Neurobiol Aging 2002;23(5): 647—54.

[9] Seeley WW, Carlin DA, Allman JM, Macedo MN, Bush C, Miller BL, et al. Early frontotemporal dementia targets neurons unique to apes and humans. Ann Neurol 2006;60(6):660—7.

[10] Mattson MP. Brain evolution and lifespan regulation: conservation of signal transduction pathways that regulate energy metabolism. Mech Ageing Dev 2002;123(8): 947—53.

[11] Victoroff J. Evolution and brain aging. Harv Ment Health Lett 2000;16(12):5—7.

[12] Vallender FJ, Lahn BT. A primate-specific acceleration in the evolution of the caspase-dependent apoptosis pathway. Hum Mol Genet 2006;15(20):3034—40.

[13] Kosik KS. The long reach of evolution and development. Effects on the Alzheimer brain. Ann NY Acad Sci 2000;924: 76—80.

[14] Arendt D. Genes and homology in nervous system evolution: comparing gene functions, expression patterns and cell type molecular fingerprints. Theory Biosci 2005;124(2):185—97.

[15] Edinger T. Palaeoneurology 1804—1966: an annotated bibliography. Adv Anal Embryol Cell Biol 1975;49(1—6): 3—258.

[16] Jerison HJ. The paleoneurology of language. Ann NY Acad Sci 1976;280:370—82.

[17] Holloway RL. Paleoneurological evidence for language origins. Ann NY Acad Sci 1976;280:330—48.

[18] Brandt M. Brain evolution of the human from the paleoneurologic viewpoint. Anthropol Anz 1993;51(4):289—308.

[19] Coppens Y. L'évolution de l'homme. Bull Mem Acad R Med Belg 1998;153(12):447—9.

[20] Bruner E. Geometric morphometric and paleoneurology: brain shape evolution in the genus. Homo J Hum Evol 2004;47(5):279—303.

[21] Chimpanzee sequencing and analysis consortium initial sequence of the chimpanzee genome and comparison with the human genome. Nature 2005; 437 (7055): 69—87.

[22] Passingham RE. Anatomical differences between the neocortex of man and other primates. Brain Behav Evol 1973;7(5):337—59.

[23] Creely H, Khaitovich P. Human brain evolution. Prog Brain Res 2006;158:295—309.

[24] Coppens Y. The anatomical and functional origin of the first bipedalism. Bull Acad Natl Med 1991;175(7):977—91.

[25] Lovejoy CO, Cohn MJ, White TD. Morphological analysis of the mammalian postcranium: a developmental perspective. Proc Natl Acad Sci USA 1999;96:13247—52.

[26] Lovejoy CO. The origin of man. Science 1981;211(4480): 341—50.

[27] Anton SC. Natural history of homo erectus. Am J Phys Antrhopol 2003(Suppl. l37):126—70.

[28] Coppens Y. East side story: the origin of humankind. Sci Am 1994;270(5):88—95.

[29] Andrews P, Matin L. Homoid dietary evolution. Philos Trans R Soc London B Biol 1991;334(1270):199—209.

[30] Foley RA, Lee PC. Ecology and energetics of encephalization in hominid evolution. Philos Trans R Soc London B Biol Sci 1991;334(1270):223—31.
[31] Weiss B, Landrigan PJ. The developing brain and the environment: an introduction. Environ Health Perspect 2000;108(3):373—4.
[32] Kuliukas A. Wading for food: the driving force of the evolution of bipedalism? Nutr Health 2002;16(4):267—89.
[33] Leonard WR. Food for thought, dietary change was a driving force in human evolution. Sci A 2002;287(6): 106—15.
[34] Uddin M, Goodman M, Erez O, et al. Distinct genomic signatures of adaptation in pre- and postnatal environment during human evolution. Proc Natl Acad Sci USA 2008;105:3215—20.
[35] Senut B. In: Ishida H, Tuttle RH, Pickford M, Ogihara N, Nakatsukasa M, editors. Human origins and environmental backgrounds. Germany: Springer Heidelberg; 2006.
[36] Anton SC. Climatic influences on the evolution of early homo? BMC Genomics 2007;8:320.
[37] Romgo JL. Neuronal interconectiom as a function of brain size. Brain Behav Evol 1991;38:1—6.
[38] La Cerra P, Bingham R. The adaptative nature of the human neurocognitive architecture an alternative model. PNAS 1998;95(19):11290—4.
[39] Pinkerton JH. Some aspects of the evolution and comparative anatomy of the human pelvis. J Obstet Gynaecol Br Commonw 1973;80(2):97—101.
[40] Ward CV. In: Henke W, Tattersall I, editors. Handbook of paloeoantrhopology Primate evolution and human origins, vol. 32. Heidelberg Germany: Springer; 2007. p. 1011—30.
[41] Alexander RM. Bipedal animals, and their differences from humans. J Anal 2004;5:321—30.
[42] Shik ML, Severein FV, Orlovksy GN. Control of walking and running by means of electrical stimulation of the midbrain. Biophysics 1966;11:756—65.
[43] Mori S, Matsuyama K, Mori F, Nakajima K. Supraspinal sites that indice locomotion in the vertebral central nervous system. In: Ruzicka E, Hallett M, Jankovic J, editors. Gait Disorders in Neurology. Philedelphia: Lippincott Willias and Wilkins; 2001. p. 25—40.
[44] Garcia-Rill E, Skinner RD, Fitzgerald JA. Chemical activation of the mesencephalic locomotor region. Brain Res 1985;330:43—54.
[45] Tagliavini F, Pietrini V. On the variability of the human flocculus and patraflocculus accessorius. J Hirfrorsch 1984;25(2):163—70.
[46] Matano S, Hirasaki E. Volumetric comparison in the cerebellar complex of anthropoids, with special reference to locomotor types. Am J Phys Anthropol 1997;103(2): 173—83.
[47] Rilling JK, Insel TR. Evolution of the cerebellum in primates: differences in relative volume among monkey, apes and humans. Brain Behav Evol 1998;52(6):308—14.
[48] Mc Leod CE, Zilles K, Schleicher A, Rilling JK, Gibson KR. Expansion of the neocerebellum in hominoidea. J Hum Evol 2003;44(4):401—29.
[49] Gramsbregen A. Postural control in man: the phylogenetic perspective. Neural Palst 2005;12(2—3):77—88.
[50] Weaver AH. Reciprocal evolution of the cerebellum and neocortex in fossil humans. PNAS 2005;102(10):3756—80.
[51] Previc FH. Dopamine and the origins of human intelligence. Brain Cogn 1999;41(3):299—350.
[52] Hikosaka O, Wurz RH, Hikosaka O, Wurz RH. Visual and oculomotor functions of monkey substantia nigra pars reticulate IV. Relation of nigra to superior colliculs. J Neurophysiol 1983;49(5):1285—301.
[53] Kesarev VS. Structural features of hypotahalmus in man and other primates (chimpanzee, macacque). Fed Proc Transl Suppl 1966;25(2):243—7.
[54] Vlahovitch B, Fuentes JM. Insular homologies. Comparative anatomy data in mammals. Neurochirurgy 1972;18(6): 511—20.
[55] Nudo RJ, Sutherland DP, Masterton RB. Variation and evolution of mammalian corticospinal somata with special references to primates. J Comp Neurol 1995;358(2): 181—205.
[56] Monza D, Soliveri P, Radice D, Fetoni V, Tetsa D, Caffara P, et al. Cognitive dysfunction and impaired organization of complex motility in degenerative parkinsonian syndroms. Arch Neurol 1998;55(3):372—8.
[57] Almquist EE. Evolution of the distal radio-ulnar joint. Clin Orthop Relat Res 1992;275:5—13.
[58] Putz RV, Tuppek A. Evolution of the hand. Handchir MikrochirPlast Chir 1999;31(6):357—61.
[59] Almecija S, Alba DM, Moya-Sola S, Köhler M. Orang-like manual adaptations in the fossil hominoid Hispanopithecus laietanus: first steps towards great ape suspendory behaviors. Proc R Soc Sci London Ser B 2007;274(1624):2375—84.
[60] Moya-Sola S, Kohler M, Alba DM, Almecija S. Taxonomic attribution of the Olduvai hominid 7 manual remains and the functional interpretation of hand morphology in robust australopithecus. Folia Primatol 2008;79(4):215—50.
[61] Dum RP. Strick Pl. Motor areas in the frontal lobe of the primate. Physiol Behav 2002;77(4—5):677—82.
[62] Kass JH. The evolution of the complex sensory and motor systems of the human brain. Brain Res Bull 2008;75(2—4): 384—90.
[63] Johnson-Frey SH. What's so special about human tool use? Neuron 2003;39(2):201—4.
[64] Stout D, Chaminade T. The evolutionary neuroscience of tool making. Neurpsychologia 2007;45(5):1091—100.
[65] Stout D, Toth N, Schick K, Chaminade T. Neural correlates of early stone age tool making: technology, language and cognition in human evolution. Philos Trans R Soc London B Biol Sci; 21 February 2008 [Epub].
[66] Wiesendanger M. Manual dexterity and the making of tools-an introduction from an evolutionary perspective. Exp Brain Res 1999;128(1—2):1—5.
[67] Wagener JS. Creativity in biology and in the human mind (manifestation of concepts). Acta Biother 1985;34(1): 3—51.
[68] Rail DL. A neural basis for symbol development. Med Hypotheses 1986;21(3):299—306.
[69] Corrucini RS, Ciochon RL. Primate facial allometry and interpretations of australopithecine variation. Nature 1979;281(5726):62—4.
[70] Polanski JM, Franciscus RG. Patterns of craniofacial integration in extant homo, pan and gorilla. Am J Phys Anthropol 2006;131:38—49.
[71] Sherwood RJ, Rowley RB, Ward SC. Relative placement of the mandibular fossa in great apes and humans. J Hum Evol 2002;43(1):57—66.
[72] Falk D. Comparative anatomy of the larynx in man and the chimpanzee: implications for language in Neanderthal. Am J Phys Antrhopol 1975;43(1):123—32.
[73] Dean C. Progress in understanding hominoid dental development. J Anal 2000;197(1):77—101.
[74] Porter R. The brain: seat of motor control. Corticospinal neurons in movement performance. Med J Aust 1984;140(8):462—72.
[75] Gilland E, Baker R. Evolutionary patterns of cranial nerve efferent nuclei in vertebrates. Evol Behav Evol 2005;66(4):234—54.

[76] Rosa-Molinar E, Krumplauf RK, Pritz MB. Hindbrain development and evolution past, present and future. Brain Behav Evol 2005;66(4):234—54.
[77] Sherwood CC, Holloway RL, Erwin JM, Hof PR. Cortical orofacial motor representation in old world monkeys great apes and humans II. Stereologic analysis of chemoarchitecture. Brain Behav Evol 2004;63(2):82—106.
[78] Sherwood CC, Hof PR, Halloway RL, et al. Evolution of the brainstem orofacial motor system in primates: a comparative study of trigeminal facial, and hypoglossal nuclei. J Hum Evol 2005;48(1):45—84.
[79] Ramani N, Behrens TE, Johansen-Berg H. The evolution of prefrontal inputs to the cortico-pontine system: diffusion imaging evidence from the macaque monkeys and humans. Cereb Cortex 2006;16(6):811—8.
[80] Sherwood CC, Broadffield DC, Holloway RL. Variability of Broca's area homolog in African great apes. Implications for language evolution. Anal Rec A Discovery Mol Cell Evol Biol 2003;271(2):273—5.
[81] Sanides F. Compartive neurology of the temporal lobe in primates including man with reference to speech. Brain Lang 1975;4:396—419.
[82] Jenson HJ. The theory of encephalization. Ann NY Acad Sci 1977;299:146—60.
[83] Holloway RL. Palenoneurological evidence for language origins. Ann NY Acad Sci 1976;280:330—48.
[84] Yeni Komshian GH, Benson DA. Anatomical study of cerebral asymmetry in the temporal lobe of humans, chimpanzee and rhesus monkey. Science 1976;192(4237): 387—9.
[85] Webster WG. Territoriality and the evolution of brain asymmetry. Ann NY Acad Sci 1977;299:213—21.
[86] Witleson SF. Anatomic asymmetry in the temporal lobes. Its documentation, phylogenesis and relationships to functional asymmetry. Ann NY Acad Sci 1977;299: 328—54.
[87] Passingham RE. Brocas' area and the origins of human vocal skills. Philos Trans R Soc London B Biol 1981;2929(1057):167—75.
[88] GannonHolloway PJ, Holloway RL, Boradfield DC, Bran AR. Asymmetry of chimpanzee planum temporale: humanlike pattern of Wernicke's brain language area homolog. Science 1998;279(5348):220—2.
[89] Varatanian JA, Chernigovskaia TV. The vocalization and speech systems of the bran: ane evolutionaty neruobiologival anaylsis. Zh Evol Biokhim Fiziol 1990;16(6): 826—36.
[90] Lieberman P. On the nature and evolution of the neural bases of human language. Am J Phys Antrhopol 2002(Suppl. 35):36—62.
[91] Lieberman DE. Palaeoanthropology: homing in on early homo. Nature 2007;449(7160):291—2.
[92] Waters GS, Fouts RS. Sympathetic mouth movements accompanying fine motor movements in chimpanzee/pan troglodytes with implications toward the evolution of language. Neurol Res 2002;24(2):174—80.
[93] Braun A. New findings in cortical anatomy and implications for investigating the evolution of language. Anal Rec A Discovery Mol Cell Evol Biol 2003;271(2):273—5.
[94] Holden C. The origin of speech. Science 2004;303(5662): 1316—9.
[95] Fisher SE, Marcus GE. The eloquent ape; genes, brains and the evolution of language. Natl Rev Genet 2006;7:19—20.
[96] Alpert M. Lateralization of the human brain. Ann NY Acad Sci 1977;299:412—4.
[97] Benton AL. Historical notes on hemispheric dominance. Arch Neurol 1977;34(2):127—9.
[98] Dawson J. An anthropological perspective on the evolution and lateralization of the brain. Ann NY Acad Sci 1977;299: 424—47.
[99] Dimond SJ. Evolution and lateralization of the brain: concluding remarks. Ann NY Acad Sci 1977;299:477—501.
[100] Levy J. The mammalian brain and the adaptative advantage of cerebral asymmetry. Ann NY Acad Sci 1977;299: 264—72.
[101] Pribram KH. Hemispheric specialization: evolution of revolution. Ann NY Acad Sci 1977;299:18—22.
[102] LeDoux JE. Neuroevolutionary mechanisms of cerebral asymmetry in man. Brain Behav Evol 1982;20(3—4): 196—212.
[103] Goedakian VA. Evolutionary logic of functional brain asymmetry. Dok Akad Nauk 1992;6:1327—31.
[104] Provins KA. Hadnedness and speech: a critical reappraisal of the role of genetic and environmental factors in cerebral lateralization of function. Psychol Rev 1997;104(3):554—71.
[105] Selnes OA. The ontology of cerebral language dominance. Brain Lang 2000;71(1):217—20.
[106] Buxhoeveden DP, Switala AEm Ltaker M, Ry E, Casanova ME. Lateralization of minicolumns in human planum temporal is absent in nonhuman primate cortex. Brain Behav Evol 2001;57(6):349—58.
[107] Vallortigara G, Rogers LJ. Survival with asymmetrical brain: advantages and disandvantages of cerebral lateralization. Behav Brain Sci 2005;28(4):575—89.
[108] Vallortigara G. The evolutionary psychology of left and right: cost and benefits of lateralization. Dev Psychobiol 2006;48(6):418—27.
[109] Tzeng OJ, Wang WS. Search for a common neurocognitive mechansism for language and movements. Am J Physiol 1984;246(6.2):R904—11.
[110] Corballis MC. From mouth to hand gesture: speech, and the evolution of right-handedness. Behav Brain Sci 2003;26(2):199—208.
[111] Corballis MC. In the evolution of language and generativity. Cognition 1992;44(3):197—226.
[112] Noll H. The digital origin of human language — a synthesis. Bioessays 2003;25(5):489—500.
[113] Kelly SD, Iverson JM, Terranova J, et al. Putting language back in the body: speech and gesture in three tune frames. Dev Neuropsychol 2002;22(1):323—49.
[114] Aboitiz F, Garcia VR. The evolutionary origin of the language areas in the human brain, a neuroanatomic perspetcive. Brain Res Brain Res Rev 1997;25(3):331—9.
[115] Aboititz F. Working memory networks and the origin of language areas in the human brain. Med Hypotheses 1995;44(6):504—6.
[116] Carpenter MB. Ventral tier thalamic nuclei. Mod Trends Neurol 1967;4:1—20.
[117] Gross CG. Hippocampus minor and man's place in nature: a case study in the social construction of neuroanatomy. Hippocampus 1993;3(4):403—15.
[118] Ullman MT. Contributions of memory circuits to language: the declarative/procedural model. Cognition 2004;92(1—2):231—70.
[119] Manns JR, Eichenbaum H. Evolution of declarative memory. Hippocampus 2006;16(9):795—808.
[120] Barco A, Bailey CH, Kandel ER. Common molecular mechanisms in explicit and implicit memory. J Neurochem 2006;97(6):1520—33.
[121] Lu ZX, Peng J, Su B. A human-specific mutation leads to the origin of a novel splice form of neuropsin (KLK8) a gene involved in learning and memory. Hum Mutat 2007;28(10):978—84.

[122] Armstrong E. Enlarged limbic structures in the human brain: the anterior thalamus and medial mammillary body. Brain Res 1986;362:394—7.
[123] Armstrong E. A quantitative comparison of hominoid thalamus II limbic nuclei anterior principalis and lateralis dorsalis. Am J Phys Anthropol 1980;52(1):43—54.
[124] Ishii S, Takahashi R. Characteristic and origin of the human olfactory organ. Rhinology 1982;20(1):27—31.
[125] Stephan H. Evolutionary trends in limbic structures. Neurosci Biobehav Rev 1983;7(3):367—74.
[126] Kling A. Ontogenic and phylogenic studies the amygdaloid nuclei. Psychosom Med 1966;28(2):155—61.
[127] Barger N, Stefanacci L, Semendefero K. A comparative anatomy of the amygdaloid complex and basolateral division in the human and ape brain. Am J Phys Antropol 2007;134(3):392—403.
[128] Sander D, Grafman J, Zalla T. The human amygdala: an evolved system for relevance detection. Rev Neurosci 2003;14(4):303—16.
[129] Kaplan HS, Robson AJ. The emergence of humans: the coevolution of intelligence and longevity with intergenerational transfer. PNAS 2002;99(15):10221—6.
[130] Sinha A. Reflective consciousness and the emergence of memes: serial evolutionary pathways? J Biosci 2002;27(7): 637—43.
[131] Hyvärinen J. Posterior parietal lobe of the primate bran. Physiol Rev 1982;62(3):1029—60.
[132] Kass JH, Lyon DC. Visual cortex organizaton in primates: theories of V3 and adjoining visual areas. Prog Brain Res 2001;134:285—95.
[133] Kass JH, Reiner A. Evolutionary neurology. The neocortex comes together. Nature 1999;399(6735):418—9.
[134] Holloway RL, Broadfield DC, Yuan MS. Morphological and histology of chimpanzee visual straite cortex indicate brain reorganization predated brain expansion in early hominid evolution. Anal Rec A Discov Moll Cell Evol Biol 2003;273(1):594—602.
[135] Haxby JV, Grady CI, Horwitz B, et al. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. Proc Nat Acad of Sci USA 1991;88(5):1621—5.
[136] Chalfin BP, Cheung DT, Muniz JA, De Lima Silverira LC, Finlay BL. Scaling of neuron number and volume of the pulvinar complex in new world primates: comparison with humans, other primates and mammals. J Comp Neurol 2007;504:265—74.
[137] Cohen-Kadosh K, Johnson MH. Developing a cortex specialized for face perception. Trends Cogn Sci 2007;11(9):367—9.
[138] Purves D, Williams S, Lotto RB. The relevance of visual perception to cortical evolution and development. Novartis Found Symp 2000;228:240—54.
[139] Joffe TH, Dunbar RI. Visual and socio-cognitive information processing in primate bran evolution. Proc Biol Sci 1997;264(1386):1303—7.
[140] Orzhekhovskaia NS. Comparative study of the frontal cortex of the brain of monkeys and man in ontogenesis. Arkh Aat Gistol Embriol 1975;68(3):43—9.
[141] Bookstein F, Schäfer K, Porssinger H, et al. Comparing frontal cranial profile in archaic and modern homo by morphometric analysis. Anal Rec 1999;257(6): 217—24.
[142] Fuster JM. Frontal lobe and cognitive development. J Neurocytol 2002;31(3—5):373—85.
[143] Di Fiore A, Rendall D. Evolution of social organisation. A reappraisal for primates by using phylogenetic methods. PNAS 1994;91:9941—5.
[144] Pasell M. The cognitive cost of extending an evolutionary mind into the environment. Cogn Process 2006;7(1):3—10.
[145] Dunbar RI, Shultz S. Evolution in the social brain. Science 2007;317(5843):1344—7.
[146] Sherry DF. Neuroecology. Ann Rev Psychol 2006;57: 167—97.
[147] Semendeferi K, Armstrong E, Schleicher A, Zilles K, van Hoesen GW. Prefrontal cortex in humans and apes: a comparative study of area 10. Am J Phys Anthropol 2001;114(3):224—41.
[148] Semendeferi K, Armstrong E, Schleicher A, et al. Limbic frontal cortex in hominoids: a comparative study of area 13. Am J Phys Anthropol 1998;106(2):129—55.
[149] Semendeferi K, Damasio H, Frank R, van Hoesen GW. The evolution of the frontal lobes. A volumetric analysis based on three-dimensional reconstructions of magnetic resonance scans of human and ape brains. J Hum Evol 1987;32(4):375—88.
[150] Semendeferi K, Lu A, Schenker N, Damasio H. Humans and great apes share a large frontal cortex. Nat Neurosci 2002;5(3):272—6.
[151] Semendeferi K, Damasio H. The brain and its main anatomical subdivision in living hominoids using magnetic resonance imaging. J Hum Evol 2000;38(2):317—32.
[152] Winterer G, Goldman D. Genetics of human prefrontal function. Brain Res Brain Res Rev 2003;43(1):134—63.
[153] Schoenmann PT, Sheehan MJ, Glotzer LD. Prefrontal white matter volume is disproprotionately larger in humans than in other primates. Nat Neurosci 2005;8(2):242—52.
[154] Oro JJ. Evolution of the brain from behaviour to consciousness in 3.4 billion years. Neurosurgery 2004;54(6): 1287—96.
[155] Geary DC. The motivation to control and the origin of mind: exploring the life-mind joint in the tree of knowledge system. J Clin Psyhol 2005;61(1):21—46.
[156] Pitt R. Warfare and homoid brain evolution. J Theor Biol 1978;72(3):551—75.
[157] Pedersen CA. Biological aspects of social bonding and the roots of human violence. Ann NY Acad Sci 2004;1036: 106—27.
[158] Whitem A. Social complexity and social intelligence. Novartis Found Symp 2000;233:185—95.
[159] Lewin R. The origin of the modern human mind. Science 1987;236(4802):668—70.
[160] Ambrose SH. Paleolithic technology and human evolution. Science 2001;291(5509):1748—53.
[161] Gibbons A. Empathy and brain evolution. Science 1993;259(5099):1250—1.
[162] Allman JM, Hakeem A, Erwin JM, Nimchinsky E, Hof P. The anterior cingulate cortex. The evolution of an interface between emotion and cognition. Ann NY Acad Sci 2001;935:107—17.
[163] Chemigovskaya TV. The mirror brain, concepts and language: the price of anthropogenesis. Neurosci Behav Physiol 2007;37(3):293—302.
[164] Phillips CS. Culture, social mind and governance in evolution. Politics Life Sci 2001;20(2):189—202.
[165] Sariola H. Genes behind humanity, rage, peace and the brain of apes. Duodecim 2004;120(15):1836—7.
[166] Davidson RJ. Darwin and the neural bases of emotion and affective state. Ann NY Acad Sci 2003;1000:316—36.
[167] Parr LA, Waller BM, Fugate J. Emotional communication in primates: implications for neurobiology. Curr Opin Neurobiol 2005;15(6):716—20.
[168] Bennett MR, Hacker PM. Emotion and cortical—subcortical function: conceptual developments. Prog Neurobiol 2005;75(1):29—52.

[169] Stone VE, Baron-Cohen S, Knight RT. Frontal lobe contributions to theory of mind. J Cogn Neurosci 1998;10(5): 640–56.
[170] Povinelli DJ, Preuss TM. Theory of mind: evolutionary history of cognitive specialization. Trends Neurosci 1995;18(9):418–24.
[171] Fehr E, Rockenbach B. Human altruism: economic, neural and evolutionary perspectives. Curr Opin Neurobiol 2004;14(6):784–90.
[172] Roth G, Dicke U. Evolution of the brain and intelligence. Trends Cogn Neurosci 2005;9(5):250–7.
[173] Kanazawa S. General intelligence as a domain-specific adaptation. Psychol Rev 2004;111:512–23.
[174] Rizzolatti G, Craighero L. The mirror-neuron system. Annu Rev Neurosci 2004;27:169–92.
[175] Towers B. Consciousness and the brain. Evolutionary aspects. Ciba Found Symp 1979;69:45–52.
[176] Eccles JC. Brain, speech and consciousness. Naturwissenchaften 1973;60(4):167–76.
[177] Eccles JC. Evolution of the brain in relation to the development of the self-conscious mind. Ann NY Acad Sci 1977;299:161–79.
[178] Eccles JC. Evolution of consciousness. Proc Natl Acad Sci USA 1992;89(16):7320–4.
[179] Arbib MA. Co-evolution of human consciousness and language. Ann NY Acad Sci 2001;929:195–220.
[180] Egnor MR. Evolution of the brain: from behaviour to consciousness in 3.4 billion years. Neurosurgery 2005;54(6):1287–96.
[181] Donald M. The neurobiology of human consciousness: an evolutionary approach. Neuropsychologia 1995;33(9): 1087–102.
[182] Jacob E. Evolution and thinking. Science 1977;196(4295):1161–6.
[183] Renfrew C. Neuroscience, evolution and the sapiens paradox: the faculty of value and of the sacred. Philos Trans Roy Soc London B Biol Sci 2008(February 21).
[184] Dimijian GG. The moral ape. Nature 1997;385(6611):12.
[185] Darlington Jr PJ. Group selection, altruism, reinforcement and throwing in human evolution. Proc Natl Acad Sci USA 1975;72(9):3748–52.
[186] Böcher W. Human behaviour between instinct, feelings and responsibility. Blutalkohol 1994;31(6):356–66.
[187] Crow TJ. A theory of the evolutionary origins of psychoses. Eur Neuropsychol 1995;5(Suppl):59–63.
[188] Randall PL. Schizophrenia as a consequence of brain evolution. Schizophr Res 1998;30(2):143–8.
[189] Brüne M. Social cognition and psychopathology in evolutionary perspective. Current status and proposed research. Psychopathology 2001;34(2):85–94.
[190] Brüne M. Schyzophrenia-an evolutionay enigma. Neurosci Biobehav Rev 2004;28(1):41–53.
[191] Brüne M, Brüne-Cohrs U. Theory of mind-evolution, brain mechanisms and psychopathology. Neurosci Biobehav Rev 2006;30(4):437–55.
[192] Burns JK. An evolutionary theory of schizophrenia: cortical connectivity, metarepresentation ad the social brain. Behav Brain Sci 2004;27(6):831–85.
[193] Yunes RA. The evolution of human mind and logic-mathematic structures. J Theor Biol 2005;236(1):95–110.
[194] Rose SP. The biology of the future and the future of biology. J Mol Biol 2002;319(4):877–84.
[195] Suddendorf T. Behavior. Foresight and evolution of human mind. Science 2006;312(5776):1006–7.
[196] Stern R, Woods CG. Evolutionary genetics: is brain evolution still continuing modern humans? Eur J Hum Genet 2006;14(7):799–800.
[197] Balter M. Evolution. Are human brain still evolving? Brain genes show signs of selection. Science 2005;309(5741): 1662–3.
[198] Balter M. AAS annual meeting. How human intelligence evolved-is it science or ''paloefantasy''. Science 2008;319(5866):1028.
[199] Niven JE. Brain evolution: getting better all the time? Curr Biol 2005;15(16):R264–6.
[200] Kleitman N. Phylogenetic, ontogenetic, and environmental determinant in the evolution of sleep-wakefulness cylces. Res Publ Assoc Res Nerv Ment Dis 1967;45: 30–8.
[201] Siegel M. Phylogeny and the function of REM sleep. Behav Brain Res 1995;69(1–2):29–34.
[202] Korth C. A co-evolutionary theory of sleep. Med Hypotheses 1995;45(3):304–10.
[203] Lee Kavanau J. Evolutionary approaches to understanding sleep. Sleep Med Rev 2005;9(2):141–52.
[204] Kavanau Jl. Sleep researchers need to bring Darwin on board: elucidating functions of sleep via adaptedness and natural selection. Med Hypotheses 2004;62(2):161–5.
[205] Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. Neurology 1993;43:268–79.
[206] Black B. Genes, brain and mind: the evolution of cognition. Neuron 1998;20(6):1073–80.
[207] Normile D. Comparative genomics. Gene expression differs in human and chimp brains. Science 2001;292(5514): 44–5.
[208] Pennisi E. Mining the molecules that made our mind. Science 2006;313(5795):1908–11.
[209] Evans PD, Gilbert SL, Mekel-Bobrov N, et al. Microcephalin, a gene regulating brain size, continues to evolve adapatively in humans. Science 2005;309(5741): 1717–20.
[210] Caceres M, Lachuer J, Zapala A, et al. Elevated gene expression levels distinguish human from non human primate brains. PNAS 2003;100(22):13030–5.
[211] Gu J, Gu X. Induced gene expression in human brain after the split from chimpanzee. Trends Genet 2003;19(2): 63–5.
[212] Evans PD, Anderson JR, Vallender EJ, et al. Adaptative evolution of ASPM, a major determinant of cerebral cortical size in humans. Hum Mol Genet 2004;13(5): 489–94.
[213] Khaitovich P, Hellmann I, Enmard W, et al. Parallel evolution in the genomes and transcriptomes of humans and chimpanzees. Science 2005;309(5742):1850–4.
[214] Mareus-Bonet T, Caceres M, Bertranpetit J, et al. Chromosomal rearrangements and the genomic distribution of gene expression divergence in humans and chimpanzee. Trends Genet 2004;20(11):524–9.
[215] Uddin M, Wildman DE, Liu G, et al. Sister grouping of chimpanzee and humans as revealed by genome-wide phylogenetic analysis of brain gene expression profiles. PNAS 2004;101(9):2957–62.
[216] Culotta E. What genetic changes made us uniquely human? Science 2005;309(5731):91.
[217] Gilbert SL, Dobyns WB, Lahn BT. Genetic links between brain development and brain evolution. Nat Rev Genet 2005;6(7):581–90.
[218] Nielsen R, Bustamante C, Clarke AG, et al. A scan for positively selected genes in the genomes of humans and chimpanzees. PloS Biol 2005;3(6):e170.
[219] Oldham MC, Horvath S, Geschwind DH. Conservation and evolution of gene coexpression networks in human and chimpanzee brain. PNAS 2006;103(47):17973–9978.

[220] Sereno MI, Tootell RB. From monkeys to humans: what do we know about brain homologies? Curr Opin Neurobiol 2005;15(2):135–44.
[221] Tannahill D, Harris LW, Keynes R. Role of morphogenes in brain growth. J Neurobiol 2005;64(4):367–75.
[222] Smith K. Homing in on genes for humanity. Nature 2006;442(7104):725.
[223] Ponting CP, Lunter G. Evolutionary biology: human brain gene wins genome race. Nature 2006;443(7198):149–50.
[224] Bakewell MA, Shi P, Zhang J. More genes underwent positive selection in chimpanzee evolution than in human evolution. PNAS 2007;104(18):7489–94.
[225] Hahn MW, Demuth JP, Han SG. Accelerated rate of gene gain and loss in primates. Genetics 2007;177(3):1941–9.
[226] Haygood R, Fedrigo O, Hanson B, Yokoyama KD, Wray GA. Promoter regions of many neural- and nutrition-related genes have experienced positive selection during human evolution. Nat genet 2007;39(9):1140–4.
[227] Pollard KS, Salama SR, Lambert N, et al. An RNA gene expressed during cortical development evolved rapidly in humans. Nature 2006;443(7108):167–72.
[228] Shi P, Bakewell MA, Zhang J. Do brain-specific genes evolve faster in humans than in chimpanzee? Trends Genet 2006;22(11):608–13.
[229] Heissig F, Krause J, Bryk J, Khaitovitch P, Enard W, Pääbo S. Functional analysis of human and chimpanzee promoters. Genome Biol 2005;6(7):R57.
[230] Andres AM, Soldevila M, Lao O, et al. Comparative genetic of functional trinucleoride tandem repeats in humans and apes. J Mol Evol 2004;59:329–39.
[231] Aboitiz F. Epigenesis and the evolution of the human brain. Med Hypotheses 1988;25(1):55–9.
[232] Cohen J. Evolutionary biology. Relative differences: the myth of 1%. Science 2007;316(5833):1836.
[233] Check E. Mix and match: the hunt fort what makes us human. Nature 2006;443(7017):8–9.
[234] Balter M. Human evolution. Why we're different: probing the gap between apes and humans. Science 2008;319:404–5.
[235] Tobias PV. The anatomy of hominization. Prog Clin Biol Res 1981;59B:101–10.
[236] Stankiewicz P, Shaw CJ, Whiters M, et al. Serial segmental duplications during primate evolution result in complex human genome architecture. Genome Res 2004;14(11):2209–20.
[237] Vargha-Khadem F, Gadian DG, Copp A, Mishkin M. FOXP2 and the neuroanatomy of speech and language. Nat Rev Neurosci 2005;6:131–8.
[238] Feuk L, Laervo A, Lipsanen-Nyman M, Skaug J, Nakabayashi K, et al. Absence of paternally inherited FOXP2 gene in developmental verbal dyspraxia. Am J Hum Genet 2006;79:965–72.
[239] Corballis MC. FOXP2 and the mirror system. Trends Cogn Sci 2004;8(3):95–6.
[240] Williams NA, Close JP, Giouzeli M, et al. Accelerated evolution of protocadherin 11X/Y: a candidate gene-pair for cerebral asymmetry in language. Am J Med Genet B Neuropsychiatry Genet 2006;141(6):623–33.
[241] Lai CSL, Fisher SE, Hurst JA, et al. The SPCH1 region on human 7q31 : genomic characterization of the critical interval and localization of translocations associated with speech and language disorder. Am J Hum Genet 2000;67:357–68.
[242] Royer B, Soares DC, Barlow PN, et al. Molecular evolution of the human SRPX2 genet that causes brain disorders of the Rolandic and Sylvian speech areas. BMC Gene 2007:72.
[243] Kim HS, Wadekar RV, Tanenaka O, et al. SINE-R C2 (a homo sapiens specific retroposon) is homologous to cDNA from post-mortem brain in schizophrenia and to two loci in the Xq21.3/Yp block linked to handedness and psychosis. Am J Med Genet 1999;88(5):560–6.
[244] Parrott Amathews MB. Novel rapidly evolving hominid RNAs binds nuclear factor 90 and display tissue-restricted distribution. Nuclei Acids Res 2007;35(18):6249–58.
[245] Fraser HB, Khaitovitch P, Plotkin JB, Pääbo S, Eisen MB. Aging and gene expression in the primate brain. PLos Biol 2005;3(9):e274.
[246] Gearing M, Triggs J, Mori H, Mirra SS. Abeta 40 is a major form of beta-amyloid in nonhuman primates. Neurobiol Aging 1996;17(6):903–8.
[247] Holtzer M, Craxton M, Jakes R, et al. Tau gene (MAPT) sequence variation among primates. Gene 2004;341:313–22.
[248] Passingham RE, Ettlinger G. A comparison of cortical function in man and the other primates. Int Rev Neurobiol 1974;16:233–99.
[249] Karten HJ. Homology and evolutionary origins of the neocortex. Brain Behav Evol 1991;38(4–5):264–72.
[250] Rakic P. Radial unit hypothesis of neocortical expansion. Novartis Found Symp 2000;228:30–42.
[251] Anderson ML. Evolution of cognitive function via redeployment of brain areas. Neuroscientist 2007;13(1): 13–21.
[252] Toro R, Perron M, Pike B, Richer L, Veillette S, Pausanova Z, et al. Brain size and folding of the human cerebral cortex. Cereb Cortex; 10 February 2008 [Epub].
[253] Toro R, Burnod Y. A morphogenetic model for the development of cortical convolutions. Cereb Cortex 2005;15(12):1900–13.
[254] Schenker NM, Desgouttes AM, Semendeferi K. Neural connectivity and cortical substrates of cognition in hominoids. J Hum Evol 2005;49(5):547–69.
[255] Neill D. Cortical evolution of human behaviour. Brain Res Bull 2007;74(4):191–205.
[256] Hayakawa T, Angata T, Lewis Al, et al. A human specific gene in microglia. Science 2005;309(5741):1693.
[257] Sherwood CC, Stimpson CD, Raghanti MA, et al. Evolution of increased glia-neuron ratios in the human frontal cortex. PNAS 2006;103(37):13606–11.
[258] Oberheim NA, Wang X, Goldman S, Nedergaard M. Astrocytic complexity distinguishes the human brain. Trends Neurosci 2006;29(10):547–53.
[259] Mesulam M. Brain mind and the evolution of connectivity. Brain Cogn 2000;42(1):4–6.
[260] Innocenti GM. Exuberant development of connections and its possible permissive role in cortical evolution. Trands Neurosci 1995;18(9):397–402.
[261] Buffill E, Blesa R. Alzheimer's disease and brain evolution: is Alzheimer's disease an example of antagonistic pleiotropy? Rev Neurol 2006;42(1):25–33.
[262] Vernier P, Moret F, Callier S, et al. The degeneration of dopamine neurons in Parkinson's disease: insights from embryology and evolution of the mesostraitocortical system. Ann NY Acad Sci 2004;1035:231–49.
[263] Skoyles JR. Human balance, the evolution of bipedalism and disequilibrium syndrome. Med Hypotheses 2006;66(6): 1060–8.
[264] Tyrell PJ. Apraxia of gait or higher level gait disorders review and description of two cases of progressive gait disturbance due to frontal lobe degeneration. J R Soc Med 1994;87(8):454–6.
[265] Tan U. Evidence for ''Uner Tan syndrome'' as a human model for reverse evolution. Int J Neurosci 2006;116(12): 1539–47.

[266] Béland R, Ska B. Interaction between verbal and gestural language in progressive aphasia: a longitudinal case study. Brain Lang 1992;43(3):355—85.
[267] Verghese J, Lipton RB, Hall CB, Kuslansky G, Katz MJ, Buscke H. Abnormality of gait as a predictor on non-Alzheimer dementia. NEJM 2002;347:1761—8.
[268] Takei A, Fukazawa T, Hamada T, Tashiro K, Cjin S. Progressive supranuclear palsy with macular degeneration: report of three cases. Rinsho Shinkeigaku 1997;37(5): 397—401.
[269] Seely S. The evolution of human longevity. Med Hypotheses 1980;9:873—82.
[270] Cutler RG. Evolution of human longevity: a critical overview. Mech Ageing Dev 1979;9(3—4):337—54.
[271] Arendt T. Alzheimer's disease as a loss of differentiation control in a subset of neurons that retain immature features in the adult brain. Neurobiol Aging 2000;21(6): 783—96.
[272] Schiehorn H. Structural change in neocortical pyramidal neurons in man in the 5th to the 9th decade. Psychiatr Neurol Med Psychol 1981;33(11):664—73.
[273] Kawamura H, Mori S, Murano S, Yokote K, Tamura K, Saito Y. Werner's syndrome associated with progressive subcortical vascular encephlaopathy of the Binswanger type. Nippon Ronen Igakkai Zasshi 1999;36(9): 648—51.
[274] Kovach MJ, Waggoner B, Leal SM, et al. Clinical delineation and localization to chromosome 9p13.3—p12 of a unique dominant disorder in four families: hereditary inclusion body myopathy, Paget disease of bone, and frontotemporal dementia. Mol Genet Metab 2001;74(4): 458—75.