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The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue

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Dopamine is an inhibitory neurotransmitter involved in the pathology of schizophrenia. The revised dopamine hypothesis states that dopamine abnormalities in the mesolimbic and prefrontal brain regions exist in schizophrenia. However, recent research has indicated that glutamate, GABA, acetylcholine, and serotonin alterations are also involved in the pathology of schizophrenia. This review provides an in-depth analysis of dopamine in animal models of schizophrenia and also focuses on dopamine and cognition. Furthermore, this review provides not only an overview of dopamine receptors and the antipsychotic effects of treatments targeting them but also an outline of dopamine and its interaction with other neurochemical models of schizophrenia. The roles of dopamine in the evolution of the human brain and human mental abilities, which are affected in schizophrenia patients, are also discussed.

Keywords: dopamine, schizophrenia, cognition, glutamate, dopamine receptors, cannabis, animal models of schizophrenia, evolution of the human brain

BRIEF HISTORY OF DOPAMINE HYPOTHESIS IN SCHIZOPHRENIA

Dopamine, adrenaline, and noradrenaline are neurotransmitters that belong to the catecholamine family. Dopamine is produced in the substantia nigra and ventral tegmental regions of the brain, and dopamine alterations are related to schizophrenia (1, 2). Dopaminergic projections are divided into the nigrostriatal, mesolimbic, and mesocortical systems. Impairments in the dopamine system result from dopamine dysfunctions in the substantia nigra, ventral tegmental region, striatum, prefrontal cortex, and hippocampus (3–5). The "original dopamine hypothesis" states that hyperactive dopamine transmission results in schizophrenic symptoms. This hypothesis was formed upon the discovery of dopamine as a neurotransmitter in the brain by Arvid Carlsson (6–12). Dopamine receptor blockade by chlorpromazine and haloperidol, proposed in 1963 by Arvid Carlsson and Margit Lindqvist, was a cornerstone in psychiatry (13). However, the association between schizophrenic symptoms and dopamine over-activity has already been questioned (14). The positive symptoms of schizophrenia include hallucinations and delusions as a result of increased subcortical release of dopamine, which augments D_2 receptor activation (15), and are thought to be due to a disturbed cortical pathway through the nucleus accumbens (16). The negative symptoms of schizophrenia include anhedonia, lack of motivation, and poverty of speech, which result from reduced D_1 receptor activation (15) in the prefrontal cortex and decreased activity of the nucleus caudatus (16). Alterations in D (3)-receptors might also be involved in the negative symptoms of schizophrenia (17). Furthermore, dopaminergic and serotonergic deviations are known to contribute significantly to both the positive and negative symptoms of schizophrenia [review by Davis et al. (18); Castner and Goldman-Rakic (19); Carlsson et al. (20)].

The "revised dopamine hypothesis" proposes hyperactive dopamine transmission in the mesolimbic areas and hypoactive dopamine transmission in the prefrontal cortex in schizophrenia patients (21–23). In addition to the mesolimbic brain areas, dopamine dysregulation is also observed in brain regions including the amygdala and prefrontal cortex, which are important

Abbreviations: AMPA, (S)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)-propionic acid; COMT, catechol-*O*-methyltransferase; CNS, central nervous system; D (1), dopamine D_1 receptor; D (2), dopamine D_2 receptor; D (3), dopamine D_3 receptor; DAT, dopamine transporter; DAOA or G72, D-amino acid oxidase activator; DLPFC, dorsolateral prefrontal cortex; GABA, γ-aminobutyric acid; H-COMT, high-activity catechol-*O*-methyltransferase; L-COMT, low-activity catechol-*O*-methyltransferase; Met, methionine; mRNA, messenger ribonucleic acid; NMDA-receptor, *N*-methyl-D-aspartate receptor; PET, positron emission tomography; PPI, prepulse inhibition; RNA, ribonucleic acid; SR, startle reflex; Val, valine.

for emotional processing (24). PET-studies (positron emission tomography) have identified differences in dopamine contents in the prefrontal cortex, cingulate cortex, and hippocampus between schizophrenia patients and neuropsychiatric healthy control subjects (25). In particular, the dopamine system in the hippocampus is overactive in schizophrenia patients [review by Grace (26)].

RECENT ANIMAL MODELS IMPLICATING DOPAMINE IN SCHIZOPHRENIA

The prepulse inhibition (PPI) of the acoustic SR (ASR) is a neurophysiologic measurement of sensorimotor gating and a marker for information-processing deficits in neuropsychiatric disorders such as schizophrenia (27–30). PPI refers to a reduced startle response to a strong sensory stimulus when the stimulus is preceded by a barely detectable stimulus (i.e., the prepulse). PPI is similar in human and experimental animal models. Deficits in PPI can be produced in rodents by administering psychotomimetics such as dopaminergic and serotonergic agonists and glutamatergic antagonists (31–34). Furthermore, dopaminergic stabilizers have been shown to restore social behavior in a rat model of schizophrenia (35), and regulatory feedback loops exist among serotonergic, GABAergic, and dopaminergic neurotransmitters (36). For example, interactions between accumbal dopamine and various non-dopamine receptors, such as *N*-methyl-D-aspartate (NMDA)-, AMPA-, GABA (A)-, and nicotinic-receptors were reported in a rodent model of schizophrenia (37). NMDA- and D (1)-receptors in the nucleus accumbens interact with other, and this interaction is controlled by PPI (38). GABA is also involved in the pathophysiology of PPI. Pregnenolone, a neurosteroid in the central nervous system (CNS), works by improving cognitive deficits through GABA, and pregnenolone improves PPI deficits in dopamine transporter knockout mice (39). Activation of GABA-receptors in the rat brain results in various receptor interactions with glutamate (40, 41), and modulation of GABA (A) a5 receptors improves cognitive deficits in rats (42). In a rat model of schizophrenia, the increase in dopamine is caused by hyperactivity of the ventral hippocampus (43). Changes in dopamine receptors (D-2) caused by antipsychotic drugs, such as quinpirole, have been demonstrated in a validated rodent model of schizophrenia (44, 45). However, recent work by Bay-Richter et al. (46) indicates that antipsychotic drugs, such as AMP, clozapine, and haloperidol, cause behavioral changes independent of D (2)-receptors in a mouse model. An up-regulation of D2-high receptors is a consistent feature in animal models of schizophrenia (47). However, alterations in D (3) dopamine receptors caused by novel antipsychotic drugs, such as cariprazine, decrease cognitive deficits in knockout mice (48). Therefore, D (3)-receptor antagonists are recommended as a new pharmacological strategy to improve cognitive function in schizophrenia [review by Nakajima et al. (49)]. Social isolation rearing in rats, which is a valid neurodevelopmental model of schizophrenia, reduces dopamine levels in the frontal cortex (50).

COGNITION IN SCHIZOPHRENIA

Cognitive deficits in schizophrenia affect working memory, language and executive function, episodic memory, processing speed, attention inhibition, and sensory processing (51). The prefrontal region is affected in cognitive discrepancies connected with working memory [see the systematic review by Smieskova et al. (52)], which consists of visual, verbal, central executive, episodic components, and working memory disturbances in schizophrenia are primarily due to altered dorsolateral prefrontal cortex (DLPFC) function (51). Episodic memory discrepancies in schizophrenia involve the medial temporal cortex, particularly the hippocampus, and the prefrontal cortex, particularly the ventral and dorsolateral prefrontal regions (51). Additionally, auditory processing involving memory procedures is impaired in the working memory of schizophrenia patients (53). Cognitive deficits correlate with a decline in dopamine in the prefrontal cortex, primarily at the level of D (1)-receptors (54–59) but also due an imbalance of D (1) and D (2)-receptors in the prefrontal cortex [review by Durstewitz and Seamans (60); Takahashi (61)]. Several studies have proposed that an inverted U-shaped relation between working memory and activation of the prefrontal cortex exists in schizophrenia patients (62). There is ongoing discussion regarding the involvement of D (1)- and D (2)-receptors in cognition in schizophrenia patients (63–66). Cognitive discrepancies and working memory deficits in the prefrontal cortex are associated with an increase in dopamine and D (1)-receptors in the prefrontal cortex in schizophrenia patients (67, 68). Atypical antipsychotics such as clozapine block D (2)-receptors in the striatum and 5-HT_{1A}-receptors in the prefrontal cortex, which results in increased dopamine activity (69, 70). By blocking D (2)-receptors through antipsychotics, the apoptotic mechanisms in the brain regions involved in cognition are impaired (71). The disturbed activity of working memory in the DLPFC in schizophrenia patients is influenced by the release of dopamine in the midbrain in schizophrenia patients, which is regulated by a deficit in glutamatergic projection from the DLPFC to midbrain dopamine neurons (72). Extrastriatal dopamine transmission is necessary for attention and working memory, and these deficits in the fronto–striato–thalamic pathway are involved in cognition in schizophrenia (73). Newer antipsychotic drugs such as olanzapine and clozapine, which have a better affinity for dopamine receptors and blocking 5-HT_{2A} receptors, decrease the hyperactivity of the mesolimbic dopaminergic pathway and improve the activity of D (1)-receptors in the prefrontal cortex (74). Furthermore, nicotine improves cognition in schizophrenia patients (75).

The COMT-Val-allele leads to a deficit in cognitive abilities. Interactions between dopaminergic and methylation mechanisms may result in cognitive deficits in schizophrenia patients. The COMT Met-allele results in lower COMT-activity, leading to greater production of dopamine and increased D (1)-receptor activity in the prefrontal cortex and, subsequently, better cognitive abilities in carriers of the Met-allele (76–82). A link between Met-carriers and smoking has been recently reviewed (83), and an association between COMT and cognitive dysfunction in bipolar disorder has also been discussed (84). The COMT-alleles are composed of two different alleles that result in varied activity levels: the low-activity COMT-allele (L-COMT) and the high-activity COMT-allele (H-COMT) (85). The L-COMT allele has the Met-/Met-genotype, and the H-COMT allele has the Val-/Val-genotype (86). Middle-aged healthy women with H-COMT who carry the

Val158 allele show better cognitive abilities, including executive processing and cognitive flexibility, than carriers of the Met allele (87).

DOPAMINE RECEPTORS AND ANTIPSYCHOTIC EFFECTS IN SCHIZOPHRENIA

Dopamine receptors are G-protein-coupled receptors and can be divided into D (1), D (2), D (3), and D (4)-receptors (88). D (1) receptors in the prefrontal cortex are decreased in schizophrenia patients and are unaffected by chronic treatment of typical neuroleptics [review by Friedmann et al. (89)]. In contrast, D (1)-receptors are increased in the parieto-temporal cortex in schizophrenia patients (90). Increased D2 mRNA has been found in the frontal cortex in schizophrenia patients when compared with neuropsychiatric healthy control subjects (91). Both the classic and -current antipsychotic drugs act primarily by increasing high-affinity D (2)-receptor expression (92–98). Haloperidol has been shown to increase high-affinity D (2)-receptors in dopamine-sensitive rats in an animal of schizophrenia (99). Dopamine agonists bind to D (2)-high and D (2)-low-receptors (93, 100). This D (2) two-state model is still controversial, although discussions tend to doubt its validity, as demonstrated by *in vitro* binding experiments (101). The action of dopamine agonists is related to dopamine hyperactivity in psychosis (102). Dopamine antagonists and, to a lesser extent, dopamine agonists increase the D (2)-high-receptors (103). This increase in D (2)-high-receptors is a necessary basic requirement for the development of a psychosis that correlates with dopamine supersensitivity (104). This specific increase in D (2)-receptors and dopamine supersensitivity might result in antipsychotic treatment failure (105, 106). Although D (2)-receptor antagonists induce dopamine activity (107), the mechanisms underlying the action of dopamine D (2)-receptor antagonists are not entirely clear. The low therapeutic advantage of dopamine D (2)-receptor antagonists and their high pharmacological selectivity require future research (108). Antipsychotic drugs block D (2) receptors and increase the release of glutamate in the striatum (109), particularly on the right side of the striatum, which is a brain region involved in cognition and reward motivation (110). Glutamate agonists have an effect on D (2) high-receptors in schizophrenia (111, 112). For example, alterations in D (2)-receptor function caused by antipsychotic medication in a rodent model of schizophrenia (44) or by the application of an amphetamine in schizophrenia patients (113) have been recently demonstrated. A D (2)-receptor occupancy of 80% is considered essential for the positive effects of antipsychotic medication (114, 115), whereas continuous high D (2)-receptor occupancy is not required [review by Kapur and Seeman (116); Remington and Kapur (117), systematic review by Uchida et al. (118); Seeman (119)]. The atypical antipsychotic clozapine results in a lower D (2) receptor occupancy than 80% but still has positive effects [review by Nord and Farde (120)]. Schizophrenia patients with extrapyramidal syndromes (EPSs) show an increased D (2)-receptor occupancy (above 80%) in comparison with schizophrenia patients with a good clinical response and no EPSs (i.e., receptor occupancy of 65–80%) [review by Nord and Farde (120)]. Lower doses of antipsychotics such as risperidone are effective and do not induce EPSs (121, 122). This specific D (2)-receptor occupancy in the striatum in schizophrenia patients interacts with the antagonistic effects of 5-HT_{2A} receptors [review by Pani et al. (123)]. D (1)-receptors and NMDA-receptors cooperate with each other (124). Furthermore, the intensification of D (2)-receptor antagonists by D (1)-receptor agonists results in better NMDA transmission, exemplified by the action of clozapine as a partial D (1)-receptor agonist (109). NMDA and D (1) dopamine receptor interaction occurs through signal transduction and phosphorylation and dephosphorylation mechanisms (125). D (1)-receptors are present in GABAergic interneurons (54). For example, valproic acid affects GABA and, subsequently, dopamine (126).

A slightly increased density of D (2)-receptors in basal condition and a significant increase in D (2)-receptors in the striatum of schizophrenia patients has been found (127). This increase of striatal dopamine D (2)-receptors in schizophrenia has also been demonstrated in neuroimaging and molecular imaging studies (128, 129). Specific neurotransmitter pathways such as those of glutamate, GABA, and acetylcholine lead to a high-affinity of the D (2)-receptor (130). Dopamine receptors such as the D (2)-receptor contain receptor mosaics (i.e., RM; dimeric or high-order receptor oligomers). These D_2/NMDA receptor mosaics have also been found in the ventral striato-pallidal GABA neurons. Decreased D (2)-receptors in the thalamus and anterior cingulate cortex in schizophrenia might suggest that they are involved in abnormalities in dopamine transmission from the thalamus to the prefrontal cortex (131).

Low doses of D (2)-receptor antagonists and signaling enhancers of NMDA-receptors are recommended as new treatments in schizophrenia [review by Fuxe et al. (132)]. In the associative striatum, an increased D (2)-receptor availability has been found in schizophrenia patients (127). Increased dopamine release in the striatum is linked to substance dependence, such as amphetamine dependency, in schizophrenia (133). For example, stimulation of NMDA/AMPA and kainate receptors by direct application of glutamate or glutamate agonists increases the dopaminergic cell-firing rate (133). However, the role of dopamine in the dysfunction of the striatum in schizophrenia patients requires future research (134).

It can be summarized that, to date, the mechanism of every effective antipsychotic medication in schizophrenia involves dopamine and its interaction with other neurochemical pathways such as those of glutamate, GABA, serotonin, and acetylcholine.

ALTERNATE NEUROCHEMICAL MODELS IN SCHIZOPHRENIA AND THEIR INTERACTIONS WITH DOPAMINE

Deviations in dopamine and glutamate have been reported in the prefrontal cortex of schizophrenia patients (135). NMDA-receptors are involved in releasing dopamine into the striatum and frontal cortex in schizophrenia patients [Ref. (136, 137), review by Castner and Williams (138); Javitt (139); Balla et al. (140); Laruelle (141)] and in rats in an animal model of schizophrenia (142). These interactions are accompanied by calcium-dependent changes (143) and exchanges between DAT and G72 in various brain regions (144). In contrast to dopamine receptors, glutamate receptors are found in the subcortical and cortical brain regions

(145). The activity of dopamine is regulated by GABA and glutamate. For example, corticostriatal glutamatergic pathways interact with dopamine terminals (146, 147), and specific glutamate receptors in the striatum, such as mGlu2, are sensitive to dopamine (112). High glutamate levels have been found in the dorsal caudate nucleus of schizophrenia patients (148). Adenosine interacts with glutamate, NMDA-receptors, and dopamine [review by Burnstock et al. (149)]. It can be summarized that NMDA-receptors and D (1)-receptors in cortical brain areas such as the prefrontal cortex and an excess of D (2)-receptors in subcortical brain areas such as the striatum are interconnected with each other through a positive feedback mechanism (150). However, through its presynaptic action, dopamine reduces the release of glutamate in the pyramidal neurons of layer V in the prefrontal cortex (151). Dopamine dysregulation in the basal ganglia of schizophrenia patients is an important intrinsic feature in the pathology of schizophrenia and not a medication side effect [review by Perez-Costas et al. (3)].

The finding by Brisch et al. (152) that astrocyte density is increased in the frontal cortex in schizophrenia suggests a disturbance in the dopamine–glutamate function. Furthermore, Sokoloff et al. (153) demonstrated that D (3)-receptors either act directly on NMDA-receptors at glutamate synapses on the terminals of pyramidal cells in the nucleus accumbens or act indirectly through dopamine at the presynaptic junction to regulate pyramidal cells in the prefrontal cortex. Indeed, injection of NMDA-antagonists such as MK801 increases glutamate concentration in the frontal, retrosplenial, and cingulate cortices (154). Glutamate dysfunction in the prefrontal cortex and hippocampus causes the release of dopamine in the striatum (155). A new focus on glutamatergic signaling mediated by NMDA and metabotropic receptors may benefit new drug developments [review by Field et al. (156); Javitt (139); Matosin and Newell (157); Moghadam and Krystal (158); Noetzel et al. (159)]. The review by Bernstein et al. (160) attributes the disturbed function of astrocytes in schizophrenia to diminished glutamate metabolism. The enzyme glutamine synthetase, which degrades glutamate into glutamine, is located in glial cells and is decreased in schizophrenia patients (161). Additionally, the glutamate transporter for astrocytes, GLT-1, is increased in schizophrenia patients (162). Although Arai et al. (163) reported no association between glutamine synthetase and schizophrenia, the enzyme glutamine synthetase displays gender-specific differences in schizophrenia (164) and is involved in suicidal behavior (165, 166). Moreover, the atypical antipsychotic agent risperidone increases glutamine synthetase levels (167).

Through NMDA-stimulated GABA-release and $GABA_B$-receptor activity, glycine reduces the release of dopamine by modulating DAT-type transporters in the prefrontal cortex and striatum (168). The $GABA_B$-receptor inhibits the release of glutamate in the ventral tegmental area (169). A synergistic interaction of adenosine and glutamate affecting the ventral striato-pallidal GABA pathway has been demonstrated in a rat model (170). The interactions of pyramidal neurons with dopamine receptors on their dendrites and pyramidal cells with glutamate on their spines, and GABAergic interneurons in the prefrontal cortex in schizophrenia patients might offer new insights into receptor-targeted therapies [Ref. (53); review by Wassef et al. (171); Lisman et al. (172)]. An increased number of GABA-cells expressing D (1)-receptors exists in the rat prefrontal cortex (173). In the nucleus accumbens, neurotensin (NT) inhibits dopamine discharge, which increases glutamate release and activates the ventral striato-pallidal GABA pathway, leading to a subsequent increase in glutamate transport from the mediodorsal thalamus to the prefrontal cortex (174). Another interaction between dopamine in the prefrontal cortex and glutamate in the mediodorsal thalamus might be responsible for the effects of zotepine, which increases the extracellular levels of noradrenaline, dopamine, glutamate, and GABA (175). GABA interacts with acetylcholine by constraining its excitatory contribution to cholinergic interneurons, which are decreased in the striatum of schizophrenia patients, resulting in prefrontal deviations in schizophrenia (176). Dopamine also interacts with acetylcholine, which increases with smoking frequency in schizophrenia patients (177). Acute nicotine administration might have positive effects on cognition in schizophrenia patients [Ref. (178, 179), review by Mackowick et al. (180)].

Dopamine neurons in the midbrain release serotonin, which is important during combined drug treatment with serotonin to prevent the so-called serotonin syndrome, a surplus of serotonin in some brain regions (181). Atypical antipsychotics involving serotonin receptors include 5-HT_{1A} receptor agonists or antagonists, 5-HT_{2A} receptor antagonists, 5-HT_{2c} receptor inverse or partial agonists or neutral antagonists, 5-HT_6 receptor antagonists, and 5-HT_7 receptor antagonists (182).

Antipsychotics (such as clozapine and aripiprazole) possessing 5-HT-$_{1A}$ agonist properties induce hippocampal neurogenesis and increase dopamine in the prefrontal cortex [review by Schreiber and Newman-Tancredi (183)]. It can be summarized that various serotonin–dopamine interactions, which include both direct and indirect feedback mechanisms, contribute to the pathology of schizophrenia [Ref. (151, 184–189), review by Arranz and de Leon (190); Alex and Pehek (191); McCreary et al. (192); Bhattacharyya et al. (193); Meltzer et al. (194); McMahon and Cunningham (195); Gao et al. (196)].

Novel antipsychotic drugs, such as asenapine, increase dopamine and glutamate levels in various subcortical and cortical areas (197). New antipsychotic drugs with novel mechanisms induce alterations in both dopamine and glutamate [review by Paz et al. (198); Seeman et al. (99); Stone (199); Leroy et al. (200); Coyle et al. (201)]. For example, metabotropic glutamate and NMDA-receptors are future targets for new drugs (202, 203). A range of dopamine/serotonin, glutamate/serotonin, and acetylcholine/serotonin interactions activate receptors and signaling molecules in response to antipsychotic drugs and have been observed in various brain regions, including the prefrontal cortex and limbic regions, in schizophrenia (20, 98, 176, 182, 194, 204–211). Future drug development should target signaling molecules involved in dopamine, glutamate, and serotonin neurotransmission such as Akt and glycogen synthase kinase-3 (98, 212, 213) as well as the control of presynaptic dopamine synthesis and release (114). Stress in schizophrenia patients causes an increased release of dopamine in the prefrontal cortex, which cannot be counteracted by reduced $GABA_A$ receptor complex activity, as well as dendritic spine loss in the prefrontal cortex (214, 215). When used in schizophrenic patients, cannabis induces hyperdopaminergic

and hypoglutamatergic activities with both positive and negative symptoms (216). In particular, cannabis increases dopamine transmission in the nucleus accumbens, which might cause or aggravate psychoses (217). A high-low activity polymorphism in COMT interacts with adolescent cannabis abuse, increasing the risk for schizophrenia (218). Further, genes such as disrupted-in-schizophrenia-1 (DISC1) play a role in stress pathways and the metabolism of dopamine in schizophrenia [review by Hains and Arnsten (219); Lipina et al. (220)].

DOPAMINE AND HUMAN EVOLUTION

The role of dopamine in human evolution has hitherto received little theoretical attention. It is still unclear to what extent dopaminergic expansion in hominin evolution was due to genetic adaptations or epigenetic factors. Dopamine has expanded throughout primate and hominin evolution and that dopamine is especially concentrated in the prefrontal cortex, which is involved in higher order functioning. The dopaminergic hypothesis contends that climatic changes occurring in sub-Saharan Africa during the Pliocene and Pleistocene periods, which resulted in increases of the Savannah belt expanded hominin locomotory range. It is also speculated that some human groups ventured to the more habitable African southern coast leading to dietary changes (i.e., increasing amounts of fish/shellfish) that aided dopaminergic expansion (221–223). Dopamine increase may have also been linked with a concomitant elevation in thyroid hormone production. Higher T4 found in *Homo* may have represented an early endocrinological difference between humans and other primates (224). In humans, T4 concentration is associated with tyrosine conversion to dopa (a precursor to dopamine); deficiencies of T4 concentrations are linked with various neurological impairments (224).

Recent research suggests that from *Homo erectus* onward, humans became persistence hunters, requiring various morphological and thermo-regulatory modifications (i.e., vascular reactivity to temperature, large body surface area, plantar arch), which provides approximately 20% energy return during running, elastic tendons, short toes, more pronounced *gluteus maximus* muscle, long legs, CNS coordination of metabolic, and cardio-vascular responses to sustained running (225). From *Homo erectus* onward there is an evident increase in stride size, which also optimized ergonomic requirements of bipedalism while diminishing energy requirements. Greater mass of slow twitch muscles would have also assisted long distance locomotion. Long distance locomotion in conjunction with greater hunting activities in ancestral hominins incorporated all aspects of the CNS such as retention and memory recall of large geographic areas, which maximized resource acquisition. The locomotion/behavior interplay, which was mediated by nerve cells and the dopaminergic system may have evolutionary expanded cortical regions and neuro-hormonal organization in ancestral hominins (225).

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