The evolutionary success of Homo sapiens is attributed to the following two factors: the upright body posture (which freed our hands and allowed unconstrained operation of various objects) and intensive development of the frontal lobes, mainly the Broca area of the brain. Underlining the uniqueness of the human brain, we often forget about the fact that the frontal lobes – the most developed part of the brain – are at the same time our greatest weakness, exposed to the action of damaging factors in our evolving environment. Is depression the cost of evolution?

MeSH Keywords: Clonal Evolution • Depression • Frontal Lobe

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Brain diseases belong to the most socially and economically burdening diseases in Europe. Approximately 800 billion euros are spent annually to fight brain diseases [1]. In 2010, 179 million Europeans suffered from the systemic autoinflammatory disease (SAID), while six years earlier, in 2004, there were only 127 million people affected by SAID, an increase in incidence of more than 30% within just six years. Among brain diseases, more than 60% of social and economic costs are generated mainly from depressive disorders and anxiety disorders [2].

According to estimates by the World Health Organization (WHO), 350 million people around the world present with symptoms of depression [3], while depressive disorders constitute nearly 4.3% of the global burden of all diseases [4]. More than half of the people who have undergone an episode of depression will be affected by at least one relapse. After two episodes of the disease, the probability of another episode is as high as 80%. Episodes of depression last more than 24 months in 20% of patients [5]. Another depressive episode will appear within the next two years of discharging from the hospital in almost half of hospitalized patients. It is estimated that some 20% of those affected with diagnosed recurrent depressive disorders experience two depressive stages during their life, and 60% have three or more such episodes (average number: 3 to 4). Every successive episode is associated with a less positive prognosis and, often, a poorer response to pharmacological treatment [6].

The aim of the paper is to present a new approach to the etiology of depression, which combines evolutionary elements with current knowledge regarding the development of depression symptoms.

Frontal lobes – the Achilles heel?

According to Paul MacLean, the human brain is composed of three parts in cooperation with one another. The oldest and the most primitive structure responsible for instinctual behavior and drive is the reptilian brain (the mesencephalon and brainstem). The mammalian brain, with a limbic system (also referred to as the paleomammalian brain), i.e., a structure regulating primary emotions (including aggressive and sexual behavior), is located above the reptilian brain. The uppermost structure of the human brain is the neocortex where mentation takes places. All these structures, closely linked to one another, guarantee effective operation of our brain [7].

The size of the brain hemispheres has gradually increased over successive millennia, accompanied by concurrent growth and development of the cerebral cortex. In humans, the cerebral cortex plays a key role in the development and regulation of the functions and capabilities of human speech, mentation, decision-making, and control of emotions and behavior [8].

The evolutionary success of Homo sapiens is attributed to the following two factors: the upright body posture (which freed our hands and allowed unconstrained operation of various objects) and intensive development of the frontal lobes, mainly the Broca area of the brain [9], which is responsible for speech production. Being able to speak and developing a language of verbal communication is the foundation for the development of social relations, learning of new skills, and transferring experiences to new generations.

The surface area of the frontal lobes in mammalian species increases, beginning from the so-called smaller species (rats and mice), to cats and dogs, and finally to primates. The frontal lobes constitute nearly 40% of the surface area of the entire cerebral cortex (between 37% and 39%). They are connected with all the remaining areas of the brain [8].

How this spectacular development in the volume of the frontal lobes evolved continues to be discussed. The relative widening of the frontal lobes during hominid phylogeny was likely a consequence of a discrete morphological change rather than a passive reflection of increasing brain size. The expansion has been associated with an underlying reorganization of the neuronal cytoarchitecture or at least with a geometric reallocation of frontal cortical volumes [10].

Underlining the uniqueness of the human brain, we often forget about the fact that the frontal lobes – the most developed part of the brain – are at the same time our greatest weakness, exposed to the action of damaging environmental factors. Although the volume of the whole neocortex increases with brain size more rapidly than does the volume of the cerebellum [11], neuron density declines faster in the neocortex [8,12].

The frontal lobes are considered the motivational and conceptual control stations of human activity. This area of the brain, which is involved in cognitive appraisal, decision-making, and subjective experience of emotions [13], seems to be the foundation of any kind of human action. However, social and cultural experiences over the last several decades clearly highlight the imperfections of the human brain. Does the evolution of the frontal lobes keep up with the technological evolution? Are the increasingly more common symptoms of mood disorders the price we have to pay for our well-being? It seems that our brains have not developed any effective mechanism to protect the valuable frontal lobes against destruction caused by everyday stress factors. A network of mutual neural connections between the frontal lobes and the hippocampal formation seems to be one of the brain’s “weak points” [14].
Figure 1 presents the mental activities in which the frontal lobes are involved functionally, together with the possible consequences of their damage.

Anatomical Structures Involved in the Etiology of Depression

The frontal lobes versus depressive disorders

Mood disorders are linked with numerous dysfunctions of connections between the medial prefrontal cortex and the remaining parts of the brain, mainly the parts that are associated with the interpretation of emotional stimuli (the amygdala, insula, central striatum, thalamic, and basal forebrain structures) [14,16].

A negative emotional attitude, typical for patients with symptoms of depression, is a result of the lack of balance between the “emotional” (limbic/ventral) and the “motivational/regulatory” (frontal/dorsal) regions of the brain [17]. The emotional “brain” of the people affected by depression is overactive in response to negative stimuli, whereas it reacts poorly to the information characterized by a positive emotional charge. The motivational/regulatory brain does not cope with the blocking of unwanted contents [18].

The described dysfunctions seem to be a permanent feature of patients with depression. They are observed also in the period of disease remission and may be responsible for its recurrence [19]. According to Opmeer et al. [20], a decrease in activation in the amygdala, the anterior cingulate cortex (ACC), and the insula during an evaluation of emotional expression in an interaction partner with a decrease in depressive pathology may predict changes in depressive state even at two-year outcome [20]. The presented template of brain’s functional activity is observed not only in adult patients with signs of depression but also in children (reduced activation of the left frontal lobe, mainly in children of depressed mothers) [21] and in adults brought up by women treated due to depression (increased activation in the limbic cortex, and drop of activation in the dorsolateral cortex when extracting recollections from autobiographical memory) [22].

At this point it is necessary to refer to a typical sign of depression such as ruminations, which mean a tendency to dwell long-term on negative emotions and events, together with their meaning and real or predictable consequences [23]. The decisive role in the occurrence of ruminations is attributed to the frontal lobes, mainly the deteriorated ability to block negative recollections. Aker et al. [24] underline that an excessive number of ruminations is a feature that differentiates the people without a history of depression treatment from the people who were previously treated (the mentioned studies were conducted with the participation of people in the period of disease remission).

The hippocampus versus depressive disorders

The hippocampal formation plays a significant role in memory and learning processes as well as in fast and adequate
reactivity to changes of the environment [25]. The main objective of the medial parts of the temporal lobes is integration of a series of information regarding objects and their mutual spatial relationships, which guarantees that our memory is consistent [26]. Together with the amygdala, it is engaged in the recovery of memories characterized by an emotional charge [27].

Abnormalities in the anatomy and function of the hippocampus (volume reduction of the grey matter, disorders in cerebral blood flow) are observed in recurrent depressive disorders (rDD) [28], in patients diagnosed with neurodegenerative diseases, as well as in other mental disorders [29]. The hippocampus is also the part of the brain that is particularly sensitive to oxygen deficiency [30]. Its correct activity is important not only for the proper course of memory processes but also for emotional processes [31].

Similarly as in cases of dysfunctions in the area of the frontal lobes, volume reduction of the hippocampus is observed in patients suffering from depression for many years, and also in young patients. Youth participants with major depressive disorder (MDD) had smaller right hippocampi than controls. The older depressed participants (20.1–25 years) had smaller hippocampal volumes than the younger participants (≤20.1 years). This age effect was not apparent in controls. Depression scores, indexed by Hamilton Depression Rating Scale (HAMD 17), correlated with hippocampal volumes in older depressed youth [32].

**The amygdala versus depressive disorders**

The amygdala is a part of the limbic system, which gives stimuli an emotional meaning, depending on previous experiences (emotional memory), in particular the negative ones. It is also involved in detecting a stressor and assigning a proper meaning to it. In response to incoming stimuli, it activates appropriate behavior patterns and physiological reactions, which enable the brain to make a proper decision [27].

In patients with rDD, increased activation of the amygdala and reduced activity of the frontal lobes are observed in response to negative stimuli [27]. On the other hand, a response of the amygdala to stimuli with a positive emotional charge is inhibited [33]. An inverse relationship can also be observed during the period of disease remission [33]. The right amygdala seems to be involved in automatic and fast detection of stimuli with emotional charges, whereas the left amygdala is responsible for a detailed analysis of such stimuli. According to Drevets [34], an excessive activity of the left amygdala in response to negative stimuli is observed in patients with rDD. The activity of the right amygdala increases with an observed positive reaction to antidepressant treatment [35].

**Brain systems, one or several?**

In recent times, a theory has emerged which indicates the presence of several brain systems engaged in the regulation of emotions and cognitive processing of information. They include: frontoparietal network (FN), default mode network (DMN), dorsal attention network (DAN), and medial temporal lobe network (MTLN) [36,37]. The first of the mentioned systems, FN, is associated with the superior regulation of emotions and attention processes. DMN manages the mental processes directed at the internal world, autobiographical memory, planning of the future, and being aware of the thought perspective of other people. DAN is in charge of directing our attention to the outer world. Meanwhile, MTLN is linked with knowledge acquisition regarding our experiences from the past [36,38]. Other systems include: affective network and ventral attention network (VAN) involved in the processing of emotions and monitoring of salient events [38]. Abnormal communication within FN may underline deficits in cognitive control, which are commonly observed in depression [39]. Certainly, the two structures are engaged in the regulation of mental processes typical for a human being, i.e., thinking, making decisions, mental representation of ourselves, our emotions, and observations regarding ourselves and others [14].

In the functional model of depression, hyperactivity in the limbic area (the amygdala, hippocampus, anterior cingulate cortex) is not sufficiently controlled by the medial cortex of the frontal lobe in response to emotional stimuli of a negative charge [40]. On the other hand, positive stimuli cause excessive inhibition in the frontal cortex [41]. Reduced activity of the amygdala in response to positive information is linked with symptoms of anhedonia [41].

Dysfunctions in the anterior and medial parts of the cingulate cortex, dorsolateral and ventromedial part of the prefrontal cortex, the anterior part of the insular cortex and the amygdala are considered the neurobiological causes of cognitive and emotional symptoms in depression [42,43]. The aforementioned regions are places whose dysfunctions are connected with a weak response to antidepressant treatment [44]. Additionally, a reduction of the grey matter in the prefrontal cortex region (PFC), the anterior cingulate cortex (ACC) [45], the hippocampus and the amygdala [46] is described in patients with rDD. Those changes are particularly visible if the onset of the disease takes place at the age of 21 or earlier [43].

**HPA Axis Versus Depressive Disorders**

Hyperactivity of the HPA axis is by some authors considered an endophenotypic feature of patients with depression, with increased daily secretion of cortisol and altered
dehydroepiandrosterone sulfate (DHEA-S), which remain during remission [47]. Increased negative ruminations, typical for patients in a depression episode, are also accompanied by an increased level of daily release of cortisol [48]. Moreover, the effects of stress on the limbic network structure in depression could reflect chronic HPA axis hyperactivation-induced allostatic load (e.g., reducing hippocampal volumes). The HPA axis is controlled by the limbic system through medial prefrontal connections with the amygdala and the hypothalamus [49]. The theoretical assumptions were confirmed among others in the experiments by Li et al. [50]. Women, who experienced more difficult life events, in the phase of a depression episode, were characterized by hyperactivity in the frontolimbic area in response to negative feedback. Those reports are compatible with the theory of depression etiology, referred to as stress sensitization/the kindling model of depression. Neurobiological changes during depressive episodes lead to increasing interdependence between negative events and depression. Such neurobiological changes can result from chronic cortisol activation, which increases atrophy of certain brain regions such as the prefrontal cortex and the hippocampus, hence affecting the ability of blocking negative emotions [48, 51]. According to LeMoult and Joormann [48], the presence of ruminations in patients with rDD is also linked with the dysregulation of cortisol secretion. In patients with a tendency to dwelling on unpleasant events, the level of cortisol was higher than in a comparative group of healthy people and among people with diagnosed depression who did not mention any ruminations. This dependence is observed even in the period of symptoms remission [52]. Neurotoxicity in the areas of the brain that are connected with the regulation of emotions and emotional memories is a consequence of prolonged secretion of cortisol [51]. These mutual anatomical, physiological, and psychological interrelations are shaped from early childhood [53].

**Inflammatory processes**

Considerations regarding dysregulation of the HPA axis lead straight to the inflammatory theory of depression linked with neurodegenerative processes [54].

**Possible Consequences? How to Connect the Frontal Lobes with the Hippocampus?**

The aforementioned systems are of significance for the occurrence of deficits in the so-called “cold” (attention, memory, executive functions) and “hot” (emotional bias) cognitive impairments, as well as those of social cognition domains (empathy, social cognition, intuition), in patients with depression (Figure 2).

**Cognitive functioning**

Deterioration of cognitive functions in patients with depression symptoms has been the subject of scientific research for many years. Deficits may be selective and mild or generalized and significantly intensified [55]. Typical symptoms include: psychomotor retardation, reduced effectiveness of memory processes, and the ability to learn new information, weakening of attention, deterioration of spatial visualization abilities, and visual-motor coordination, verbal fluency, as well as the so-called executive functions (among others problems with inhibiting reactions, planning and solving problems) [56]. Due to limitations of the space in this article, we only briefly mention this issue. This subject matter was described in detail in another article published by us in 2015 [57].

**Regulation of emotions and social cognition**

Regulation of emotions takes place in three collaborating areas of the brain. The structures of the brainstem are responsible for the most elementary, innate, and unconscious impulsive reactions (excitation versus inhibition, autonomous reactions). The limbic system, including mainly the hippocampus and the amygdala, modifies our emotional reactions depending on the incoming environmental stimuli (unconscious reaction). On the other hand, the prefrontal cortex is responsible for control over emotions and feelings [58].

Social cognition is yet another area that combines cognitive and emotional processes. The very term “social cognition” refers to the abilities of collecting, identifying, and interpreting socially significant stimuli [59], transferred both verbally as
well as non-verbally (emotional expression of the face, emotional prosody, gestures, or words uttered). A dysfunction in this domain is observed among people with diagnosed schizophrenia [60], bipolar affective disease [61], autism-related disorders [62], and in social anxiety disorders (SAD) [63].

In cases of depressive disorders, disadaptation methods of regulating emotions are a prognostic factor for the occurrence of symptoms, have an influence on disease duration, on intensification of symptoms, as well as may increase susceptibility to subsequent episodes [64]. Difficulties in identification, naming, and analyzing the emotional states experienced subjectively and observed in others are observed in patients suffering from depression relapse [65]. According to Levens and Gotlib [66], increased concentration on stimuli characterized by an emotional charge is typical also in the period of disease remission, whereas intensification of deficits in the scope of social cognition is negatively associated with the severity of the disease. It seems that deficits in the scope of “cold” (attention, memory, executive functions) and “hot” (emotional bias) cognitive impairments, as well as those of social cognition domains (empathy, theory of mind), are observed in the course of depressive disorders.

At this point, it is possible to ask a question whether intensive development of the frontal lobes, mainly the Broca’s area, had an impact on the deterioration of the ability to use non-verbal communication, which impaired us to a certain extent. Is using a verbal code the price we need to pay for intuition, empathy, insight into our own emotional states, or depression?

**Autobiographical memory**

The information stored in autobiographical memory concerns ourselves and has a strong impact on our well-being; additionally, it determines to a large extent the types of actions undertaken by us in the future [67]. The executive mechanisms present in autobiographical memory steer not only the operation of this very memory, but also take part in the regulation of emotional processes [68]. We may make attempts to reduce or increase the level of emotional tension by “blocking” specific recollections in our memory [69]. Dysfunctions of autobiographical memory in the patients with recurrent depressive disorders have been an area of interest for scientists in recent times [70].

**Prospective memory**

The issues of prospective memory in patients with symptoms of depression, orientation on the future and emotional prognostication of the future (predicting what may happen in the future and how I will feel then) seem to be an interesting area of further research studies and experiments [71].

**Why women?**

The term sexual dimorphism refers to the differentiation in terms of size or anatomy of male and female specimens of the same species. It is probably a result of varied engagement of every sex in the extension of species [72].

The most significant sex differences in the anatomy of a male and female brain have been observed in the temporal lobes. Women show no significant asymmetry of the temporal gyri, while men demonstrate clear left-hemispheric asymmetry of the medial temporal gyrus and the superior temporal gyrus. These areas are closely linked with the understanding of human speech (this is where the Wernicke area is located) and auditory-verbal memory. Additionally, the inferior areas of the frontal lobes in both hemispheres are activated in the brains of women when performing language tasks. Such a reaction is observed in men only in the left hemisphere. The female brain, due to the size of the corpus callosum combining the two hemispheres, is also more homogeneous in its action as compared to the male brain [73,74].

At this point, we may ask a hypothetical question, whether sexual dimorphism – in connection with the specificity of the functioning of the frontal lobes and the hippocampal formation – is one of the factors responsible for the prevalence of depressive disorders among women [75]. This hypothesis is supported by the previously described theory of depressive ruminations by Susan Nolen-Hoeksema [23]. The author suggests that ruminations should be treated as an element which affects increased spreading of depression symptoms among women compared to men (ruminations are an essential feature for the cognitive style of women). Results of contemporary research studies conform with this theory and indicate an increased activity of the amygdala in women as a response to emotional stimuli [76]. Reports indicating sex differences in the activity of frontal lobes are ambiguous [76,77].

**Short Summary**

Separating emotions from cognition seems an impossible task in a human being’s everyday experiences, similarly to the functional separation of frontal lobes and hippocampal formations. The majority of emotional experiences are linked with cognitive processes, and emotions are an indispensable element of cognition (the so-called principle of cognition compatibility with mood). This principle affects not only memory processes but also includes perception, attention, or linguistic abilities [78,79]. It seems that the so-called “reptilian brain” is in charge of steering our choices, while “rational” frontal lobes are always one step behind. The pace of evolutionary changes does not keep up with the intensity of civilization changes.
Therefore, symptoms of depression may be one of the forms of adaptation to excessively high requirements of the environment. When summing up our deliberations regarding the etiology of depression, can we simply claim that Nature has not finished its work? We will leave this question without an answer.

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Conclusions

In functional terms, frontal lobes are not capable of meeting all civilization requirements of the contemporary world, which may be of key importance in the etiology of depression.
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