

Cognitive dysfunctions in depression – significance, description and treatment prospects

Agnieszka Czerwińska, Tomasz Pawłowski

Wrocław Medical University, Department of Psychiatry,
Division of Psychotherapy and Psychosomatic Medicine

Summary

Cognitive dysfunctions are part of the symptomatology of depressive disorders but they may persist even after the patient reaches symptomatic remission. As persistent symptoms of depression, cognitive dysfunctions may inhibit and restrict the patient's functioning in many spheres and significantly impair its quality. In addition, they increase the risk of somatic diseases and contribute to the increase of benefits disbursed from state aid. Furthermore, it is a factor negatively affecting the prognosis of depressive disorders because it increases the risk of recurrence of depression and reduces the susceptibility to pharmacotherapy. Neural network dysfunctions and changes in morphometry in particular areas of the brain are responsible for the persistence of cognitive deficits after MDD treatment. Most of currently used thymoleptics facilitate remission of depressive disorders but do not lead to reversal of cognitive deficits. There is growing evidence that antidepressants used in clinical practice can improve cognitive functions regardless of their impact on the affective component. The aim of the present study is to discuss the neurobiological mechanisms of cognitive dysfunctions and their clinical symptoms, and to present therapeutic prospects for patients with persistent cognitive dysfunctions in depressive disorders.

Key words: depressive disorders, cognitive dysfunctions, vortioxetine

Introduction

Major depressive disorder (MDD) constitutes today the most common cause of disabilities worldwide [1]. On the one hand, this may result from the wide reach of this disorder: between 11 and 15% of global population will be affected by MDD at some point in their life; on the other, remission is difficult to achieve [2]. In a STAR*D survey, only 27% of patients met the remission criteria (measured using the HAM-D scale) after the first stage of treatment (with citalopram), whereas the accumulated remission ratio after the complete four stages of treatment was 67% [3].

For the remission according to the American College of Neuropsychopharmacology (ACNP), less than 3 depressive symptoms are required (with no mood depression, loss of interest and anhedonia) for a minimum of 3 weeks. This might mean that a situation is possible when the symptoms of depression, referred to as residual symptoms, are still present and their severity is greater than the minimum [4]. Residual symptoms are a continuation of symptoms brought on by depressive episodes which cannot be ascribed to previous personality problems or side effects of medication [5]. They might persist for months, even after an MDD episode has been classified as in remission.

The main aim in MDD treatment should be reaching a complete remission without residual symptoms because their occurrence might reduce the time to the relapse of MDD and signal an increased risk of the relapse of MDD [6]. Residual symptoms have been considered predictors of a relapse, regardless of whether the patient received pharmacotherapy or underwent psychotherapy [7].

Depending on their nature, 3 categories of residual symptoms can be distinguished:

- 1) low intensity symptoms characteristic of diagnostic criteria of depression;
- 2) somatic pain symptoms;
- 3) cognitive dysfunctions.

Even though depression is generally considered an affective disorder, a gradually greater significance is ascribed to cognitive dysfunctions which might accompany it. Cognitive dysfunctions – along with energy slumps and sleeping disorders – are dominant symptoms during a depressive episode, lasting for 85–94% of the total duration of the episode and 39–44% of remission [8]. Thus, they are among the most commonly reported ailments which have a significant bearing on the quality of the patients' life. In clinical practice, the attention of psychiatrists, and the pharmacotherapy resultant from their diagnoses, has tended to focus predominantly on treating affective symptoms, in accordance with the time-honored conviction that cognitive dysfunctions result from mood disorders and are therefore of a lesser importance in the patient's overall treatment, whereas in fact cognitive dysfunction belong to the endophenotypes of depression helping to identify the genetic background of the illness which could be a strategic link between a symptom-oriented and cause-oriented understanding of depression.

In this light, the authors of the present article wish to highlight this particular category of symptoms because they are on the one hand a predictor of therapeutic response, and on the other hand affect the patient's functioning (functional remission) and predominate among residual symptoms.

The characteristic of cognitive dysfunction in MDD

In their discussion of cognitive dysfunction in depression, Gonda et al. [9] suggested a division based upon their relationship to affective symptoms. Thus, 'hot' cognitive functions are those dependent on the affect, while 'cold' – those independent

therefrom. Disorders of ‘hot’ cognitive functions can be captured in interviews with patients, while in order to determine disorders of ‘cold’ cognitive functions recourse has to be made to neuropsychological tests or neurophysiological examinations [10, 11]. A disorder of ‘hot’ cognitive functions in depression leads to cognitive distortions, whereas a disorder of ‘cold’ cognitive functions results in cognitive deficits.

Cognitive distortions consist in an erroneous information processing. Patients with depression present increased reactivity to negative information, which results in a negative attitude towards the world and a worse perception of themselves and others [12]. Through focusing on negative information and stimuli, the patients ignore or deny the existence of any positive aspects of themselves, their immediate positions and relationships, which indicates faulty information processing and erroneous interpretation of experiences [9]. A distorted view of reality – by enhancing faulty and/or irrational thought patterns – leads to the formation of misguided approaches to the external world. In this way, cognitive distortions enhance, perpetuate and intensify depressive symptoms [13].

Most common cognitive deficits in depression include disorders of executive functions, attention, short-term memory, and psychomotor skills [9]. It is estimated that ca. 20–30% of patients with MDD suffer from cognitive functions deficits understood as notion formation, information comprehension and its effective processing, and problem solving and decision making [14]. Executive functions perform two major roles in human life: first, they serve the purposes of deliberate, intentional and volitional activity which helps achieve plans for particular feats, and second, they constitute an important system of control which extinguishes and postpones reactions that are improper and inadequate to the actual situational context [15]. Executive functions deficits which accompany MDD prevent patients from setting their life goals and going about their realization, including even the most mundane everyday tasks, leading them also to withdraw from assuming social roles.

Attention in the sense of a cognitive function is related to processes of perception and as such serves the purpose of information selection. It can be characterized by concentration and focus on a given aspect of a person’s immediate circumstances, and shiftability. Attention disorders are frequently revealed in the course of a psychiatric examination but they can be objectified using neuropsychological tests.

The memory function is subject to the attention function. Short-term memory includes, among others, sensory memory and working (or operational) memory [16]. Patients with MDD exhibit disturbances in the field of sensory memory, i.e., visuospatial and auditory-verbal memory, understood as the ability to receive, process and store visual and auditory experiences [17]. Operational memory is responsible for temporary storage and processing of information, and plays a major role in modulating human cognitive activity, that is – language processing (verbal memory), learning and reasoning [18].

The relationship between cognitive functions and physical skills such as coordination, slickness, and fast response, is what defines psychomotor skills. Psychomotor retardation as a frequent symptom in MDD is subject to close scrutiny which involves evaluation of a patient’s speech, facial expressions, eye movements, and the speed and

reach of the patient's motor span [19]. Psychomotor retardation might include on the one hand physical symptoms such as gait slowdown, stooping, low voice timbre, poorly modulated affect; on the other hand, cognitive processes impairment [20].

The above-presented cognitive dysfunctions are important not only insofar as they significantly impair the patient's overall functioning during an MDD episode, but also because they may persist even after a marked improvement with regards to depressive symptoms, as well as after reaching complete clinical remission, thus disturbing the functioning of an otherwise 'cured' patient [21].

Pathomechanisms of cognitive functions impairment in MDD

Increased responsivity to negative information and cognitive deficits in depression constitute the endophenotypes of depression [22]. As such, they testify to the immunological hypothesis of depression [23]. Research into their pathomechanisms facilitates a better insight into the etiopathogenesis of depression. Among patients with MDD who exhibit cognitive distortions (increased responsivity to negative information), information processing requires a stronger and longer period of activity of the amygdala [24, 25]. Increased activity of the amygdala frequently occurs in combination with an increased concentration of noradrenaline and cortisol, which are responsible for memory enhancement. This could explain the tendency of MDD patients towards a continuous and excessive focusing on negative memories. The heightened activity of the amygdala might be maintained due to disorders of dorsolateral prefrontal cortex (dlPFC), which normally acts as a brake to amygdala [26].

The most crucial area of the cerebral cortex involved in the production of cognitive deficits is the anterior cingulate cortex (ACC), which integrates neuronal circuits responsible for emotion processing and affect regulation [27]. The ACC is conventionally divided into ventral and dorsal anterior cingulate cortex. The role of the ACC in the regulation of cognitive functions is presented in Table 1.

Table 1. The role of the anterior cingulate cortex (ACC) in the regulation of cognitive functions

ACC	Role in the regulation of cognitive functions [28]
Dorsal anterior cingulate cortex (dACC)	Executive functions processing of stimuli decision-making error detection performance monitoring risk assessment
Ventral anterior cingulate cortex (vACC)	Emotions motivation asks with high emotional load

It has been confirmed that in the course of MDD cellular abnormalities in the cerebral and sub-cerebral structures disrupt monoaminergic transmission. Since monoaminergic receptors are placed on glial cells, the processes which occur in them affect the neurotransmission of, among others, serotonin, noradrenaline and dopamine – the major neurotransmitters in MDD [29]. Serotonin also influences the prefrontal cortex through regulating glutaminergic and GABA-ergic transmission [30]. Patients with depression demonstrate a reduced activity of the vACC which results in a weaker stimulation of dopamine secretion in the limbic system [31].

Research suggests that serotonin and noradrenaline play a major part in regulating cognitive functions such as attention, operational memory and cognitive flexibility. Dysfunctions in systems of neurotransmitters lead to negative reception of stimuli which in turn might be the cause of inaccurate emotional reactions [9].

Glucose metabolism and cerebral blood flow (CBF) in particular areas of the brain reflects the neurons' activity and testifies to the amount of energy spent on synaptic transmission [32]. This seems further corroborated by the observation that in patients with MDD the areas of the brain which exhibited an increased glucose metabolism in a PET scan were found to be afflicted with a reduction of grey matter of the cerebral cortex in an MRI scan. Given that 85–90% of glucose metabolic activity is spent on glutaminergic transmission, areas of the brain with an increased glucose metabolism suffer from an overstimulation of the N-methyl-D-aspartate (NMDA) receptors and an excessive secretion of glutamine. Glutamic acid is a major neurotransmitter stimulant in the PFC and the hippocampus. MDD impairs the plasticity of glutaminergic synapses, thus damaging both their structure and function. Increase in glutaminergic transmission in pyramidal neurons of the PFC leads to the impairment of operational memory in patients with MDD [33]. The site for glutamine intake in the CNS is made up from glial cells, which play an important part in regulating the activity of the NMDA receptor. Glial cells, especially astrocytes, through supervising the level of glutamine, protect neurons from apoptosis [29]. Microglia acts as the immune system in the CNS, through, among others, the ability to rebuild synapses, to produce correct synaptic connections, and to synthesize neurotrophic factors, which is proven by the increased activity of these cells in areas of the brain sensitive to stress, i.e., in the hippocampus, the cerebral cortex and the amygdala.

In response to chronic stress, which facilitates the development of MDD, the immune system activates neurobiological mechanisms affecting the processes of learning and memory. Stimulation of the immune system leads to an increase in the level of inflammatory mediators such as IL-1 β , IL-6, and BDNF (brain-derived neurotrophic factor) and TNF- α (tumor necrosis factor), which results in the activation of microglia [34]. Microglia activation is a response to the fall in the levels of the CX3CL1 protein which takes place when neurons are damaged. CX3CL1 is a chemokine which regulates neuroimmunization, participates in synaptic plasticity and regulation of cognitive functions. History of inflammation in the CNS which results in neuron apoptosis is corroborated by research conducted on mice in which

a deficit of CXCR1 was related to increased expression of IL-1 β in microglial cells as a response to LPS stimulation. Increased expression of IL-1 β is related to the increased rate of mortality among nerve cells located predominantly in the hippocampus, which holds the densest number of sites for IL-1 β binding. The results of these changes included impairment of learning mechanisms, of associative and spatial memory, and led to distortions in motoric learning, that is, in acquiring motor skills [35].

Research on humans revealed that administering endotoxin led to a greater activation of the amygdala and the dACC [36] – which in practice means that any inflammation in a human organism might increase the reactivity of the amygdala to psychosocial stressors. Given that inflammation is always a result of disease or injury, the mechanism of increased activation of the amygdala and the dACC leads to increased responsivity to negative information which, in biological terms, is supposed to help an organism avoid potential environmental hazards that it could not combat during the inflammation. Additionally, glucocorticosteroids which take part in the reaction to stress might bring about a permanent allergy of microglial cells related to their prolonged activation while extinguishing the stress reaction [37]. The whole phenomenon might be responsible for the persistence of cognitive functions deficits after having reached a remission of depressive symptoms.

The impact of a chronic stress reaction in MDD on neurobiological changes in the brain is also illustrated by increased activity of the hypothalamus–pituitary–adrenal axis (HPA) which enhances glutaminergic transmission [32]. A chronic activation of the stress axis induces the apoptosis of brain cells which manifests itself in a decrease in neuropil in the cortex-limbic system [38].

A slightly different mechanism leads to the decrease of hippocampus volume in patients with MDD by 8 to 19%, which results from a rise in the density of glial cells distribution and a fall in the number of dendritic connections. Structural changes affect the clinical course of depression in that it has been proven that patients with MDD who have suffered from decrease in grey matter volume of the hippocampus have poorer prognosis, stand a greater risk of relapse and a more chronic course of the illness [32]. Moreover, it has been shown that changes in grey matter in patients with MDD facilitate the occurrence of cognitive functions deficits, the slowdown of stimuli processing, and weakening of memory [39].

Prospects for treatment of cognitive disorders in MDD

Implementing effective treatment at the earliest stage of MDD is crucial because the longer the duration of the illness, the greater the reduction of grey matter volume in the cortex-limbic structures [30] and the lower the receptivity to pharmacotherapy [40]. Patients who have cognitive deficits in MDD and those who have managed to achieve remission of depressive symptoms, but still have cognitive dysfunctions could benefit from being administered medications of a proven pro-cognitive effect.

Research shows that classic anti-depressants (tricyclic antidepressants – TCA) are not very effective in treating cognitive dysfunction in patients with MDD, probably due to their anticholinergic effect [41]. There is also evidence suggesting that some medications from the SSRI (selective serotonin reuptake inhibitor) and SRNI (serotonin norepinephrine reuptake inhibitor) group, as well as dopamine modulators (bupropion), noradrenaline and serotonin modulators (mirtazapine), and norepinephrine inhibitors (reboxetine) have a pro-cognitive effect [42], though medications affecting more than one neurotransmitter seem to be a better choice for patients with cognitive functions disorders.

Among the SSRI medications, escitalopram [43–45], paroxetine [46–49] and fluoxetine [50–52] lead to a general improvement of cognitive processes, while sertraline positively affects executive functions, attention and helps counter psychomotor retardation [53]. Venlafaxine from the SNRI group also improves attention and executive functions [50], while duloxetine additionally improves memory processes [43, 44, 45].

Research with bupropion as inhibitor of noradrenaline and dopamine reuptake (which hardly affects serotonin reuptake) revealed its pro-cognitive effect in improving information processing and verbal and audio-spatial memory [45, 47, 55]. Mirtazapine, which belongs to the group of noradrenergic and specific serotonergic antidepressants (NaSSA), intensifies noradrenergic and serotonergic transmission through its influence on the 5-HT_{1A} receptor. In patients taking this medicine for 6 months improvement has been noted in operational memory, information processing and executive functions [56]. Reboxetine is a selective noradrenaline reuptake inhibitor and has been confirmed to have a positive effect on restoring proper cognitive functions and attention maintenance skills on the 56th day of treatment, as compared to paroxetine and placebo [46].

When choosing an antidepressant in a patient with cognitive deficits in the course of MDD, it is worth considering a large meta analysis in which the procognitive action of the drugs was evaluated in terms of patients' improvement in the DSST (Digit Symbol Substitution Test). Among the classes of antidepressants, SSRI, MAO inhibitors and TCA, were found to have less effect on the DSST compared to placebo, with TCA significantly worse than placebo. Comparing individual antidepressants with the use of vortioxetine, duloxetine and sertraline, an improvement in the DSST was observed, with vortioxetine being the only antidepressant with statistically significant difference from placebo [57].

Despite being categorized as an SSRI group medication, vortioxetine is described as a “multimodal serotonin modulator”. It has an antagonistic effect on the 5-HT₃, 5-HT₇ and 5-HT_{1D} receptors; it is an agonist of the 5-HT_{1A} receptor, partial agonist of the 5-HT_{1B} receptor, and an inhibitor of the 5-HT transporter. This in turn influences how vortioxetine affects extra-cellular concentrations of serotonin, acetylcholine, noradrenaline, and histamine [58].

Research on animals has shown that vortioxetine has a stronger impact on the rise of serotonin level in the hippocampus and the medial prefrontal cortex, that is in areas responsible for cognitive disorders in MDD. Vortioxetine also increases the

extra-cellular concentration of noradrenaline, dopamine, acetylcholine, and histamine (HA) in the prefrontal cortex, probably due to serotonin modulation [58]. This influences clinical results because it has been affirmed that in order for SSRI to be effective they must be administered in doses saturating the serotonin transporter in ca. 80%. Vortioxetine doses of 5 mg, 10 mg and 20 mg have achieved saturation levels of 50%, 65% and above 80%, respectively [30].

Improvement of cognitive functions after vortioxetine results from the impact it has on the brain's neuroplasticity [30, 57]. This occurs within the mechanism which regulates the expression of genes modulating growth factors, receptors and signal proteins involved in neurogenesis and production of new synaptic connections. These include, among others, the brain-derived neurotrophic factor (BDNF), calcium-/calmodulin II-dependent kinase, Wnt protein family and glutaminergic receptor subunits, which all play important roles in processes of learning and memory at the level of the hippocampus [30].

An important aspect of vortioxetine effect is its anti-oxidant potential which helps halt oxidative stress in the immune system cells. Additionally, its influence on the response of the immune system is illustrated by the decrease in the process of monocyte differentiation into macrophages which participate in the inflammatory reaction. The medication also halts the expression of a gene responsible for the peroxisome proliferator-activated receptor (PPAR γ), which is related to cell proliferation and the course of inflammation. Agonists of this receptor might show an anti-depressive effect through their ability to reduce levels of pro-inflammatory factors such as IL-1 β , IL-6 and TNF- α . Vortioxetine's neuroprotective effect, thus, stems not only from its halting of the 5-HT $_3$ receptor, but also from its influence on nuclear receptors at the level of immune system cells [54].

The above data indicate that vortioxetine is a good choice as a first-line drug in depression with cognitive impairment, and that its use should be recommended in the treatment of MDD where cognitive dysfunctions persist despite antidepressant treatment.

Duloxetine is an inhibitor of both serotonin and norepinephrine reuptake. Its two-directional effect and, similarly as in the case of vortioxetine, its neuroprotective properties are responsible for the improvement of cognitive deficits in MDD [59]. Studies conducted on the hippocampus of mice intoxicated with kainic acid revealed that after administering duloxetine neuron apoptosis was halted. Moreover, duloxetine showed an immunomodulating effect through reducing the activation of microglial cells responding to oxidative stress which resulted in a suppression of pro-inflammatory cytokines participating in MDD pathogenesis [60, 61]. A significant aspect of duloxetine treatment is that, when administered to elderly patients in the dose of 60 mg per day, it facilitates memory and verbal learning improvement but does not differ from placebo with regards to enhancement of attention and executive functions [59].

A comparative study assessing the effects of treatment with vortioxetine (5 mg per day), duloxetine (60 mg per day) and placebo in elderly patients with MDD has

revealed that in comparison to vortioxetine, patients on duloxetine were nearly twice as likely to drop the treatment due to side effects (9.9% duloxetine, 5.8% vortioxetine). Both medications influenced memory and verbal learning improvement but only vortioxetine also had a significantly positive effect on executive functions, attention and drive. Vortioxetine also had advantage over placebo in tests assessing information processing and verbal memory [62].

A meta-analysis of 3 randomized clinical trials using vortioxetine and duloxetine also showed that only in the case of vortioxetine a statistically significant improvement in the DSST compared to placebo was obtained. Comparing vortioxetine with duloxetine also showed statistically significant difference in DSST results in favor of vortioxetine [63].

An alternative for MDD treatment when pharmacological methods fail is repetitive transcranial magnetic stimulation (rTMS). The therapy is accepted in treating pharmaco-resistant depression and consists in inducing electrical activity with the aid of the magnetic field, especially in the dorsolateral prefrontal cortex [64, 65]. Several large randomized clinical case studies have confirmed the existence of a relationship between rTMS and improvement of cognitive functions [66].

Recapitulation

When treating patients with MDD we should pay attention not only to affective symptoms, whose alleviation is the main goal of our therapeutic actions in everyday clinical practice, but also to cognitive disorders which may persist even after the patient achieves remission of depressive symptoms. Treatment of cognitive disorders is crucial not only because they compromise the quality of our patients' lives but also because indirectly (as endophenotypes of depression) they yield information on the pathophysiological process in the CNS which lies at the core of depression. Cognitive dysfunctions as symptoms of this process increase the risk of relapse of depression and reduce the patients' receptivity to pharmacology.

Today we are gathering gradually more evidence proving that anti-depressive medications that we administer to patients might also improve their cognitive functions, regardless of their influence on affective symptoms. The majority of data supports the benefit of vortioxetine and duloxetine, with studies showing that vortioxetine has a greater impact on cognitive functions.

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Address: Agnieszka Czerwińska
Department of Psychiatry
Division of Psychotherapy and Psychosomatic Medicine
Wrocław Medical University
50-367 Wrocław, Wybrzeże L. Pasteura Street 10
e-mail: psych.agnieszka.czerwinska@gmail.com