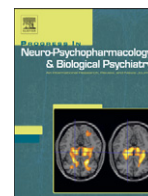




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Review article

Functional brain asymmetry as a determinative factor in the treatment of depression: Theoretical implications

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ABSTRACT

Depression is characterized by the functional insufficiency of both left and right hemispheres. Patients who respond to antidepressants are characterized by a relatively higher left hemisphere activity in comparison to non-responders, and successful treatment with antidepressants increases left hemisphere activity. Left hemisphere is responsible for the goal-oriented behavior that includes search activity as a state opposite to depression, which accounts for the positive outcome in depression following activation of the left hemisphere. However, it is not a pathogenetic but a palliative treatment, because the core reason for depression is the inability of the right hemisphere to correspond to the demands of the polydimensional environment. The article suggests that in order to achieve stability, treatment has to combine methods that restore left hemisphere activity with methods that restore right hemisphere efficiency.

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1. Introduction

The previous review of the literature and its theoretical integration (Rotenberg, 2004) has shown that depression is characterized by the functional insufficiency of the right hemisphere. According to the concept of brain hemisphere functions (Rotenberg, 1979; 1994) left and right hemispheres in humans are characterized by the opposite modes of organizing the contextual connections between elements of information. Left hemisphere so organizes any sign material (whether symbolic or iconic) as to create a strictly ordered and unambiguously understood monosemantic context. Its formation requires an active choice from the many connections between the multiform objects of a

few definite connections. The function of the right hemisphere is a simultaneous capture of an infinite number of connections and the formation of an integral polysemantic context that is relevant to the polydimensional world. The functional insufficiency of the right hemisphere in depression (the inability to create a polysemantic context) is combined in depression with the physiological over-activation of the right hemisphere, particularly the right frontal lobe (Bruder et al., 1989; Henriques, Davidson, 1990) as an unsuccessful attempt to compensate this insufficiency (Rotenberg, 2004). The recent research of Fingelkurts et al. (2007) supports this conclusion showing the increase of the number and strength of long functional connections for the right hemisphere as a sign of the attempt to compensate its functional insufficiency. It was also emphasized (Rotenberg, 2004) that depressed patients, in addition to the right hemisphere insufficiency, are characterized by the functional insufficiency of the left hemisphere. However, in contrast to the right frontal lobe, the insufficiency of the left hemisphere is combined with the

Abbreviations: EEG, electroencephalography; LH, left hemisphere; Rh, right hemisphere; TMS, transcranial magnetic stimulation; DA, dopamine; NE, norepinephrine; 5-HT, serotonin; SSRI, selective serotonin reuptake inhibition.

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relative decrease of physiological activity (increased alpha-index) of the frontal lobe and some other structures of the left brain (Henriques, Davidson, 1991).

If in depression, both hemispheres are functionally insufficient, the questions are, what is the contribution of each hemisphere in the pathogenesis of depression? and, what are the interrelationships between them in the process of the development of depressive symptoms? In this article we attempt to analyze the interrelationships between the clinical response of depressed patients to the different types of treatment and the functional state of the right and the left hemisphere.

2. Functional and electrophysiological brain asymmetry in drug responders

The studies of Bruder et al. (1997; 1999; 2001; 2004), Mayberg et al. (1997), Stewart et al. (1999), Gershon et al. (2003) provide support for relating response to treatment with the function or activity in specific brain regions.

Bruder et al. (2001) have compared EEG and perceptual asymmetry before treatment in depressed patients who subsequently responded on fluoxetine with those patients who showed no response. Alpha-rhythm asymmetry of non-responders indicated a greater activation of the right hemisphere in comparison to the left one. In fluoxetine responders, this difference between hemispheres was absent, particularly in the eyes-open condition. Thus, according to this variable (alpha-rhythm activity), fluoxetine responders are relatively closer to healthy subjects than non-responders because healthy subjects display either no alpha asymmetry or a subtle activation of the left frontal lobe (Graae et al., 1996) but not the right one.

Non-medicated patients who subsequently responded to fluoxetine displayed a greater right ear (left hemisphere, LH) advantage for dichotic presentation of words and less left ear (right hemisphere, RH) advantage for complex tones when compared with non-responders. This suggests that based on the listening to the dichotic words presentation, fluoxetine responders are also closer to healthy subjects who usually display a left hemisphere advantage with this task. In another investigation, Bruder et al. (2004) confirmed the previous data that patients who responded to fluoxetine differed from non-responders in favoring left over right hemisphere processing of dichotic stimuli. Moreover, they differed in the same direction from healthy adults, which means that they display an exaggeration of the left hemisphere advantage for dichotic words. This exaggeration was especially prominent in depressed women who respond on antidepressants. Depressed women who failed to respond to fluoxetine had a reduced right ear (left hemisphere) advantage for dichotic words while in fluoxetine responders this advantage was increased even compared to healthy women (Bruder et al., 2001) who usually display less lateralization of verbal functions in comparison to men (Pine et al., 2000).

The recent investigation of Bruder et al. (2007) has shown that among a cohort of depressed patients most of whom failed to respond to fluoxetine, those who subsequently responded to bupropion also had markedly larger left hemisphere advantage for words on a dichotic words test compared to non-responders. The authors emphasized that all patients having above normal left hemisphere advantage for words responded well to treatment with bupropion. Those having less than normal or no left hemisphere advantage had only a 9% response rate to bupropion. Thus the high sensitivity of the left hemisphere to verbal material predicts the positive outcome not only to fluoxetine but also to bupropion treatment.

In addition, the decreased left ear advantage for complex tones means that even by performing this task in healthy subjects is usually in the competence of the right hemisphere, fluoxetine responders demonstrate a relative increase of the left hemisphere activity.

Women with above normal left hemisphere advantage on the fused-words test had a 94% response rate to fluoxetine but only 11%

response rate to placebo. Differences for responders and non-responders were less marked for men (see Bruder et al., 2004).

The reduced right hemisphere advantage for dichotic tones perception was present only among men who responded on the fluoxetine treatment. Thus their left hemisphere was involved in this task almost on the same level as the right one (what is not typical for healthy men), while non-responders showed a right hemisphere advantage for dichotic tone perception and processing that did not differ significantly from healthy men. This suggests that their left hemisphere is not hyperactive in contrast to responders. Bruder et al. (2004) emphasized that the reduced right hemisphere advantage in men who responded to fluoxetine was due to the better than normal right ear performance for tones which may be due to left hemisphere hyperactivity and not more severe right hemisphere dysfunction in comparison to non-responders.

However, this difference was not found between male bupropion responders and non-responders (Bruder et al., 2007). These authors emphasized that both bupropion responders and non-responders belonged to the group of fluoxetine non-responders. Nevertheless, those who responded to bupropion treatment differed from non-responders in the relatively higher left hemisphere advantage for dichotic words but did not differ in right hemisphere advantage for dichotic tones. Because all these patients (men and women) have been selected from patients who do not respond to fluoxetine, it is possible to suggest that their left hemisphere advantage for dichotic words (that reflects the relative potential predisposition of the left hemisphere to be activated) was not enough to respond to fluoxetine, but was enough to respond to bupropion. Bruder et al. (2007) concluded that men who have both larger than normal left hemisphere advantage for words and normal right hemisphere advantage for tones benefit more from treatment with bupropion than with fluoxetine.

Some investigators (Hugdahl et al., 2003) found normal left hemisphere advantage for perceiving dichotic consonant vowel syllables in depressed patients, most likely because the investigated group was mixed and contained antidepressant responders and non-responders.

The relative advantage of the left hemisphere for dichotic words shows that treatment responders display relatively more normal functions and a more normal physiological state of the parieto-temporal part of the left hemisphere in comparison to non-responders. This data suggests that treatment responders display a potential preservation or even a compensatory overactivation of the left hemisphere functions that corresponds with a positive response to antidepressant treatment. Most likely, in these patients the ability to overcome the depressive state in the process of treatment is achieved by means of the left hemisphere activity that is potentially available. At the same time, non-responders display an inappropriate attempt to compensate the right hemisphere deficiency by right hemisphere activation. It is inappropriate because right hemisphere frontal lobe does not need additional physiological activation for normal functioning (for details see Rotenberg, 2004). Such activation is irrelevant because depression remains very prominent.

Bruder et al. (1996) found no changes in perceptual asymmetry following treatment. This means that the difference between responders and non-responders represents stable state independent characteristics and the improvement of clinical state does not change these characteristics. To the contrary, exactly these state independent characteristics determine the success or failure of the treatment. Henriques and Davidson (1990) suggested that the presence of abnormal frontal and parietal alpha asymmetries in previously depressed patients supports the view that they represent a vulnerability to negative affect. In the previous review (Rotenberg, 2004) this vulnerability was attributed to the functional insufficiency of the right hemisphere. This functional insufficiency seems to be a common general characteristic of all types of depression. However it is the level of the left hemisphere activity that determines the presence or absence of the response to antidepressant treatment.

There are findings that depressed patients as a group are characterized, in contrast to healthy subjects, by the relatively reduced left prefrontal activation (Henriques and Davidson, 1991). Probably the left hemisphere of drug responders inclines to compensate its functional deficiency; however, this inclination can only be achieved with treatment. Women in general are initially more predisposed to the activation of the left hemisphere structures (Heller, 1993) and for this reason such activation is more prominent in responding women.

3. The interpretation of some contradictions

Bruder et al. (1996) suggested that it is decreased left prefrontal activity that may release left temporo-parietal regions of depressed patients from inhibition, resulting in the enhanced left hemisphere advantage for dichotic perception in fluoxetine responders. However, why does this mechanism not work in non-responders? It is possible to suggest that the enhanced left hemisphere advantage for a dichotic perception in responders is a special sign of the preserved left hemispheric skills that determine fluoxetine response.

In this context, it is of interest that in healthy adults serotonin-releasing drugs (SSRI) increased glucose metabolism exactly in the left prefrontal cortex and temporo-parietal areas (that are relatively more sufficient in depressed patients who are drug responders), and at the same time it decreased metabolism in the right prefrontal cortex (Mann et al., 1996a). What this means is that the SSRIs increase in healthy subjects the normal activity of left hemisphere structures that are relevant to goal-oriented behavior, while normal functions of the right prefrontal functions are accompanied by the relative decrease of its physiological activity (Rotenberg, Arshavsky, 1991). This effect of SSRIs was absent in depressed patients. However, it is important to note that in the cited investigation (Mann et al., 1996a) depressed patients were not divided into subgroups according to drug response, and most likely the effect was absent due to the domination of non-responders.

On the other hand, in the investigation of Davidson et al. (2003) depressed patients in comparison to healthy subjects displayed significantly less relative activation in the left insular cortex and left anterior cingulate cortex in response to negative versus neutral stimuli at baseline, before the treatment. After 2 weeks of treatment with venlafaxine (performed on depressed patients) the difference between the two groups was completely eliminated. After 8 weeks of treatment patients showed greater activation relative to the healthy subjects, thus displaying a more “healthy” reaction than control normal subjects. The magnitude of activation in left anterior cingulate cortex at baseline predicted treatment response. Patients with greater activation of this area to the negative versus neutral pictures at baseline show the fewest and least severe symptoms after 8 weeks of treatment.

Bruder et al. (2001) proposed that women are more likely to ruminate when depressed which involves increased activity of the left hemisphere structures. However, if rumination were to play an important role in brain asymmetry in depression, then brain asymmetry would probably decrease after successful therapy (and, correspondingly, after disappearance of rumination) but it does not happen.

Probably, in the absence of the relevant treatment, rumination may exploit left hemispheric skills that are used quite differently in the process of the relevant treatment. Ruminations may perform in this condition the same role as delusions in schizophrenia that are also based on the activated left hemispheric mental skills in the context of the right hemisphere insufficiency (Rotenberg, 1994). If this left hemispheric “niche” is already occupied by ruminations (stereotyped mental constructions) it becomes an obstacle to successful treatment.

4. Brain asymmetry and neurotransmitters

According to Bruder et al. (2004) one possible explanation of the differences in brain asymmetry between responders and non-responders

is that the neurotransmitter system affected by SSRIs has an asymmetrical distribution between brain hemispheres (Tucker and Williamson, 1984). Although postmortem findings are inconsistent, individual differences among depressed patients in regional brain activity are related to the subsequent response to SSRIs and other antidepressants: greater activity of the rectal gyrus (Buchsbaum et al., 1997), anterior cingulate (Davidson et al. 2003) or prefrontal regions (Hoehn-Saric et al., 2001) on the left part of the brain was predictive of favorable response to antidepressants.

Gershon et al. (2003) have shown an antidepressant effect of high-frequency repetitive Transcranial Magnetic Stimulation administered also to the left prefrontal cortex. Baseline activity in the inferior frontal lobe was higher in patients who responded to rTMS. High frequency rTMS increases cortical excitability and metabolism.

The pathology of the brain monoamine system is presumably a common feature of responders and non-responders; however only those who are able to activate the compensatory left hemisphere mechanisms respond on the antidepressants.

This is consistent with data that cognitive therapy responders versus non-responders had twice the right ear advantage and corresponds to the orientation of cognitive therapy to the left hemisphere. However, cognitive therapy responders did not show the reduced left ear advantage for tones seen for fluoxetine responders (Bruder, 2003). It is not clear whether this represents less prominent left hemisphere activation or less prominent deficiency of the right hemisphere functions.

At the same time, I have not found any evidence for the physiological or functional activation of the right frontal lobe by SSRIs and other antidepressants.

How can the positive response of the different types of treatment of depressed patients be explained in the context of the relatively increased activity of the left hemisphere that is displayed in alpha-rhythm asymmetry and dichotic listening?

Actually, it is the main question that is not discussed in the literature. However, the modern view on the pathogenesis of depression allows some speculative explanations of these relationships.

5. Data interpretation in the frame of the Search Activity Concept

According to the Search Activity Concept (Rotenberg, 1984; 2003) depression represents a state of renunciation of search. This statement was confirmed in our recent investigations (Rotenberg, Cholostoy, 2004; Rotenberg et al., 2007). Search activity is a common feature of different goal-oriented types of behavior (fight, flight, creative activity, active estimation of the situation) and is designed to change the situation or the subject's attitude to it, with uncertainty regarding the results (outcomes) of this activity, but with constant monitoring of the results at all stages of activity. Search activity is the most adaptive form of behavior in stressful conditions and increases body resistance (Rotenberg, Arshavsky, 1979). Renunciation of search is opposite to search activity, is maladaptive and manifests itself in giving up and helplessness (Rotenberg, 1984). Helplessness and hopelessness are considered as etiological factors for explaining the onset and maintenance of depression (Henkel et al., 2002) and belong to the strongest factors that characterize major depression (McGlinchey et al., 2006).

Search activity can start in wakefulness in the presence of a certain critical level of the brain monoamines (dopamine (DA), norepinephrine (NE) and serotonin (5-HT)) which are utilized as “oil” in the course of search behavior. DA provides “reward” and “reinforcement” and is important in novelty seeking that includes exploratory behavior, attention and excitement in response to novel stimuli (Benjamin et al., 1996; Cloninger et al., 1996; Ebstein et al., 1996; Gottesmann, 2002). In the frontal cortex which is very important in the organization of the goal-directed behavior (that includes search activity), DA transporters are under the strong modulating influence of NE nerve terminals (Stahl, 2003). NE and 5-HT are responsible for the partial cortical inhibition that provides the discrimination between meaningful and

meaningless information elicited by the environment (Woodward et al., 1979). Such discrimination makes goal-oriented behavior and search flexible and productive.

Search activity itself, once it starts, further stimulates the synthesis of the brain monoamines and ensures their availability (Rotenberg, 2006). Thus the more pronounced the search activity, the sooner the turnover and synthesis of monoamines will be, in turn maintaining search behavior (positive feedback system).

In a state of renunciation of search accompanied by distress that causes intense monoamine expenditure without its subsequent restoration, monoamines display a tendency to drop. As a result, monoamine functioning completes a vicious circle: renunciation of search leads to a drop in the brain monoamines level, which in turn leads to the renunciation of search becoming more prominent.

According to this concept, in order to overcome depression characterized by this vicious circle it is necessary not only to restore brain monoamines (by using antidepressants) but also to “switch on” the opposite positive feedback. I suggest that only when renunciation of search is stably replaced by search activity, do monoamines stabilize on an appropriate level. As a result, the number and/or sensitivity of the postsynaptic receptors in the brain become diminished, which probably correlates with the clinical efficacy of antidepressant treatment. Thus, the therapeutic tactic, according to this concept, has to be directed to the behavioral and intellectual activation of patients in the process of drug treatment.

These theoretical assumptions are confirmed by some recent investigations. Hopko et al. (2003) showed that the so-called brief behavioral activation treatment for depression (BATD) increases exposure to positive activities and helps to alleviate depressive affect. When activity increases from the easiest stereotypic behavior to more complicated behavior that requires flexibility and search activity (like writing complicated texts) depression is reduced and positive thoughts and feelings appear. Pure behavioral activation effect is comparable to antidepressant medication and both outperform cognitive therapy (Dimidjian et al., 2006).

6. Search Activity Concept and brain laterality

Now let us turn to the question how Search Activity Concept is related to brain laterality. According to some literary data (Tucker, Williamson, 1984; Reynolds, 1983) the activity of the DA system of the left hemisphere is higher than that of the right one – dopamine pathways favor the left hemisphere over the right and the number of DA receptors is increased in the left subcortical structures (Weinberger, 1987) making the left hemisphere more sensitive to dopamine.

According to some investigations, the activity of the serotonin system is also different in the left and right hemispheres. Citalopram administration in healthy controls decreased glucose metabolism in the right anterior cingulate gyrus, right superior and right middle frontal gyrus, right parietal cortex, right superior occipital gyrus, and increased metabolism in the left superior temporal gyrus and left occipital cortex (Smith et al., 2002). The serotonin-releasing agent and reuptake inhibitor, fenfluramine, also increased metabolism in the left hemisphere and decreased it in the right hemisphere in healthy volunteers (Mann et al., 1996b; Soloff et al., 2000). At the same time, in depressed patients in general, serotonin synthesis is lower in the left hemisphere (Nishikawa et al., 2003) and has to be compensated by SSRI administration.

On the other hand, the left hemisphere, and especially the frontal part of the left hemisphere, is responsible for the executive functions and goal-oriented behavior (probability forecast, Meerson 1986, and estimation of cause-and-effect relationships, Rotenberg, 2007). The “left-hemispheric” search behavior is relatively restricted and more precisely directed in comparison to the “right-hemispheric” integrative creativity.

The notion of search activity (changing the situation and the environment with a constant feedback between the behavior and its outcome) corresponds to the left hemisphere functions and it can

explain the connections between brain monoamine functions and brain laterality. It corresponds also to the concept of Davidson et al. (1990) that the left hemisphere is responsible for the approach behavior (Coan and Allen, 2003). Anger, in contrast to depression, often provokes active aggressive behavior that includes search activity, and although anger belongs to the domain of negative emotions it is characterized by high left hemispheric activity (Harmon-Jones, 2004). Consequently, profound inhibition of the left hemisphere activity is an important part of the pathogenesis of depression. If the potential capability of the left hemisphere to become active by means of complicated behavioral tasks, by cognitive therapy or by antidepressants is at least partly preserved, search activity can be restored and helps to overcome depression. It can explain the correlation between the response to different types of treatment and increased physiological activity of different brain zones of the left hemisphere in depressed patients (Buchsbaum et al., 1997; Hoehn-Saric et al., 2001; Davidson et al., 2003) as well as the abovementioned left hemisphere advantage to dichotic listening in these responders.

What this means is that the left hemisphere function in some depressed patients is relatively flexible and its insufficiency may display itself with great variability that can determine the success or failure of treatment.

It corresponds also to the conclusion of Davidson et al. (2003) that subjects with greater activation in the left prefrontal cortex exhibit increased capacity to regulate negative affect in a task that explicitly assessed the capacity to voluntarily regulate negative affect.

7. Not to forget about the right hemisphere

Along with the above features of the left hemisphere, the functional deficiency of the right hemisphere seems to be a more stable characteristic of depression (see Rotenberg, 2004). A subject's inability to create a polysemantic context that is relevant to the polydimensional and complicated reality, especially to the reality of the emotional interpersonal environment, puts the subject in a stable state of stress where he/she feels unequipped to master a demanding environment. This right hemisphere deficiency determines a stable predisposition to mental and psychosomatic disorders including depression (Rotenberg, 1995) that can be only partly and temporary compensated by the mobilized left hemisphere skills and search activity. Right hemisphere skills are less sensitive to antidepressants and are not restored in the process of drug treatment (although the drop in depression may temporarily decrease the load on these skills and decrease the irrelevant compensatory right frontal lobe hyperactivation, see Rotenberg, 2004). Stable right hemisphere deficiency may be responsible for the relapses of depression.

Stewart et al. (1999) found even poorer left ear accuracy for dichotic consonant vowels among imipramine responders compared with non-responders, placebo responders and controls. Of course, left ear accuracy for dichotic consonant vowels is based on temporoparietal activity and is not equal to the ability of the right frontal lobe to create polysemantic context; but it is also a function of the right hemisphere, and the data of Stewart et al. suggest that right hemisphere functions are not restored by antidepressants and remain distorted even after the successful treatment. Interestingly, consonant vowel left ear accuracy was greater among placebo responders versus placebo non-responders and controls. It is possible to speculate that placebo responders are more sensitive to suggestions than other investigated groups of patients. Such sensitivity may be based on the patient's ability to imagine a possible effect of placebo as a sign of the partly preserved right hemisphere functions.

8. Conclusion

Our main conclusion is that the most modern methods in the treatment of depression are actually only palliative according to their

nature. They are just helping patients to use their left hemispheric skills in order to partly compensate the core and fundamental distortion – the deficiency of the right hemispheric skills and the inability to feel themselves integrated in the polydimensional world through the creation of a polysemantic context. Almost all methods of treatment, with the possible exception of the alternative states of consciousness and deep psychotherapy, do not help patient to solve this existential problem, but only temporarily and partly to adapt to the complicated environment by using active behavior managed by the left hemisphere. Effective treatment, therefore, is obliged to combine antidepressants, active behavior that includes search activity and different types of psychotherapy oriented toward the restoration of the right hemisphere functions: interpersonal deep psychotherapy (see Schore, 2003; Brody et al., 2001), induction of altered states of consciousness and art therapy. Such combinations have the potential to produce a stable and lasting effect in depression.

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