

IDEAS & PERSPECTIVES

“GENES OF HAPPINESS AND WELL BEING” IN THE CONTEXT OF SEARCH ACTIVITY CONCEPT

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The goal of this article is to discuss that the long allele of the serotonin transporter gene that was considered in some publications to be a gene of “happiness” and “well-being” is actually a gene that is responsible for the predisposition to the search activity that by itself contains positive emotional feelings. This statement is confirmed by the comparison of the results of different investigations and helps to solve many contradictions in psychobiology of emotional sensitivity, fear, depression, suicide attempts, of relationships between stressful conditions and well-being.

Key words: *Consciousness; Gene of happiness; Search activity concept*

1. GENETIC PREDISPOSITION TO WELL-BEING

An interest to the reasons of happiness and to the distribution of the feeling of happiness is very strong in human society. Diener (1996) found in his investigation that most people report a positive level of subjective well-being and say that they are satisfied with marriage, work and leisure. This statement seems to be overoptimistic but author may be correct proposing that such positive attitude to the life helps to resist negative events and to cope with them. Positive self point may motivate human’s sociability, drive free exploration and creativity. Thus it may be a feedback between well-being and the active position in human life.

In the recent years appeared a new branch of human psychobiology: a genetic approach to well-being and happiness. In a comprehensive investigation (Lykken & Tellegen, 1996) happiness (subjective well-being) was measured on a birth-record-based sample of several thousand middle-aged twins using the Well-Being scale of Multidimensional Personality Questionnaire. Socioeconomic status, educational attainment, family income, marital status, an indicant of religious commitment could not account for more than about 3% of the variance in well-being. However, from 44% to 52% of the variance in well-being were associated with genetic variation. When twins have been retested after few years, authors found that the heritability of the stable component of subjective well-being approaches 80%. High social status or wealth by themselves do not determine positive mood states as well as people in the opposite social condition (lower end of the social ladder) are only slightly more vulnerable to negative mood state. Lykken and Tellegen on the basis of disattenuated

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monozygote (MZ) correlation suggest that the stable component of well-being (trait happiness) is largely determined genetically. Heritability of the stable component of well-being was according to cited authors about 80%. Unshared environmental effects must then account for the remaining 20% of variance in the stable component of happiness. Interpersonal emotional relationships, satisfaction with job, goal achievement may be reasons of happiness but they also may be the outcome of feeling happy – behavior and well-being produce a feedback system.

Bartels and Boomsma (2009) showed the high heritability (40%-50%) of a subjective well-being (SWB): a total sum of cognitive and emotional reactions of people when they compare what they have and do in life with their aspirations, needs and expectations. It was shown that 36%-50% of individual differences in subjective well-being are accounted for by genetic factors and the remaining variance is accounted for by non-shared environmental factors.

However, what are the concrete genetic mechanisms that predispose subject to well-being? Today it is possible to propose an answer on this question. According to some investigations (De Neve, 2011) it is a genetic predisposition towards the emotional well-being and feeling of happiness, and the crucial role in these feelings belongs to the particular serotonin-transporter gene (5 HTTLPR) that encodes the distribution of a mood regulator serotonin (5HT) in brain nerve cells. There are two functional versions of this gene called the long one (L) and short one (S), and L produces more transporter-protein molecules and leads to more serotonin transporters in neuron cell walls than S thus providing higher activity of the serotonin-dependent brain system that regulates mood and behavior. According to De Luca et al. (2006), L allele has also two versions (A and G) and only the LA is associated with the high level of 5 HTTmRNA expression while LG is more similar to the S allele that determines a relatively low level of serotonin transporter (5HTTmRNA).

Each subject has two versions (called alleles) of each gene, one from each parent. As a result some people have two S alleles, some have two L alleles and other have one L and one S alleles. Those people who have at least one L (LA) allele display a general satisfaction with their life on 8% more often than those who do not have L allele et all, and those who have two L alleles display such satisfaction on 17% more often in comparison to those people who have only S alleles. In subjects with L version 35% are very satisfied with life, 34% are satisfied while in subjects with S version only 19% are satisfied (De Neve, 2011).

In parallel with the increase of the satisfaction with life increases the number of people who display the increase of both long (L) alleles from 20% to 35% (De Neve, 2011). At the same time the S alleles are the highest in individuals who are extremely unsatisfied with their life and in these subjects the combination of the S-L and L-S alleles are equally distributed.

On the other hand, serotonin influences normal fear (Hariri et al., 2002) that is necessary for the mobilization of body resources in the dangerous and indefinite situation. Thus happiness (emotional well being, free exploration and creativity) on the one hand, and a fear in dangerous situation on the other hand are both related to the high activity of the brain serotonin system. How is it possible to integrate these data in the holistic concept and to avoid contradictions between well-being and fear and at the same time explain how the genetic alleles of the serotonin system interact with the environment producing well-being?

2. SEARCH ACTIVITY CONCEPT – MAIN STATEMENTS

I suppose that the search activity concept can help to solve this problem. This concept was already discussed in the comprehensive way in many my previous publications (for review see Rotenberg, 2009) and I am going now only to mention its main statements that are most important for the topic of the present article.

By search activity is understood activity designed to change the situation or the subject's attitude to it in the absence of a definite forecast of the results of such activity (i.e., in the case of pragmatic indefiniteness), but with constant monitoring of the results of such activity. According to this definition certain behavioral categories cannot be linked with search

activity. This applies to stereotyped behavior having a quite definite forecast of results. Panicky behavior differs from search activity by the absence of the feedback between the activity and its regulation – the results of the activity are not considered at any stage and cannot be used for the correction of behavior. Renunciation of search is opposite to search behavior and in animals may assume the form of freezing or learned helplessness and in humans corresponds to depression and maladaptive (neurotic) anxiety.

Search activity is a component of many different forms of behavior: self-stimulation in animals, creative behavior in humans, as well as exploratory and active defense (fight/ flight) behavior in all species. In all these forms of behavior the probability forecast of the outcome is indefinite, but there is a feedback between the behavior and its outcome enabling the subject to correct his behavior in accordance to the outcome.

In research conducted together with V. Arshavsky (for review Rotenberg, 2009) we found that all forms of behavior which include search activity increase body resistance to the stress and prevents different forms of artificial pathology (artificial epilepsy, extrapyramidal disturbances caused by neuroleptics, anaphylactoid edema, heart arrhythmia etc.) while renunciation of search decreases body resistance, suppress immune system and predisposes subjects to the development of these disorders. We suggested that search activity defends subjects from different somatic disorders. In other words search activity saves health.

This statement got recently an unexpected confirmation in the investigations of authors who are not aware about the search activity concept. Frenkel et al. (2011) investigated the so-called “exceptional patients”, who had cancer considered incurable by medical report and who subsequently became disease-free or experienced unexplained survival time given the nature of their disease or treatment. The main common feature of these patients with different types of cancer (in USA and Israel) was personal activism. This was manifested in taking charge and getting involved in the process of diagnosis and treatment as well as becoming more altruistic (it means active in their altruistic attitudes to others). It was not only an active fight with the disease – it was also a general responsibility for their own life, they were doing the things they love, they had a feeling of the mission in their life. The common point of all these behavioral attitudes is search activity.

Exploration and creativity includes the most relevant realization of search activity and at the same time brings subject a feeling of happiness.

Search activity not only helps subject to cope with stressful life events and protects health. The process of search activity by itself does not matter whether it helps to achieve pragmatic goals or not, determines a positive feedback between behavior and brain monoamines. It means that definite level of brain monoamines is required to start search activity while search activity stimulates brain monoamine systems and helps to restore the level of brain catecholamines that have been used in the process of behavior. Such feedback causes an excitement and feeling of happiness like it happened not only in the process of creativity but also in the process of agitated fight, of goal achieving, of moderation the environment. It is a very special type of happiness – it is not a happiness of relaxation after the goal achievement, it is a happiness caused by the process of achievement.

Search activity in wakefulness is based on the combination of activating (ACh – acetylcholine and DA – dopamine dependent) and selective inhibitory (NE- norepinephrine and 5-HT – serotonin dependent) influences on cortical neurons. This combination determines the regulation of behavior, its goal direction, its relevance to the actual tasks. The predisposition to the goal-oriented selective activity (search activity) requires discrimination between meaningful and meaningless information elicited by the environment. Such discrimination depends especially on 5-HT that makes search activity flexible and relevant to the objective reality. Exactly in this sense it is possible to speak about the long allele of the serotonin transporter gene as a gene of happiness. It is happiness and well being based on our search activity.

3. THE SHORT AND LONG ALLELE OF 5-HTTLPR IN DEPRESSION AND ANXIETY

At the same time depression is characterized by the decreased activity of the brain serotonin system and the most effective antidepressants are based on serotonin and norepinephrine reuptake inhibition and increase the brain 5-HT and NE. Serotonin is an important factor in the regulation of the broad spectrum of behavior from feeding, sexual and motor behavior up to the cognitive activity.

The role of behavioral attitudes in the development of depression was also shown in our investigations (Rotenberg et al., 2007). We have investigated depressed patients among Russian-speaking new-comers in Israel using the Hamilton rating scale of depression and test BASE (Venger et al., 1996)— a projective questionnaire for the evaluation of different behavioral attitudes: search activity, stereotyped behavior, panic, and renunciation of search. In healthy subjects search activity and stereotyped behavior have always positive meanings while panic and renunciation of search have negative meaning. In depressed patients search activity is decreased and renunciation of search is increased (Rotenberg, & Cholostoy, 2004). However Hamilton rating scale values do not correlate with behavioral attitudes (Rotenberg et al., 2007). It was no difference in the mean values of BASE scales between patients with high (>31) and low (<22.7) scores of Hamilton Rating Scale. At the same time the level of depression was significantly higher in patients with the inverted structure of BASE (panic and/ or renunciation of search is higher than search activity and/ or stereotyped behavior) than in patients with the normal BASE structure. We come to the conclusion that the level of depression does not determine the configuration of behavioral attitudes but depends on this configuration. It means that normalization of behavioral attitudes may predict (or cause) the decrease of depression in patients while the inversion of behavioral attitudes may lead to the exacerbation of depression. This conclusion is in agreement with some methods of treatment based on the stimulation of active and constructive behavior. It means that neither depressive state nor behavior represent the direct outcome of the level of brain monoamines but it is a flexible feedback between mood, brain monoamines and behavior.

A meta-analysis of many investigations of interaction between the serotonin transporter gene (5-HTTLPR), stressful life events and risk of depression (Risch et al., 2009) have shown that only the number of stressful life events was significantly associated with depression. No significant association was found between %-HTTLPR genotype and depression. It means that genotype alone did not determine depression. There were also no definite evidences that serotonin transporter gene in interaction with stressful life events is associated with an elevated risk of depression although such association was found in some investigations. It means that the S allele of the serotonin transporter gene is not a gene of depression. S allele determines only a predisposition to the renunciation of search but this type of behavior may represent itself in different states, not only in depression. Moreover, subject may display an active reaction on stressful events even if the level of brain serotonin is initially low (in another case it would be impossible to improve the emotional state of depressed patients through stimulation of their active behavior. It is also well known that the severity of depression can suddenly drop in some cases when patient is in front of some unexpected and unavoidable events he has to cope with in order to help relatives or friends. In the process of such coping brain serotonin has a chance to increase).

It was already emphasized that serotonin influences normal fear (Hariri et al, 2002; Hariri, 2009) that is necessary for the mobilization of body resources in the dangerous and indefinite situations. Thus, it is related to all forms of behavior that include search activity (the regulation of behavior in the indefinite situation by mean of the estimation of the all nuances of environment and of the outcome of own activity in order to make this activity more relevant and goal oriented).

It was also shown (Kuhnen, & Chiao 2009) that a very special form of novelty-seeking (search) behavior – financial risk taking – is also determined by 5-HTTLPR long allele. 5 – HTT LPR S/ S allele carriers (the domination of short allele) take 28% less risk than those

carrying the S/ L or L/ L alleles of the gene (it means with the domination of the long allele or at least equal representation of the long and short alleles).

Some investigations have shown that effective antidepressants that are increasing the metabolism and activity of serotonin in the brain (SSRI) have a tendency to activate predominantly the left hemisphere (for review see Rotenberg, 2008). I have proposed in this review that it can be explained by the role of the left hemisphere in the outward oriented search activity: orientation in environment and selection of different opportunities of activity according to the desirable goals. Left hemisphere with its ability to discriminate relevant and irrelevant information and to focus on the goal is relevant for this task.

Urry et al. (2004) have investigated 84 right handed middle-aged subjects. They completed self-reported measures of eudaimonic well-being, hedonic well-being and positive affect prior to EEG registration in a resting condition. Authors found that greater left than right superior frontal activation was associated with higher levels of both forms of well-being. What seems to be especially interesting in this investigation, that hemisphere specific analysis documented the importance of goal-directed approach tendencies beyond those captured by approach-related positive affect for eudaimonic but not for hedonic well-being. It is possible to suggest that hedonic well-being is related to relaxation. Authors emphasized that appropriately engaging sources of appetitive motivations that are opposite to the hedonic relaxation (and in my terms requires active search based on the left hemisphere prefrontal activation) may encourage the experience of well-being.

In this context it seems important to discuss the investigation performed by Van de Vliert (2013). He investigated the members of different societies around the world, their subjective well-being, self-expression, individualism and democracy, and divided these societies according to the three types of habitats: a) demandingly cold or hot habitats with poor monetary resources, b) undemanding temperate habitats (comfortable climate) in poor or rich areas, and c) demandingly cold or hot habitats with rich monetary resources. The first condition from the author's point of view is threatening because the demands of the hard climate are not satisfied enough in the poor society. The last condition is a challenging one because although the climate is equally hard its demands can be satisfied. Author found that "although threatening and challenging habitats are both more stressful than comforting habitats, subjective livability in threatening habitats is worse than in comforting habitats, whereas subjective livability in challenging habitats may be experienced as even better than in comfortable habitats".

Author comes to the conclusion that the difference in monetary resources by itself determines this difference in well-being between the first and the last societies. However a question remains why the monetary resources are different in these societies and would it be enough for well-being if the poor society in the demanding condition will be supported from outside by monetary resources? Such opportunity seems to be in contradiction with the proposed difference between threatening and challenging habitats because if money resources will come from outside without goal-directed efforts of the society members they will not create a challenge. And how it happened that in the similar climate one society is poor and another is rich? These questions are out of the consideration of the article.

From my point of view the demanding climate stimulated search activity in the members of the last society due to some additional historical and cultural conditions (it has to be checked), and due to the high search activity this society achieved its high economical status and well-being. It is search activity that made them open-minded. Thus economical status is not the cause of well-being, but as well as well-being by itself, it is an outcome of the relevant reaction on the challenge – of the active search for problem solutions. When the same demands and challenges do not produce search activity (that has to be trained in the society in the process of cultural development and in the process of individual maturation), they became threatening being unavoidable how it happens in the first society. And due to the general tendency to give up instead of searching for the solution of the problem this society is poor and is characterized by the low level of well-being and happiness. In this condition the support must be oriented on the stimulation of search activity.

The undemanding comfortable climate in the intermediate group predisposes subjects to relaxation and does not stimulate search activity for meeting common needs of existence. However it also does not cause stress and does not suppress search activity being not threatening, and some groups and members of the society may display search activity for intrinsic satisfaction and for growth needs while other groups and members remain relaxed. Poor people in these societies often have a pleasure from the calm (easily achieved) comfort and rich people became satisfied by the realization of their own open-minded goals.

My hypothesis is confirmed by data that depression, anxiety, perceived ill health and unhappiness are more prominent in poor populations residing in more demanding climate, intermediately prevalent in populations residing in undemanding climate irrespective of income, and least prevalent in rich populations residing in demanding climate. I have already emphasized the role of search activity in health protection in stressful conditions.

Search activity concept helps also to reconsider very interesting data of Chiao and Blizinsky (2010). These authors found that the societies of East Asia are characterized on the one hand by the prevalence of cultural values of collectivism (opposite to the cultural values of individualism in Western societies of Europe and USA) and on the other hand by prevalence of the S allele of the 5-HTTLPR. And quite opposite to what is going on in Western societies and what was stressed previously in this manuscript, nations with a higher frequency of S allele carriers in East Asia showed a low prevalence of anxiety and mood disorders.

First of all it confirms that a serotonin transporter gene is not a gene of happiness. If it would be a gene of happiness we would have to expect a negative correlation of anxiety and mood disorders (states opposite to well-being) not with the S allele but with L allele. Authors of this investigation believe that in these societies a prominent collectivism protects subjects with the dominating S allele from anxiety and mood disorders. It is correct but from my point of view the roots of these relationships are more deep. They are in the essence of the cultural values of these Far East societies that were for many centuries oriented not on changing the outside environment (that requires search activity based on the domination of the left hemispheric style of thinking) but on the integration in the environment and in the society, on the dissolution in it and merging with it. It does not require search activity and do not promote individualism. Collectivism produces for such integration a comfortable social climate comparable with the soft climate of nature. Moreover, in such conditions individualism and high individual search activity may be even frustrating being in opposition to the general values and attitudes of the society. However it is possible to suggest that in special stressful conditions that require high search activity members of these societies may be less protected. It is confirmed by the greater historical and contemporary prevalence of disease-causing pathogens or infectious diseases in these societies.

My proposition, as I have already stressed, is that what is supposed to be a gene of happiness and well-being (the long allele of 5HTT LPR) is a genetic predisposition to search activity and the realization of search activity determines well-being. Of course, search activity may represent itself in the adaptive fear and anxiety that are not associated with feeling of happiness and subjective well-being. It may be one of the reasons why even in subjects with two L versions of the gene more than 30% are not satisfied with their life.

Subjects with one or two copies of the short allele (S) of the serotonin promoter polymorphism associated with reduced 5-HTT expression and function also may display an increased fear and anxiety related behavior. However, it is possible to suggest that it is not a normal adaptive fear that accompanies active search but a pathological destructive fear and anxiety combined with panic behavior that accompanies renunciation of search (Rotenberg, Boucsein, 1993). This proposition may be partly confirmed by data (Hariri et al., 2002; Mann 1998) that individuals with short allele exhibit greater amygdala neuronal activity in response to fearful stimuli compared with individuals that are homozygous for the long allele. Low concentration of the metabolite of serotonin in the cerebrospinal fluid predicted by short allele is also associated with suicide attempts (De Luca et al., 2005, 2006).

4. PARADOXES OF SUICIDALITY

However, it is necessary to take into consideration that these data are confirmed not by all investigators. For instance, Belliver et al., (2000) have found no associations between S allele of the 5-HTT LPR and suicide attempts. This contradiction requires a comprehensive discussion.

Among patients with the history of suicide attempts S allele frequency was the highest in those who had attempted suicide by violent behavior (.58). According to 5HTT LPR polymorphism patients without suicidal behavior were similar to the control subjects. Authors suggest that probably S allele represents a vulnerability factor for suicidal behavior, and especially violent suicidal behavior in affective disorders. It is necessary to take into account that depression can display itself in a form of passive behavior, total renunciation of search, and in this case a chance for suicidal behavior is not very high. Nevertheless it can appear as a final step of the road of giving up that leads to the finish of life. In this case it will be a quiet and not violent behavior. However, a combination of depression with a tendency towards the chaotic (violent) behavior increases the chance for suicide as an active attempt to escape stressful condition, as a protest, as a search for a mysterious alternative. Such violent suicidal behavior (attempts) can be considered as a maladaptive misdirected search activity (see Weinberg, 2000) mixed with renunciation of search that is more typical for pure depression and passivity.

I have discussed the role of the misdirected search activity in the pathogenesis of psychotic disorders (Rotenberg, 1994) and the violent suicidal behavior is another form of such misdirected and maladaptive activity. It is a desperate attempt to cope with unbearable experience. Regular suicidal attempts occurred among the subjects who continued to feel helplessness and display renunciation of search between the episodes of depression. However it is remarkable that some subjects a week after the suicidal attempt display lower levels of hopelessness, depression and suicidal ideation, their problem solving ability improves, as if suicidal attempt paradoxically increased their search activity. But it is not surprising if suicidal behavior represents a misdirected search activity. Search activity increases inner resources of body and activates brain catecholamines does not matter where it is directed (Rotenberg, 2009).

According to Weinberg (2000) there are two groups of patients with suicidal attempts: 1. Those who demonstrate extreme renunciation of search, helplessness and hopelessness and 2. Those who display renunciation of search coupled with misdirected search activity. Both groups are unable to use environmental feedback for the redirection of their activity. Special investigations have shown (see Weinberg, 2000) that the relationships between brain monoamines and suicidality differ from the relationships between brain monoamines and depression by itself. Low level of brain 5-HT does not lead to suicide. Among persons with the suicidal attitudes 5-HT depletion decreases these tendencies while suicide attempts are frequently followed by increase of NE and 5-HT at least for a short period. It confirms the statement that suicidal attempts often represent not a direct outcome of depression and not a natural part of depression but an active, impulsive and irrelevant reaction on depression.

It is well known that antidepressants (SSRIs) may on the first step of treatment cause or exacerbate the suicidal attempts (Goldblatt, Shatzberg, 1991). Of course search activity incorporated in suicidal behavior is not leading to the solution of the problem that caused depression, it is leading to a deadlock and to the further renunciation of search. Suicidal behavior is a part of a vicious circle and does not allow patient to turn to the constructive search and exactly for this reason differentiate treatment resistant depressive patients from the non-resistant.

Thus suicidal behavior often includes a destructive search activity. With the exception of demonstrative suicide, it is not directed outside and this destructive search activity cannot have long lasting positive perspective. It is reasonable to take into consideration that in some cases suicide may not display misdirected search activity but only a definite and strong wish not to be, to finish with life as a top point of renunciation of search. Probably just in these

cases 5-Ht in depressed subjects with suicide attempts is lower than in depressed patients without suicide, and the difference between these two versions of suicide may explain the difference in the investigations of 5-HT system in depressed subjects with suicide.

It is a special and very serious problem of suicide attempts performed by creative individuals. On the first glance it looks paradoxically in the context of the present concept because creativity by itself is a pure and highest form of human's search activity. However many creative persons are suffering from bipolar disorders, and while creativity is associated with hypomanic episodes, depression, that regularly appears after hypomania, may predispose subjects to suicides, especially those subjects who have a regular experience of the extreme activity in hypomania. The relationship between creativity and hypomania may be bidirectional because both states are based on the same brain mechanisms and on the similar brain monoamine systems (DA).

At the same time when creative people are out of the state of creative activity they may be predisposed to depression not only due to their bipolar disorders. Creative people are very sensitive to the environment – it is a normal condition for creativity, but it means that they are highly sensitive also to many life events and to emotional experiences that may cause, if negative, a state of helplessness and hopelessness. For the same reasons after finishing creative tasks gifted people may suffer from the disappointments of achievements and dissociations between the imaginative expectations of creative activity and its real outcomes, from painful discrepancy between their ideal view of the possible results of creativity and the real results that are only a pale copy of ideal. Problems with self-realization may cause depression and renunciation of search.

At the present time, the attention of the investigators displays a tendency to shift from searching direct relationships between gene alleles and emotional state of subjects toward more complicated interactions between gene alleles, environment (including life stress) and mood. After the consideration of the results of investigations, De Neve (2011) comes to the conclusion that the unique and single gene of happiness does not persist and that it is a combination of genes that are influencing the subjective well-being in relationships with the factors of environment. It seems to be more close to the approach proposed by search activity concept that is also considering the interactions between the environmental conditions, behavior and health (mental and physical) (Rotenberg, 2009). The environmental conditions and especially stressful conditions require active search, and active search requires a high level of brain serotonin that at least partly depends on the gene alleles. The deficiency of active search is leading to mental and somatic disorders, especially in stressful conditions.

Search activity is important also in the non-stressful conditions but in these conditions its level may be not so high for adaptation and for this reason the deficiency of the serotonin system may be less harmful.

Grabe et al. (2005) found no independent associations of genotype with mental and physical distress however they found interaction between genotype, unemployment and chronic diseases in females. It was an interaction between short allele of the gene and environment (stress of unemployment). It can be also related to the difference in behavioral attitudes between genders. According to our investigations (see Rotenberg 2009) in men search activity in demanding conditions has a tendency to be higher than in women. I cannot exclude that this difference is related to the process of maturation. Men may become more active due to the requirements of the society and a special training of search activity in the process of maturation.

Munato et al. (2008) have also shown a modest association between the 5 HTTLPR short (S) allele and increased negative affect and risk for depression in the context of environment adversity. This relationship may be mediated by increased neuroticism. It was also a more robust link between S allele and heightened amygdala activation to emotional stimuli vs. neutral stimuli. Authors proposed a hypothesis that the heightened amygdala activation (especially right amygdala activation) to the environmental threat may mediate the association between S allele and increased trait-negative affect as well as risk for mood disorders in response to stress.

Of course the deficiency of the protective search behavior determined by the functional weakness of the brain serotonin system may be a key to mood disorders in the threatening environment and the hyperactivity of the right amygdala may be a sign of the increased sensitivity to stress.

5. BRAIN MECHANISMS OF EMOTIONAL SENSITIVITY AND GENES

There are data that subjects with the domination of short allele demonstrate the activation of amygdala while passively viewing pictures with emotionally negative content (in comparison to neutral pictures) and while reading words with negative meaning or viewing faces with expressions of fear and anger (see Pezawas et al., 2005). It may mean that the short allele is related to the increased emotional sensitivity. However it may have also another explanation.

In subjects with the domination of S allele the gray matter of amygdala and anterior cingulate cortex is reduced and the functional connectivity between these systems is disturbed (see Pezawas et al., 2005). It may be a reason of the decreased adaptive ability, of the deficient response of amygdala to negative stimuli, of the low functional ability of this system. It may determine the vulnerability to depression. The abovementioned physiological activation of the right amygdala may be an outcome of this low functional ability in the same way as the general physiological activation of the right hemisphere is an outcome of its functional deficiency in depression (Rotenberg, 2004). This explanation seems to be in a good agreement with data that subjects with the domination of S allele are predisposed to depression.

It is reasonable to take into consideration also another opportunity. Healthy subjects with the S allele display a decreased activity of different brain structures (including amygdala) while performing cognitive tasks without emotional load in comparison to the control passive relaxed state without particular tasks (Pezawas et al., 2005).

In this context some data of the investigations are especially important. Thus, it was shown, that the relatively increased reaction of the amygdala on the negative emotional stimuli vs. neutral stimuli in subjects with high S allele is not a sign of the INCREASED reaction on the negative emotional cues (Canli et al., 2005, Canli, Lesch, 2007, Pezawas et al., 2005). Actually it is an outcome of the DECREASED reaction on the neutral stimuli in comparison to the fixation rest - relaxed wakefulness without any tasks. Activation decreases in amygdala across active but emotionally neutral tasks relative to passive state in subjects with S allele in comparison to subjects with L allele. It means that in subjects with high S allele neutral stimuli do not evoke any interest and do not stimulate its investigation that characterizes healthy subjects with the long allele and is a sign of spontaneous search activity. In comparison to these neutral stimuli negative stimuli in subjects with the domination of S allele causes some activation because they need attention and create an unavoidable emotional tension.

At the same time the activation of amygdala on emotionally neutral tasks that have to be solved according to the task conditions is even less prominent in subjects with domination of S allele than in the passive state that causes relaxation in people with the domination of L allele. It means that in this passive state subjects with the domination of S allele are relatively tensed like depressed patients, it is a destructive tension similar to neurotic anxiety, and at the same time they are unable to mobilize themselves in a constructive way even for the solution of simple emotionally neutral tasks - also just like depressed patients.

Amygdala and hippocampus showed a gene-environment interaction effect (Pezawas et al., 2005): activation at rest (compared to an active face processing) correlated positively with life stress in subjects with S allele, but negatively in subjects with L allele, and in subjects with S allele stress caused depression. It means that activation of these structures during rest typical in subjects with the dominating S alleles reflects the predisposition to the maladaptive reaction on stress.

Our explanation corresponds also to the negative correlation between S allele and social “agreeableness” because such “agreeableness” requires mental flexibility that may display search activity.

Thus subjects with the domination of S display the decreased activation of some brain structures on the neutral stimuli instead of the increased activation on the negative stimuli, although their sensitivity to negative information is high. It is confirmed by data that it is no difference in amygdala activation between the S group and L group in response to negative-fixation stimuli (Canli et al., 2005). These subjects display a tonic activation of amygdala in the state of rest combined with its phasic deactivation by performing tasks that require active behavior. It is very similar to what happened with physiological brain activation in depression (see Rotenberg, 2004). It means that amygdala in subjects with short alleles displays a tonic (and functionally irrelevant) activation due to the decrease of the 5-HT transportation. It is a sign of enhanced emotional sensitivity that displays itself also in the increased reaction of the right insula and putamen not only on negative but also on neutral words (Canli et al., 2005). Activation of putamen, caudate nucleus and thalamus as a reaction on negative stimuli corresponds to the role of these structures in modulation of emotional distress. This distress is high when in stressful conditions search activity is low (Rotenberg, Boucsein, 1993). The activation of brain structures (right amygdala) as a reaction on negative vs. neutral words was always higher in subjects with short alleles than in subjects with long alleles (Canli et al., 2005). However, it happens because the S group show decreased activation in response to neutral stimuli (not due to the increased activation to negative stimuli).

Activation of the left hemisphere was also more prominent in subjects with short alleles on positive vs. neutral words. It needs explanation. Probably positive words are relaxing subjects with L allele but are unable to relax subjects with S allele?

In the state that has to be a calm state of relaxation subjects with the S allele display a more prominent blood flow in amygdala (Pezawas et al., 2005). Presumably it means that a “rest state” in these subjects is a state of the stable inner emotional tension. Such tension has no objective reasons and is destructive like distress (See Rotenberg, Boucsein, 1993). This destructive tension is increased by the negative information but this reaction on the negative information is also not constructive, it does not contain search activity, it is not an active defense. As it was already mentioned, brain activation in the state of rest in these subjects correlates positively with the life stress and in subjects with the domination of L allele it correlates with the life stress negatively. It confirms our proposition that this activation in subjects with S allele reflects the destructive tension while in subjects without the domination of S allele stress causes the constructive mobilization that correlates negatively with the destructive activity in the state of rest.

This explanatory proposition is also confirmed by data that subjects with the dominating S allele are characterized by ruminations during the life stress (Pezawas et al., 2005). Ruminations are destructive by themselves.

Subjects without the domination of S allele display more physiological tension while solving tasks vs. the state of relaxation, and this difference is relevant.

According to Pezawas et al. (2005) subjects with S allele are characterized by the decrease of gray matter in those parts of the limbic system that are critical for processing negative emotions (especially in amygdala and perigenual cingulate).

When healthy subjects with L allele are dealing with events that can cause fear they display fight coupling in amygdala-cingulate circuit as a sign of feedback system that has a task to decrease a negative affect (see Pezawas et al., 2005). Subjects with S allele do not display such coupling. The amount of the fight coupling negatively correlates with anxiety. This system is important for the regulation of emotions and is deficient in subjects with the domination of S allele. Exactly the level of coupling in amygdala-cingulate circuit, more than the volume of these structures and more than their activity, predicts harm avoidance as behavioral trait what from my point of view is relevant to search activity.

According to Caspi et al. (2010) subjects with the 1-2 S alleles are characterized by the increased neuroticism and by the predisposition to depression and in these subjects the reaction of amygdala on the threat is increased (however, as I have already emphasized, it seems to be a destructive reaction).

There are data (see Caspi et al., 2010) that short allele (S) moderates the connections between a bad insufficient care of the small child (that determines the stabilization of the natural tendency toward renunciation of search in a small child instead of helping to overcome it) and the development of depression and psychosomatic disorders. Children who are characterized by the domination of the short allele and at the same time have suffered from the bad care in childhood are more sensitive to negative experiences and are predisposed to the bad self-regulation. In stressful conditions they are more anxious. It was suggested that a short allele of 5HTTLPR is a genetic predisposition to neuroticism, however this predisposition determines the development of the disease only in the condition of stress. From my point of view it is a real predisposition towards renunciation of search.

Serotonin is very important for the mediation of connections between amygdala and medial prefrontal cortex. The latter is responsible for the goal directed behavior that contains search activity and limits reactivity of the amygdala (because the constructive search activity blocks the destructive emotional tension). In subjects with the domination of S allele and with the deficiency of 5-HT transportation the functional activity of this system is disturbed and the gray matter of amygdala and medial prefrontal cortex is decreased. The general sensitivity to stressful events is increased and it is difficult for the subject to switch attention from these frustrating events although this attention does not determine the constructive protective behavior.

It was shown (Spinelli et al., 2007) that young monkeys with the domination of S allele display less prominent active coping and protest being separated from the mother. At the same time they display more prominent anxiety, agitation, stereotype behavior, increased HPA and ACTH reactions on stress, and it is opposite to the constructive search activity and corresponds to renunciation of search. The authors concluded that according to the results of all investigations on humans and on animals it is unreasonable to search for a special genetic predisposition to the mental disorders and it is more reasonable to search for the influence of different genes on the vulnerability to stressful events and for the relationships between genetic particularity and environment factors as a real reason of mental disorders. It is also in agreement with the search activity concept: the renunciation of search is especially dangerous and vulnerable in stressful conditions that require search activity for coping and survival. Caspi et al. (2003) have shown that subjects with the short allele demonstrate more prominent depression in stressful conditions than subjects with long allele.

According to Fox et al. (2009) allele variation in the promoter region of the serotonin transporter gene (5-HTTLPR) is associated with differential biases for positive and negative affective pictures. Individuals homozygous for two L (LL) version showed a marked bias to selectively process positive affective material alongside selective avoidance of negative affective material. This potentially protective pattern was absent among individuals carrying the S allele of gene (S or SL combination) who displayed an orientation towards negative affective material and avoidance of positive stimuli. It was observed when affective material (pictures with positive and negative valence) was presented during 500 msec., thus it was the first reaction on the affective stimuli, performed immediately after its holistic grasping and before its successful integration. It means that individuals with the domination of S allele are initially predisposed towards fixation on negative affective information. It is a sign of high emotional sensitivity probably combined with the deficiency of protective strategy that includes search activity.

However, some investigations contain on the first glance opposite results. Beevers et al. (2011) investigated the attention to positive and negative facial expressions in subjects with the long and short alleles. Those with the S alleles and with LG (long allele with guanine that is close to S allele) demonstrated the preference of the gaze toward the positive stimuli. Subjects with LA (long allele with adenine that determines the most prominent serotonin

activity) do not demonstrate preferences to any emotional stimuli. However it is necessary to take into consideration that in this investigation was used a more long period of the presentation of affective stimuli – 5 sec. or even longer while in the investigation of Fox et al. it was 500 msec. Beevers et al. propose that in the later stages of information processing highly sensitive subjects with S allele, who are unable to integrate the negative affective information prefer to orient their attention on positive images. It looks out as if subjects with the S and LG alleles were looking for any opportunity to reduce their emotional tension caused by negative stimuli. For the subjects with LA allele it is not necessary because their high brain mechanisms of integration the potentially threatening information (right frontal lobe, see Rotenberg 2007) are more flexible and more active. Beevers and al. (2011) mentioned that when healthy people are instructed to regulate their emotions volitionally they also view negative emotional images less often and positive images more often. It means that they direct their attention on positive images. It is important that subjects with the domination of S/ LG allele viewed neutral stimuli in a similar fashion to their viewing of sad and fearful facial expressions. Subjects with S/ LG allele either actively directed attention toward happy faces (rather than simply avoiding negative stimuli) or they viewed neutral faces as negative one like it happened in high trait and state anxiety.

It is necessary to take into consideration that the concentration on the positive stimuli and attempts to avoid negative stimuli not on the initial stage of perception but during the all processes of perception is similar to the perceptual psychological defense and is not constructive in the real life because it determines the “blindness” to a real danger. Such perceptual defense means that subject cannot adopt himself to the negative experience, to integrate it in his mental life. In combination with a high emotional sensitivity that was already mentioned (and that display itself also in the just cited investigation, Beevers et al., 2011) it determines attempts of subjects with the dominating S allele to avoid and ignore important information that causes emotional tension instead of coping with it. Probably these subjects like schizophrenic patients have a tendency to perceive even neutral facial expressions as negative and dangerous (see Rotenberg, 2011) and try to concentrate their attention on happy faces. In subjects with S/ LG allele the functioning of the serotonergic system is decreased (what determines low search activity) and is accompanied by the increased sensitivity to negative emotional stimuli, while subjects with LA allele related to the increase of the transcriptional 5HT activity are more protected from stressful events.

6. CONCLUSION

From the all abovementioned data it is possible to make the following conclusion. The so-called genes of happiness and well-being actually represent the genetic predisposition to search activity that is stimulated by the new and stressful events of the environment. Search activity not only protects mental and somatic health but also brings subject an exciting feeling of overcoming obstacles, of finding new solutions, of achieving goals, of creating new reality and for all these reasons it is subjectively perceived as well-being or even happiness.

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