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Review

Depression: The Importance of Etiology and the Involvement of Dopaminergic Reward System

Rowena Kong*

Department of Psychology, The University of British Columbia, Canada

ABSTRACT

Depression is multi-faceted, and the level of its symptom severity is variable along different biological and psychosocial dimensions between individuals with such disorder. This paper discusses the importance of focus on the disorder etiology in practical clinical setting and context in the process of diagnosis and treatment. With increasing research exploring the role of dopamine in the pathology of the disorder, the probability of its target in future treatment is assessed. The need for more collaborative research methods which seek to integrate discrete concepts and models of depression to better understand mechanisms of causes is emphasized to build a more unified strategy against the disorder. Finally, an alternate perspective of mood dysregulation as an adaptive response to counter negative elements in life is proposed in association with the body's natural tendency to maintain homeostasis.

Keywords: Depression; Clinical; Etiology; Causality; Dopamine; Reward; Anti-depressant

INTRODUCTION

Clinical depression is a debilitating mood disorder which negatively impacts one's productivity leading to the burden of disability that requires treatment to promote recovery and prevent relapses. To date, there exists a range of diverse treatment interventions for depressive disorder to reduce its negative outcomes on the health and daily functioning of individuals. Pharmacological and psychotherapy treatments may not always produce anticipated positive results and relapses are common depending on the unique symptom profile of the individual [1,2]. The etiology of depression is varied and spans a multi-faceted range of factors associated with genetic, early life stress and trauma, anxiety, cognitive, sociobehavioral and recently neurochemical aspects of an individual that are relevant to the prognosis of the condition. The causes of onset of depression are as multi-faceted as the symptom clusters of the disorder itself, ranging from genetic susceptibility to early life trauma and stress, and comorbidity with related neurological conditions such as Alzheimer's disease [3-9]. However, the diagnostic criteria for a depressive disorder as laid out in DSM-5 remain brief in accounting for the latest cumulative progress in research. In actual clinical settings, patient observation and counselling are the primary means for a mental health professional to reach a conclusion of diagnosis and level of functioning of the individual without extended procedures such as genetic testing and brain imaging. The modest level of specificity and uniqueness of diagnostic criteria profile and absence of neuroimaging evidence may explain the poor prognosis of certain groups of patients due to disorder variability and heterogeneity that could have stemmed from a broad range of biopsychosocial causes [10]. As such, the association of symptoms with causes in patient clinical assessment is less prioritized in psychiatry which represents a potential area for examination in the development of future treatment strategies.

In the process of pharmacological treatment of depressive symptoms, there is a general tendency to presume that cause(s) and symptoms exist as separate entities and that a continuum between them is ignored, if not dismissed as insignificant. An inadequate understanding of cause and symptom matching for each unique depressive individual may result in mistargeted treatment which is evidenced by negative response and poor prognosis. For instance, merely targeting neurotransmitter imbalance may not be sufficient when a social conflict stressor repeatedly impacts an individual and subsequently prolongs the depressive episode, during which the cause may interact with symptoms on a continual reinforcing basis that makes passive coping an emotional and mental burden.

***Correspondence to:** Rowena Kong, Department of Psychology, The University of British Columbia, Canada, E-mail: rowena.kong@alumni.ubc.ca

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Often, the benefit of neuroscientific research on depression may be compromised by the presumption of dissociation between internal neurochemical activity and the influence of external stimuli on neurotransmitter imbalance. There seems to be a lack of explanation which links macro level causal elements with dysregulated processes occurring at the neurotransmitter level. For instance, the duration criteria for a negative social experience to cause a lasting modification of serotonin and other related neurotransmitter levels in the brain, which is one of main targets in antidepressants, could be further elucidated in research. Building an understanding of the significance of temporal factor in the initiation and continuance of depressive episodes beyond the short-term duration of diagnostic criteria for the disorder can have implications for the efficacy of current range of treatment.

Although the clinical practice of psychiatry places less weight on the significance of causes of depression onset, this does not deter research from actively exploring a broad range of theories and methods which are close to answering the fundamental question of etiology. There is a surge of interest in utilizing neuroimaging methods to uncover possible brain structural anomalies associated with the disorder. There are now more hypotheses put forward to explain the mechanism of depression which was once limited by serotonin deficit hypothesis [11]. Perhaps the reason why the serotonergic system is one of the first neurotransmitter pathways to be associated with depression is due to main disorder characterization of mood dysregulation, in which serotonin plays a key role in modulating [12,13]. Nevertheless, it has come to be known that other symptom manifestations of depression extend beyond the oversimplification of negative mood persistence. Depression as an occurrence of low or negative mood is a part of our everyday emotional cycle and it is not considered a disorder until it is prolonged for at least two weeks, after which it is maladaptive [14]. It is therefore important to identify factors which contribute to the lasting duration of depressive symptoms, not only the characteristics and associations of the disorder. On the other hand, whether the accompanying secondary symptom criteria for the disorder, e.g. sleep disturbances, fatigue or loss of energy, psychomotor agitation or retardation, precede or result from primary negative mood dysfunction remains to be further investigated. However, the diagnostic challenge of symptom cluster variation between depressed individuals hints at multiple biopsychosocial factors that interact dynamically in producing the depression subtype.

LITERATURE REVIEW

Increasing focus on dopamine and the Brain's reward pathway

An area of research which has received much recent attention delves into the role of dopaminergic reward system in the neuropsychopathology of depression, paying particular attention to impaired response to positive rewarding stimuli in depressed individuals [13,15-19]. Dopamine is a neurotransmitter which belongs to the class of monoamines like serotonin and is known to be involved in a variety of mental and physical functions such as motivation, reward learning and locomotor activity [20-22]. The implication of decreased activation of dopaminergic neurons being involved in the mechanism of depression is that the progression of the disorder would have a far-reaching impact on a number of aspects of an individual's functioning as opposed to solely mood dysregulation. The activation of dopaminergic neurons for processes required in motivation, learning and movement which leads to performance of action by an individual can have a role to play in the depressed physical functioning of the disorder. Although it remains to be tested, the negative effect of impaired reward reinforcement learning in depression likely develops over time to produce lasting effect into adulthood. Exploring the variation between short-term and long-term depressive periods of study subjects in relation to imaging evidence of dysfunctional dopaminergic activity could offer insight into the temporal workings and probable causality role of the brain's reward circuits.

We are still yet to see the correlation of this impaired dopamine function with long-term exposure to negative stimuli and past life experiences that could have produced dampened response to positive elements in an individual due to lasting modification of relevant neural circuits. Prospective studies are useful in this case for the study of children and adolescents at probable high risk for depression, based on variables such as disadvantaged living conditions and lack of social support, and to include these sociobehavioural measures with concurrent neuroscientific findings to better explore the temporal mediating factor in depression onset. On the other hand, the measure of level of positivity and negativity of stimuli and/or themes sample in studies is related to characteristic of valence, which entails emotional perception and evaluation, hence the brain's limbic region and associated pathways play an important part in the processing of emotional response by participants. Localized region and circuit connection abnormalities are equally significant in the disorder pathology [23,24]. A dysfunction in the limbic-cortical network along with reduced volume of certain prefrontal cortical regions have been discovered in depressed individuals [25]. It is also likely that responses to drug treatment can be modulated by abnormalities in limbic-subcortical network, thus emphasizing structural and functional aspects as additional challenging targets for treatment and the inadequate and temporal efficacy of standard medication. A question that could be raised is whether drug targets of neurotransmitter release produces a more transient or short-lived process that is subjected to daily fluctuations of both internal and external cues. It would be useful to draw a hierarchical stage-wise model of the process of depression beginning from the fundamental localized micro to region-wide macro levels. Nevertheless, it is difficult to determine the direction of effect which considers the role of neurotransmitter dysregulation, reduced dopaminergic activation and structural modification to answer the question of precedence in causality. Hence, it would be interesting to see studies with a more comprehensive design in methodology that attempt to combine multi-level concepts to benefit current understanding of dynamic neuronal interactions as opposed to examining them as discrete units or concepts.

Pharmacological treatment intervention which targets dopaminergic regions is still in its early stages of experimentation with less specific direction to take. Furthermore, it is unclear as to what early factors contribute to the impaired reward processing and imbalance in sensitivity to positive and negative rewards displayed by individuals with depression. Inconsistent and ineffective drug treatment outcomes for clinically depressed individuals have encouraged further research of the disorder in various directions, such as cognitive-behavioral strategies and brain neural stimulation, with the goal of expanding the range of better and promising alternative therapies in alleviating persistent symptoms. Previous understanding which strongly associates neurotransmitter serotonin imbalance with depressive disorder bears limitation in explaining causality and present research now turns to the dysfunctional reward processing perspective [26].

The mesolimbic dopaminergic reward pathway of the brain which is made up of neuronal projections that run from the midbrain region to the nucleus accumbens has long fascinated researchers with its significant role in reward-seeking behaviour, addiction and impulsivity. Research is increasingly exploring the theory of impaired reward processing which could contribute to the psychopathology of depression. A reward is anything with an attractive value which creates a tendency for an individual to approach and consume it [27]. These approach and consuming behaviour are the anticipatory and consummatory components of reward processing respectively. Studies with depressive patients have demonstrated their reduced sensitivity to reinforcement of positively rewarding stimuli, possibly due to dysregulation in reward learning which happened to also lead to atypical response of decreased aversion of negative stimuli [28,29]. Anhedonia, a decreased response and affect towards pleasurable stimuli, is exhibited by depressive individuals. Pizzagalli [18] reported that a region in the basal ganglia, the caudate, has reduced volumes in depressed study participants which were associated with their higher scores of an hedonic symptom. This stresses the role of volumetric brain differences between depressed and non-depressed individuals that could account for the reduced interneuronal connectivity and sites of activation in regions where dopaminergic receptors are concentrated. To achieve a more thorough understanding of the psychopathology of depression, it is important to draw relevant connections between the social basis of reward-related learning and the accompanying underlying neurochemical processing in the brain's internal network which together promote the vulnerability to the disorder. Thus, early life experiences and brain development and neuronal organization during such crucial stages of childhood and adolescence are significant in their contribution to the shaping of one's attitude towards reward-related learning and the behavioral tendencies, thus the extent of insensitivity towards value of reward and the severity of dysfunctionality which result and act on the neurochemical processes of brain development. Nevertheless, there is also bidirectionality in the way one interacts with the environment and the genetic susceptibility to certain types of stressors unique to an individual should not be excluded from the overall picture.

Although dampened dopaminergic activity in response to positive stimuli likely contributes to the persistence of depressive mood in susceptible individuals, the exact causal mechanism which sets such anhedonic symptom in motion remains to be investigated in-depth and may not be a one-size-fits-all answer but entail a combination and integration of neural processes which span multiple levels of neuropsychological hierarchy. Given the knowledge of reduced dopaminergic transmission in the mesolimbic pathway, can dopamine agonists (ligands which bind to and activate dopaminergic receptors) be part of the future avenue of pharmacological treatment for clinical depression? The answer is that it is still too early to tell as there has yet to be an acquaintance with a comprehensive list of possible side effects associated with a handful of agonist drugs being developed. As an example, although preclinical animal testing of the dopamine D1 receptor potentiator, DETQ, supports its potential use in the treatment of depression and related neuropsychiatric disorders, it also casts immunological and sleep-wake cycle concerns by raising histamine levels [30]. Thus, a profitable connection between feasibility in medical use and benefit-over-cost clinical outcome(s) would determine the progress in the future implementation of dopaminergic agonist drugs as intervention candidates for depressive disorder. With the heterogeneity of individuals' depressive symptom profile, it is best to formulate a general standard guideline to determine the level of disorder severity that is suited to its associated medication dose amount.

Symptom context and the possibility of an adaptive mechanism

Research has also been turning into the field of genetic markers to determine the difference in susceptibility of individuals to clinical depression. However, the probability of an individual developing depressive-like symptoms and in the form of a clinical disorder does not invariably begin with genetics. Given a certain amount of exposure to highly stressful events, genetic susceptibility does not play a singular role in increasing the probability that one would succumb to depression. On the other hand, it can be questioned about the extent to which an episode of depressed mood can occur as an adaptive normal part of the response process to a negative circumstance or interpersonal exchange, whether it is anticipated or unexpected. The question of a person's state of depression as an adaptive response to negative stimuli and circumstances could be answered by asking to what extent a positive and pleasurable mood response to a negative setback should be considered maladaptive or abnormal. Hence, the nature of the context in which one's response is generated bears significance such that if we were to base our evaluation of the possibility of a depressive disorder solely on the duration and nature of symptoms in DSM-5 diagnostic criteria, a misapproach in rushed or impulsive treatment may ensue. When symptoms are of low severity and non-life-threatening, it can be considered whether there is an alternative option of pre-treatment through close monitoring of the natural time course of restoration of the brain's neurochemical homeostasis. Thus, a less explored yet interesting concept is the consideration of the factors and substrates which are responsible

for maintaining the brain's homeostatic balance as future targets for emotional regulation in depression treatment [31].

DISCUSSION

When causes are of a psychosocial nature, it should not be ruled out that mood dysregulation can occur as a mechanism of response to adapt to the changing demands of a situation to facilitate active coping and problem-solving strategies to re-establish one's control over the situation. However, a decision-making process is involved in every internal-external conflict and there are factors which influence one's effectiveness in response. Intuitively, such mood-dysregulation adaptive strategy may be a facilitator of the need for response and action. Although the observation of monoamine neurotransmitter imbalance has been widely documented in research, the initiation and specific time point of such occurrence of neurochemical disturbance in individuals is still unclear. Does the onset of symptoms arise as a cause or outcome of the disturbance or vice versa? There are likely multiple answers to this question. What is now needed is the filling of the knowledge gap of mapping explicit continual time course of events with initiation of disorder symptoms and internal neurochemical deficits. Ideally, this would begin with animal models. Nevertheless, the consideration of recognition of mood dysregulation as an emotional responsive mechanism with its associated duration of effect that is comparable to the action-initiating "fight-or-flight" response could offer therapeutic strength as a means for depressed individuals to regain their locus of control to initiate changes over situations and events.

CONCLUSION

In conclusion, a multi-faceted disorder of depression requires more action-oriented treatment strategies that have been inadequately met by current psychiatric approach and pharmacological targets. Time is likely a significant mediator in the reinforcement of mechanisms which contribute to neurotransmitter dysregulation and structural abnormalities that manifest overtly in the form of depressed psychological state and physical functioning. Most neuroscientific studies tend to investigate the differences between depressed and non-depressed subjects. To gain more in-depth understanding of the symptom variation in depression, it would be necessary to expand focus on comparing among depressed individuals with different time points in onset and episode duration of depression. On the other hand, what has also not been examined is whether longer term induced increased exposure to positive stimuli and situations as a compensatory mechanism to past excessive negative experiences would reverse the impairment inflicted on relevant neural networks in the brain and restore homeostasis to the level of healthy individuals. Research has yet to test this as it would require a generation of wide scope of creative variables and measures to gauge the effectiveness of such a holistic strategy.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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