Demiroglu Science University Florence Nightingale Journal of Transplantation2021;6(1-2):45-51
doi: 10.5606/dsufnjt.2021.025

Subgenual anterior cingulate cortex and psychiatric disorders

Berfin Sıla Akdoğdu[1], Oytun Erbaş[1,2]

[1]*Institute of Experimental Medicine, Gebze-Kocaeli, Turkey*
[2]*Department of Physiology, Medical Faculty of Demiroğlu Bilim University, Istanbul, Turkey*

ABSTRACT

Psychiatric disorders have various underlying causes, which have piqued people's interest since ancient times. Examples include genetics, neurological problems, and environmental influences. For psychiatric disorders, there is no single care plan or treatment method. To develop a definitive cure, we need to better understand the diseases' underlying causes. As a result, we focused on abnormalities of the subgenual anterior cingulate cortex and amygdala in this review.

Keywords: Amygdala, brain, cingulate cortex, major depressive disorder, subgenual anterior cingulate cortex

The only brain area that is activated when learning to help people is the subgenual anterior cingulate cortex (sgACC). Since this part of the brain is not equally active in everyone, the ability to empathize and help others is not the same in every individual.[1] It is also the only active region in the brain in case of uncertainty.[2] This region of the brain is also associated with the concepts of altruism and generosity. It has been observed that individuals with a more active sgACC are more generous.[3] Experiments on the sgACC have examined its relationship with fear in humans. They found that sgACC was active in individuals when acting boldly and not succumbing to fear. However, after choosing to act boldly, the activity of the amygdala decreased.[4] The sgACC is thought to act as a bridge between emotional and cognitive processing regions.[5] The sgACC interacts with many brain regions. One of the regions where the sgACC interacts is the amygdala. Interaction with this region has many consequences, and positive-social emotion regulation is one of them. In individuals with anxiety, the connection between these two areas is decreased.[6] The sgACC is known to be linked to fear. Recent studies also point to the link between fear, amygdala, and the sgACC.[7] Individuals need to balance reason and emotion to lead a healthy life. It is a proven fact that the sgACC is linked to emotions. The sgACC needs to connect with the pregenual anterior cingulate area 32 to balance logic.[8,9]

MAJOR DEPRESSIVE DISORDER

Major depressive disorder (MDD) is one of the most common psychological disorders. The general treatment method is based on antidepressants.[10] Despite being such a common disorder, the rates of misdiagnosis are substantially high. The primary reason for this is the lack of reliable biomarkers.[11] Another negative aspect of the lack of reliable biomarkers is that it becomes difficult to control the treatment progress.[12]

It is a well-known fact that major depression is related to abnormalities in the brain. The studies conducted to prove this has shown the relationship between MDD and sgACC.[13-17] In particular, two different abnormalities were found in experiments

Correspondence: Berfin Sıla Akdoğdu. Deneysel Tıp Enstitüsü, 41470 Gebze-Kocaeli, Türkiye.
e-mail: berfinsila2001@gmail.com

Cite this article as:
Akdoğdu BS, Erbaş O. Subgenual anterior cingulate cortex and psychiatric disorders. D J Tx Sci 2021;6(1-2):45-51.

where the sgACC and medial temporal lobe (MTL) were examined. The first of these is the significant increase in the connection between the sgACC and MTL. The other is the reduced white matter integrity in the uncinate fascicle.[13] In another experiment demonstrating the connection of the sgACC with MDD, an abnormal state in resting-state functional connectivity (RSFC) of the sgACC was detected in adolescents. It was observed that the connections between the sgACC and the amygdala and the insula also have high activity.[14] There is a correlation between the rates of hyperactivity of the sgACC and the levels of sadness of individuals during MDD. The higher the hyperactivity, the greater the level of sadness they feel.[15] Subgenual anterior cingulate cortex hyperactivity is similarly associated with stress in these individuals.[16] Similarly, a recent study has shown that children at risk (with family members with this disease) have significant differences in their sgACCs from their childhood. In this study, abnormalities in the amygdala and sgACC functions were found by functional magnetic resonance imaging (fMRI).[17]

The evidence regarding the relationship between MDD and the sgACC studies has led to studies on MDD treatment. Repetitive transcranial magnetic stimulation was administered to the left dorsolateral prefrontal cortex, resulting in improved connectivity between the amygdala and ventromedial prefrontal cortex, as well as improved sgACC and default mode network (DMN) connectivity.[18] To better understand the effects of electroconvulsive therapy (ECT) in MDD, research has been carried out using fMRI in resting state. As a result of these studies, it has been established that ECT is an efficient treatment method with its effect on the sgACC.[19] However, research on this subject is not limited to this. Some studies resulted in the opposite of expectations. The sgACC volumes of pediatric-onset MDD patients were compared with adult-onset MDD patients, and it was determined that the sgACC volumes of pediatric-onset patients were on average the same as healthy individuals. Therefore, the use of sgACC as a biomarker created a question mark in minds.[20] Although sgACC volumes did not show similarity with healthy individuals in the younger age group, it was found that there are abnormal connections between multiple cortical and subcortical regions of the sgACC in children with a history of preschool-onset MDD.[21] Antidepressants used in patients with MDD do not always provide full benefit. When the reasons for this have been investigated, many reasons have emerged. The striking point in the experiments is that the conditions in which the antidepressant can be more effective are neurologically determined. For example, it has been determined that regular antidepressant use will be effective in cases of atrophy detected in the sgACC.[22] One of the symptoms of MDD patients is the presence of self-generated thoughts (SGTs). Maltreated children are at greater risk of developing MDD than other children, and in these children, positive SGTs are not common, but rather negative SGTs can be associated with depression. In these children, RSFC with sgACC is reduced in the frontoparietal network.[22,23]

DEPRESSION

Depression is a chronic condition associated with physical symptoms.[24] There are different types of depression.[25] Psychotherapy, drug treatments, and ECT are generally used in the treatment.[26] There are potential biomarkers for monitoring the response to treatments. Examples of these are the sgACC, amygdala, and anterior insula parts of the brain.[27] However, in some cases, individuals may not respond to treatment, this type of depression is called treatment-resistant depression (TRD). For the individuals to be diagnosed with TRD, they must have received drug treatment twice.[28] We can observe the results of accelerated intermittent theta-burst stimulation used in the treatment of TRD, with improved connections between the sgACC and medial orbitofrontal cortex, as well as a decrease in feelings of hopelessness.[29] It has been argued that the effects of the sgACC are not limited to hopelessness in individuals but may also cause anorexia.[30] Anhedonia, one of the symptoms of depression, can distract the individual from the social environment, or sometimes the individual may be excluded from the social environment.[30] It has been observed that exclusion from the social environment increases sgACC activity in people with depression. Studies have demonstrated that even the expectation of social loss has an effect of increasing sgACC activity.[31]

Depressed individuals have increased blood flow in their sgACCs, and decreased blood flow can be interpreted as a sign of improvement in depression.[32]

Depression can sometimes be seen with different diseases, such as internet gaming disorder (IGD). The differences between individuals with IGD and depression and individuals with IGD without depression need to be investigated since these differences may help us determine biomarkers that can assist in diagnosis. Experiments performed prove that there are significant differences in abnormal functional connectivity (FC) in the sgACC and DMN.[33] The coexistence of depression with different diseases is not specific to IGD. It has been found that girls in early adolescence are more susceptible to psychological disorders. These disorders are not limited to depression but also cause other disorders, such as addiction, anxiety, and delinquency. This is thought to be caused by anomalies in their brains. Reduced gray matter volumes (GMVs) were observed in the sgACC of precocious girls.[34] What should be noted here is that there are differences in sgACC FC according to sex. It has been observed that women are more prone to depression and brain activity is higher in negative emotions than men.[35] It also differs by sex in the prefrontal-limbic system. Therefore, the attitudes towards help-seeking also differ by sex. It showed that women were more likely to seek help and that they were more receptive to advice.[36] Studies have shown that reducing sgACC linkages in patients with depression helps treatment.[37] Electroconvulsive therapy has been shown to reduce the sgACC activity of depressed individuals.[38] Thus, the symptoms of depression have been found to be reduced.

ANXIETY

Anxiety can be defined by the fear created due to the expectation of a threat that does not exist.[39] Fear is vital for individuals as it is an emotion that helps us protect ourselves and survive in our lives.[40] However, in anxiety, this emotion is so extreme that it can be examined pathologically. It is also linked to things that are not considered threats. The things that trigger anxiety can be different, such as an object, being in a social environment, or being in a closed space.[41] Anxiety is also seen in adolescents. The approach of the family is crucial in the treatment of this disease. It has been observed that sgACC activity decreases in adolescents who feel loved and listened by their families.[42] The increase in the duration of a generalized anxiety disorder causes a decrease in GMV. The effect of the sgACC on GM volume has been established.[43] In a study conducted with obese individuals after the importance of the GM was understood, it was found that the GMV decreased with the weight of the person, and the obese individuals were more prone to anxiety and depression.[44]

The sgACC is effective on fear, one of the most basic emotions of anxiety. It enables sick individuals to feel a sense of fear as a result of their interaction with the basolateral amygdala subnucleus. Understanding how fear, which is the main symptom of anxiety, occurs is a big step in understanding the disease and guiding its treatment.[45] The effects of the sgACC are observed in all types of anxiety. In trait anxiety, amygdala and sgACC activities were found to be more sensitive and higher.[46] In addition, it has been observed that pre-long-term potentiation (LTP) secreted from the anterior cingulate cortex (ACC) plays an active role in anxiety and chronic pain, and anxiety decreases due to the prevention of pre-LTP secretion.[47] The association of chronic pain with the sgACC differs by sex, and women are more prone to chronic pain. Understanding the reasons for this is critical for identifying the correct treatment.[48] It has been observed that the fear and anxiety caused by excessive sgACC activity last longer, and these individuals have trouble regulating their emotional state.[49] Another thing that can reduce anxiety is meditation.[50]

BIPOLAR DISORDER

Bipolar disorder (BD) can be defined as the change of euphoric and unhappy moods. Although it was recognized before the Common Era, BD has not been studied much until recently.[51,52] The disorder is divided in to two as bipolar 1 and bipolar 2.[53] Bipolar 1 and 2 also have subtypes within themselves. For example, one of the subtypes of bipolar 2 is cyclothymia.[54] Bipolar disorder can occur in advanced age.[55] Drugs have been produced

to prevent episodes of mood swings.[56] A substantial proportion of those with this disease commit suicide.[57] Studies on this topic have investigated the causes of suicide in individuals with bipolar 2 disease. These studies have shown that sgACC plays a role. An abnormal link between the sgACC and raphe nucleus is thought to play an active role in individuals committing suicide.[58] In patients with BD, sgACC metabolism and GMV in the cortex are decreased.[59] Bipolar patients are not always in a non-euthymic (uncontrolled) mood, and sometimes they are also euthymic (in control). Increased connectivity is seen between the sgACC and amygdala in BD.[60] The entorhinal cortex and sgACC, which are two significant parts of mood regulation, are important in bipolar patients since the link between these two regions show hyperactivity in patients with BD. The entorhinal cortex is not the only region where the sgACC junction shows hyperactivity; it is also thought to have higher activity in its junctions with sgACC, pregenual ACC, dorsomedial prefrontal cortex, and insula.[61]

ADDICTION

Addiction is divided into two categories as drug-related and non-substance addiction. Examples of drug addiction include cigarette, drug, and alcohol addiction. Examples of non-substance addiction include gambling, food, internet, mobile phone, and exercise addiction.[62,63]

If we consider cigarette addiction, it is thought that the feeling of longing underlies the craving to smoke. Reducing this feeling of longing will also reduce the desire to smoke. If we find out what lies at the root of the longing, we can find a cure for this addiction. Studies have found that sgACC affects the sense of longing. It has been determined that sgACC hyperactivity increases the feeling of longing, and awareness-based interventions have been found to be effective in the treatment since these interventions reduce sgACC activity.[64] The craving that triggers smoking is also linked to the orbital and medial prefrontal cortex (OMPFC) network. However, this region does not function alone. Another region with which this region is linked is the sgACC. It is known that increased connectivity between the sgACC and OMPFC is associated with the feeling of craving.[65] One of the things that affect smoking cessation is the ACC's relation to craving. Anterior cingulate cortex activity is seen in early withdrawal. If the activity of the ACC can be reduced during the early withdrawal period, it may be easier for smokers to quit smoking.[66]

Internet addiction (IAD) shows insufficient ACC activity, unlike cigarette addiction. This inadequate activity leads to decreased connectivity between the ACC and amygdala.[67] Individuals with IAD have reduced error-monitoring ability, and a study on this revealed that ACC activity is increased during error tracking.[68]

Other more significant problems may arise in individuals addicted to games. It has been determined that game addicts identify with their characters in the game more than themselves.[69] The ACC was found to show higher activity when thinking about game characters in these individuals. Likewise, ACC activity varies in relation to playing time.[70] A decrease was observed in the ACC activity of recovering game-addicted individuals compared to when they were ill.[71] Similar to IAD from smartphone addiction, it shows lower ACC activity compared to healthy individuals.[72] The ACC has been found to exhibit hypoactivity in tasks that require emotional attention in drug users.[73]

In conclusion, as the most difficult aspects of treating psychological disorders for doctors are determining the correct diagnosis and monitoring therapy progress, examining the changes in the body produced by psychiatric problems is critical. Many studies have been conducted to show that the sgACC is involved in the regulation and processing of emotions, as were discussed in this review. With few exceptions, it has been discovered that this region can be a good biomarker for the follow-up of psychiatric disorders. However, the most apparent feature is the variation in activity rates in this region based on age and sex. Individuals' susceptibility to psychiatric disorders is also affected by this condition.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Lockwood PL, Apps MA, Valton V, Viding E, Roiser JP. Neurocomputational mechanisms of prosocial learning and links to empathy. Proc Natl Acad Sci U S A 2016;113:9763-8.
2. Rubio A, Van Oudenhove L, Pellissier S, Ly HG, Dupont P, Lafaye de Micheaux H, et al. Uncertainty in anticipation of uncomfortable rectal distension is modulated by the autonomic nervous system--a fMRI study in healthy volunteers. Neuroimage 2015;107:10-22.
3. Cutler J, Campbell-Meiklejohn D. A comparative fMRI meta-analysis of altruistic and strategic decisions to give. Neuroimage 2019;184:227-41.
4. Nili U, Goldberg H, Weizman A, Dudai Y. Fear thou not: Activity of frontal and temporal circuits in moments of real-life courage. Neuron 2010;66:949-62.
5. Ho TC, Yang G, Wu J, Cassey P, Brown SD, Hoang N, et al. Functional connectivity of negative emotional processing in adolescent depression. J Affect Disord 2014;155:65-74.
6. Scharnowski F, Nicholson AA, Pichon S, Rosa MJ, Rey G, Eickhoff SB, et al. The role of the subgenual anterior cingulate cortex in dorsomedial prefrontal-amygdala neural circuitry during positive-social emotion regulation. Hum Brain Mapp 2020;41:3100-18.
7. Sharma KK, Kelly EA, Pfeifer CW, Fudge JL. Translating fear circuitry: Amygdala projections to subgenual and perigenual anterior cingulate in the macaque. Cereb Cortex 2020;30:550-62.
8. Joyce MKP, García-Cabezas MÁ, John YJ, Barbas H. Serial prefrontal pathways are positioned to balance cognition and emotion in primates. J Neurosci 2020;40:8306-28.
9. Gupta A, Labus J, Kilpatrick LA, Bonyadi M, Ashe-McNalley C, Heendeniya N, et al. Interactions of early adversity with stress-related gene polymorphisms impact regional brain structure in females. Brain Struct Funct 2016;221:1667-79.
10. Rahman S, Alzarea S. Glial mechanisms underlying major depressive disorder: Potential therapeutic opportunities. Prog Mol Biol Transl Sci 2019;167:159-78.
11. Vöhringer PA, Perlis RH. Discriminating between bipolar disorder and major depressive disorder. Psychiatr Clin North Am 2016;39:1-10.
12. Kang SG, Cho SE. Neuroimaging biomarkers for predicting treatment response and recurrence of major depressive disorder. Int J Mol Sci 2020;21:2148.
13. de Kwaasteniet B, Ruhe E, Caan M, Rive M, Olabarriaga S, Groefsema M, et al. Relation between structural and functional connectivity in major depressive disorder. Biol Psychiatry 2013;74:40-7.
14. Connolly CG, Wu J, Ho TC, Hoeft F, Wolkowitz O, Eisendrath S, et al. Resting-state functional connectivity of subgenual anterior cingulate cortex in depressed adolescents. Biol Psychiatry 2013;74:898-907.
15. Schwartz J, Ordaz SJ, Kircanski K, Ho TC, Davis EG, Camacho MC, et al. Resting-state functional connectivity and inflexibility of daily emotions in major depression. J Affect Disord 2019;249:26-34.
16. Hsu DT, Kirouac GJ, Zubieta JK, Bhatnagar S. Contributions of the paraventricular thalamic nucleus in the regulation of stress, motivation, and mood. Front Behav Neurosci 2014;8:73.
17. Chai XJ, Hirshfeld-Becker D, Biederman J, Uchida M, Doehrmann O, Leonard JA, et al. Altered intrinsic functional brain architecture in children at familial risk of major depression. Biol Psychiatry 2016;80:849-58.
18. Philip NS, Barredo J, van 't Wout-Frank M, Tyrka AR, Price LH, Carpenter LL. Network mechanisms of clinical response to transcranial magnetic stimulation in posttraumatic stress disorder and major depressive disorder. Biol Psychiatry 2018;83:263-72.
19. Liu Y, Du L, Li Y, Liu H, Zhao W, Liu D, et al. Antidepressant effects of electroconvulsive therapy correlate with subgenual anterior cingulate activity and connectivity in depression. Medicine (Baltimore) 2015;94:e2033.
20. Jaworska N, MacMaster FP, Yang XR, Courtright A, Pradhan S, Gaxiola I, et al. Influence of age of onset on limbic and paralimbic structures in depression. Psychiatry Clin Neurosci 2014;68:812-20.
21. Gaffrey MS, Luby JL, Repovš G, Belden AC, Botteron KN, Luking KR, et al. Subgenual cingulate connectivity in children with a history of preschool-depression. Neuroreport 2010;21:1182-8.
22. Niida A, Niida R, Matsuda H, Motomura M, Uechi A. Analysis of the presence or absence of atrophy of the subgenual and subcallosal cingulate cortices using voxel-based morphometry on MRI is useful to select prescriptions for patients with depressive symptoms. Int J Gen Med 2014;7:513-24.
23. Hoffmann F, Viding E, Puetz VB, Gerin MI, Sethi A, Rankin G, et al. Evidence for depressogenic spontaneous thoughts and altered resting-state connectivity in adolescents with a maltreatment history. J Am Acad Child Adolesc Psychiatry 2018;57:687-695.e4.
24. Rakel RE. Depression. Prim Care 1999;26:211-24.
25. Serefko A, Szopa A, Wlaź P, Nowak G, Radziwoń-Zaleska M, Skalski M, et al. Magnesium in depression. Pharmacol Rep 2013;65:547-54.
26. Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. Biol Psychiatry 2010;67:110-6.
27. Chakrabarty T, Ogrodniczuk J, Hadjipavlou G. Predictive neuroimaging markers of psychotherapy

response: A systematic review. Harv Rev Psychiatry 2016;24:396-405.
28. Pardo JV, Sheikh SA, Schwindt G, Lee JT, Adson DE, Rittberg B, et al. A preliminary study of resting brain metabolism in treatment-resistant depression before and after treatment with olanzapine-fluoxetine combination. PLoS One 2020;15:e0226486.
29. Baeken C, Duprat R, Wu GR, De Raedt R, van Heeringen K. Subgenual anterior cingulate-medial orbitofrontal functional connectivity in medication-resistant major depression: A neurobiological marker for accelerated intermittent theta burst stimulation treatment? Biol Psychiatry Cogn Neurosci Neuroimaging 2017;2:556-65.
30. Alexander L, Gaskin PLR, Sawiak SJ, Fryer TD, Hong YT, Cockcroft GJ, et al. Fractionating blunted reward processing characteristic of anhedonia by over-activating primate subgenual anterior cingulate cortex. Neuron 2019;101:307-320.e6.
31. He Z, Zhang D, Muhlert N, Elliott R. Neural substrates for anticipation and consumption of social and monetary incentives in depression. Soc Cogn Affect Neurosci 2019;14:815-26.
32. Yang TT, Simmons AN, Matthews SC, Tapert SF, Frank GK, Bischoff-Grethe A, et al. Adolescent subgenual anterior cingulate activity is related to harm avoidance. Neuroreport 2009;20:19-23.
33. Lee D, Lee J, Namkoong K, Jung YC. Subregions of the anterior cingulate cortex form distinct functional connectivity patterns in young males with internet gaming disorder with comorbid depression. Front Psychiatry 2018;9:380.
34. Okada N, Yahata N, Koshiyama D, Morita K, Sawada K, Kanata S, et al. Smaller anterior subgenual cingulate volume mediates the effect of girls' early sexual maturation on negative psychobehavioral outcome. Neuroimage 2020;209:116478.
35. Li CR, Zhang S, Hung CC, Chen CM, Duann JR, Lin CP, et al. Depression in chronic ketamine users: Sex differences and neural bases. Psychiatry Res Neuroimaging 2017;269:1-8.
36. Li HJ, Sun JZ, Zhang QL, Wei DT, Li WF, Jackson T, et al. Neuroanatomical differences between men and women in help-seeking coping strategy. Sci Rep 2014;4:5700.
37. Taylor SF, Ho SS, Abagis T, Angstadt M, Maixner DF, Welsh RC, et al. Changes in brain connectivity during a sham-controlled, transcranial magnetic stimulation trial for depression. J Affect Disord 2018;232:143-51.
38. Liu Y, Du L, Li Y, Liu H, Zhao W, Liu D, et al. Antidepressant effects of electroconvulsive therapy correlate with subgenual anterior cingulate activity and connectivity in depression. Medicine (Baltimore) 2015;94:e2033.
39. American Psychiatric Association: Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
40. Dunsmoor JE, Paz R. Fear generalization and anxiety: Behavioral and neural mechanisms. Biol Psychiatry 2015;78:336-43.
41. Cohen SD, Cukor D, Kimmel PL. Anxiety in patients treated with hemodialysis. Clin J Am Soc Nephrol 2016;11:2250-5.
42. Butterfield RD, Silk JS, Lee KH, Siegle GS, Dahl RE, Forbes EE, et al. Parents still matter! Parental warmth predicts adolescent brain function and anxiety and depressive symptoms 2 years later. Dev Psychopathol 2021;33:226-39.
43. Chen Y, Cui Q, Fan YS, Guo X, Tang Q, Sheng W, et al. Progressive brain structural alterations assessed via causal analysis in patients with generalized anxiety disorder. Neuropsychopharmacology 2020;45:1689-97.
44. Gupta A, Mayer EA, Sanmiguel CP, Van Horn JD, Woodworth D, Ellingson BM, et al. Patterns of brain structural connectivity differentiate normal weight from overweight subjects. Neuroimage Clin 2015;7:506-17.
45. Hakamata Y, Mizukami S, Izawa S, Moriguchi Y, Hori H, Kim Y, et al. Basolateral amygdala connectivity with subgenual anterior cingulate cortex represents enhanced fear-related memory encoding in anxious humans. Biol Psychiatry Cogn Neurosci Neuroimaging 2020;5:301-10.
46. Barrett J, Armony JL. Influence of trait anxiety on brain activity during the acquisition and extinction of aversive conditioning. Psychol Med 2009;39:255-65.
47. Canadian Association for Neuroscience. "Better understanding of links between pain, anxiety reveals treatment opportunities." ScienceDaily. Available at: www.sciencedaily.com/releases/2015/05/150527191649.htm [Accessed: May 27, 2015]
48. Osborne NR, Cheng JC, Rogachov A, Kim JA, Hemington KS, Bosma RL, et al. Abnormal subgenual anterior cingulate circuitry is unique to women but not men with chronic pain. Pain 2021;162:97-108.
49. Alexander L, Wood CM, Gaskin PLR, Sawiak SJ, Fryer TD, Hong YT, et al. Over-activation of primate subgenual cingulate cortex enhances the cardiovascular, behavioral and neural responses to threat. Nat Commun 2020;11:5386.
50. Zeidan F, Martucci KT, Kraft RA, McHaffie JG, Coghill RC. Neural correlates of mindfulness meditation-related anxiety relief. Soc Cogn Affect Neurosci 2014;9:751-9.
51. Smith DJ, Whitham EA, Ghaemi SN. Bipolar disorder. Handb Clin Neurol 2012;106:251-63.
52. Freund N, Juckel G. Bipolar disorder: Its etiology and how to model in rodents. Methods Mol Biol 2019;2011:61-77.
53. Müller JK, Leweke FM. Bipolar disorder: Clinical overview. Med Monatsschr Pharm 2016;39:363- 9.
54. Parker G, McCraw S, Fletcher K. Cyclothymia. Depress Anxiety 2012;29:487-94.

55. Sajatovic M, Chen P. Geriatric bipolar disorder. Psychiatr Clin North Am 2011;34:319-33.
56. Keck PE Jr, McElroy SL, Arnold LM. Bipolar disorder. Med Clin North Am 2001;85:645-61.
57. Dilsaver SC. Bipolar disorder. Am Fam Physician 1989;40:156-66.
58. Wang H, Zhu R, Dai Z, Tian S, Shao J, Wang X, et al. Aberrant functional connectivity and graph properties in bipolar II disorder with suicide attempts. J Affect Disord 2020;275:202-9.
59. Drevets WC, Savitz J, Trimble M. The subgenual anterior cingulate cortex in mood disorders. CNS Spectr 2008;13:663-81.
60. Rey G, Piguet C, Benders A, Favre S, Eickhoff SB, Aubry JM, et al. Resting-state functional connectivity of emotion regulation networks in euthymic and non-euthymic bipolar disorder patients. Eur Psychiatry 2016;34:56-63.
61. Apazoglou K, Küng AL, Cordera P, Aubry JM, Dayer A, Vuilleumier P, et al. Rumination related activity in brain networks mediating attentional switching in euthymic bipolar patients. Int J Bipolar Disord 2019;7:3.
62. Zou Z, Wang H, d'Oleire Uquillas F, Wang X, Ding J, Chen H. Definition of substance and non-substance addiction. Adv Exp Med Biol 2017;1010:21-41.
63. Weinstein A, Weinstein Y. Exercise addiction-diagnosis, bio-psychological mechanisms and treatment issues. Curr Pharm Des 2014;20:4062-9.
64. Westbrook C, Creswell JD, Tabibnia G, Julson E, Kober H, Tindle HA. Mindful attention reduces neural and self-reported cue-induced craving in smokers. Soc Cogn Affect Neurosci 2013;8:73-84.
65. Janes AC, Farmer S, Frederick Bd, Nickerson LD, Lukas SE. An increase in tobacco craving is associated with enhanced medial prefrontal cortex network coupling. PLoS One 2014;9:e88228.
66. Allenby C, Falcone M, Wileyto EP, Cao W, Bernardo L, Ashare RL, et al. Neural cue reactivity during acute abstinence predicts short-term smoking relapse. Addict Biol 2020;25:e12733.
67. Cheng H, Liu J. Alterations in amygdala connectivity in internet addiction disorder. Sci Rep 2020;10:2370.
68. Dong G, Shen Y, Huang J, Du X. Impaired error-monitoring function in people with internet addiction disorder: An event-related fMRI study. Eur Addict Res 2013;19:269-75.
69. Choi EJ, Taylor MJ, Hong SB, Kim C, Kim JW, McIntyre RS, et al. Gaming-addicted teens identify more with their cyber-self than their own self: Neural evidence. Psychiatry Res Neuroimaging 2018;279:51-9.
70. Kim H, Kim YK, Lee JY, Choi AR, Kim DJ, Choi JS. Hypometabolism and altered metabolic connectivity in patients with internet gaming disorder and alcohol use disorder. Prog Neuropsychopharmacol Biol Psychiatry 2019;95:109680.
71. Dong GH, Wang M, Zhang J, Du X, Potenza MN. Functional neural changes and altered cortical-subcortical connectivity associated with recovery from internet gaming disorder. J Behav Addict 2019;8:692-702.
72. Horvath J, Mundinger C, Schmitgen MM, Wolf ND, Sambataro F, Hirjak D, et al. Structural and functional correlates of smartphone addiction. Addict Behav 2020;105:106334.
73. Goldstein RZ, Alia-Klein N, Tomasi D, Carrillo JH, Maloney T, Woicik PA, et al. Anterior cingulate cortex hypoactivations to an emotionally salient task in cocaine addiction. Proc Natl Acad Sci U S A 2009;106:9453-8.