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Original Article

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Regional Cerebral Glucose Metabolism in Novelty Seeking and Antisocial Personality: A Positron Emission Tomography Study

So Hyeon Park[1,2#], Hyun Soo Park[1,2,3#] and Sang Eun Kim[1,2,3*]

[1]Department of Transdisciplinary Studies, Graduate School of Convergence Science and Technology, Seoul National University, Seoul 16229, [2]Department of Nuclear Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam 13620, [3]Advanced Institutes of Convergence Technology, Suwon 16229, Korea

Novelty seeking (NS) and antisocial personality (ASP) are commonly exhibited by those who suffer from addictions, such as substance abuse. NS has been suggested to be a fundamental aspect of ASP. To investigate the neurobiological substrate of NS and ASP, we tested the relationship between regional cerebral glucose metabolism and the level of NS, determining the differences between individuals with and without ASP. Seventy-two healthy adults (43 males, mean age±SD=38.8±16.6 years, range=20~70 years; 29 females, 44.2±20.1 years, range=19~72 years) underwent resting-state brain positron emission tomography (PET) 40 minutes after ^{18}F-fluorodeoxyglucose (FDG) injection. Within 10 days of the FDG PET study, participants completed Cloninger's 240-item Temperament and Character Inventory (TCI) to determine NS scores. Participants with and without ASP were grouped according to their TCI profiles. Statistical parametric mapping analysis was performed using the FDG PET and TCI profile data. NS scores positively correlated with metabolism in the left anterior cingulate gyrus and the insula on both sides of the brain and negatively correlated with metabolism in the right pallidum and putamen. Participants with ASP showed differences in cerebral glucose metabolism across various cortical and subcortical regions, mainly in the frontal and prefrontal areas. These data demonstrate altered regional cerebral glucose metabolism in individuals with NS and ASP and inform our understanding of the neurobiological substrates of problematic behaviors and personality disorders.

Key words: Neural Substrate of Personality, Novelty Seeking, Antisocial Personality, FDG PET, Statistical Parametric Mapping (SPM)

INTRODUCTION

Previous studies using Cloninger's temperament and character model [1] have provided important information for investigating individual differences in cognitive behaviors and basic stimulus-response characteristics [1, 2]. In this model, personality is divided into the categories of temperament and character. Temperament primarily consists of four dimensions: novelty seeking (NS), harm avoidance, reward dependence, and persistence. Character reflects acquired behavioral, emotional, and thought patterns and has three dimensions: self-directedness, cooperativeness, and self-transcendence. Cloninger's Temperament and Character Inventory (TCI) has been used to assess personality profiles and consists of

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*To whom correspondence should be addressed.
TEL: 82-31-787-7671, FAX: 82-31-787-4018
e-mail: kse@snu.ac.kr
#So Hyeon Park and Hyun Soo Park contributed equally to the present study in the experimental design, manuscript writing, and discussion.

seven dimensions based on the socio-biological personality model. As a biological basis of personality, the TCI profile is known to indicate an individual's propensity for mental abnormalities or problematic behaviors [3-7]. The TCI profile also has neurological implications for healthy individuals, as well as those with personality disorders associated with abnormal neurotransmitter activity [5, 8]. In particular, several lines of evidence suggest that dopaminergic neurotransmission is involved in NS [5, 9]. For example, human genetic studies have reported that dopamine D4 receptor [10, 11] and dopamine D2 receptor polymorphisms were associated with NS [12]. NS has been found in substance abusers, and it is associated with dopamine D2 receptors on both the genetic and endocrine levels [3-5, 13].

A previous study reported that high NS predisposes individuals to adult antisocial personality disorder [1, 14, 15] that is closely related to a hypersensitive brain reward system modulated by the dopamine neurotransmitter systems [16]. NS involves behavioral activation and describes a genetic disposition towards being excitable, impulsive, exploratory, and quick-tempered. Antisocial personality disorder is characterized by a pervasive pattern of disregard for, or violation of, the rights of others. Increasing evidence indicates that deficits in prefrontal functioning are characteristic of violent, antisocial persons as indicated by both positron emission tomography (PET) [17, 18] and single-photon emission computed tomography [19].

In the present study, we investigated the relationship between regional cerebral glucose metabolism and NS scores, and the differences in level of regional cerebral glucose metabolism (cerebral activation or deactivation) of individuals with ASP compared to those without ASP using FDG PET and TCI profile data acquired from healthy individuals.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Seoul National University College of Medicine and the Seoul National University Bundang Hospital. All participants were informed about the study procedures in detail and subsequently provided written informed consent for their participation.

Participants were recruited by community bulletin boards and internet advertisements. Seventy-two right-handed healthy volunteers (43 males, mean age±SD=38.8±16.6 years, range=20~70 years; 29 females, 44.2±20.1 years, range=19~72 years) participated. Researchers obtained a self-reported clinical history for each participant in order to exclude individuals with neurological abnormalities that might affect brain metabolism. All participants answered that they did not have any neurological or psychiatric history and that they were drug-free.

We used a Korean version of the TCI with 240 items [20] to assess participants' TCI profile. Within 10 days after the FDG PET study, participants completed a TCI of seven dimensions. Based on individual TCI profiles, participants were allocated into one of eight personality categories (antisocial, histrionic, passive-aggressive, explosive, obsessional, schizoid, cyclothymic, and passive-dependent) using quartile statistics [12, 13]. First and second quartile scores were defined as low scores, and third and fourth quartile scores were defined as high scores for each personality dimension [2]. Finally, of the 72 participants, 18% (n=13) were assigned to the antisocial personality category; 12.5% (n=9) to the histrionic personality category; 6.9% (n=5) to the passive-aggressive personality category; 11.1% (n=8) to the explosive personality category; 15.3% (n=11) to the obsessional personality category; 15.3% (n=11) to the schizoid personality category; 9.7% (n=7) to the cyclothymic personality category; and 11.1% (n=8) to the passive-dependent personality category.

PET data were acquired using an Allegro PET scanner operating in the three-dimensional (3D) mode. Participants fasted for at least 6 hours before scanning. Prior to imaging, participants were administered an intravenous injection of 4.8 MBq/kg FDG in a dimly lit, quiet waiting room and were instructed to remain lying comfortably during a 40-minute FDG equilibration period. Participants were then led to an adjacent imaging suite and positioned within the PET scanner so that the head was aligned relative to the canthomeatal line. Ten-minute emission scans and attenuation maps using a Cs-137 transmission source were obtained. Attenuation-corrected images were reconstructed using PET data and a 3D row-action maximum-likelihood algorithm with a 3D image filter of 128×128×90 matrices and a pixel size of 2×2×2 mm.

Spatial preprocessing and statistical analyses were performed using SPM2 (Institute of Neurology, University College of London, UK) implemented in MATLAB (Mathworks Inc., Natick, MA, USA). Every image was spatially normalized to the standard MNI template (Montreal Neurological Institute, McGill University, CA) of SPM2 in order to eliminate within-subject anatomical variability [21]. Spatially normalized images were smoothed by convolution with an isotropic Gaussian kernel with 12 mm full width at half maximum to increase the signal-to-noise ratio and accommodate variations in subtle anatomical structures. Glucose metabolism of each voxel was also normalized by using proportional scaling with the mean glucose metabolism of global gray matter set at 100.

To identify regions showing relationships between resting-state patterns of regional cerebral glucose metabolism and the NS

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scores, SPM correlation analyses were performed for each voxel with a general linear approach. NS scores were incorporated as covariates of interest, whereas age was set as nuisance variable to regress out its effects. The height threshold (u), used to interpret correlations in terms of the probability level, was set at z=3.28 (p<0.001, uncorrected). The extent threshold (k) was set at 100 voxels, which was sufficient to remove any small noisy clusters that may have reached significance by chance.

Neurobiological differences in ASP were investigated using the mean image of the ASP group and the mean image of all other individuals. The height threshold (u), used to interpret the mean difference in terms of the probability level, was set at z=2.58 (p<0.005, uncorrected). The extent threshold (k) was also set at 100 voxels.

RESULTS AND DISCUSSION

The cerebral metabolic correlates of NS are provided in Table 1. Positive correlations between cerebral glucose metabolism and NS scores were found in the left anterior and middle cingulate gyrus (peak activation at x=-4, y=32, z=14; Z=4.41, k=1996), and the insula (right insula, peak activation at x=-38, y=-20, z=-10; Z=3.49, k=835; left insula, peak activation at x=-44, y=-10, z=-4; Z=4.10, k=581), whereas negative correlations were found in the right hemisphere, including the pallidum and putamen (peak activation at x=22, y=-10, z=6; Z=3.63, k=195). The present results are in accordance with those of previous studies on regional cerebral metabolic correlates of the TCI. Consistent with Sugiura et al. [22], metabolism in the left anterior cingulate gyrus and right insula positively correlated with NS scores (Fig. 1). Positive correlations between the NS score and metabolism in the anterior cingulate gyrus and insula suggest that these regions play a critical role in NS. The anterior cingulate gyrus modulates impulsivity, attention control [4, 23], and addiction [24]. The insula mediates emotional behavioral responses [25, 26], especially craving behaviors [27, 28]. In a functional MRI study, the abstinence-induced urge to smoke

Table 1. Brain regions showing significant correlations between regional glucose metabolism and novelty seeking scores

Region		Clusters (k)	Coordinates			Z scores
			x	y	z	
Positive correlations with NS score						
L	Anterior cingulate gyrus	1996	-4	32	14	4.41
R	Middle cingulate gyrus		8	18	30	4.22
R	Insula	835	38	20	-10	3.49
L	Insula	581	-44	-10	-4	4.10
Negative correlations with NS score						
R	Pallidum	195	22	-10	6	3.63
R	Putamen		28	0	14	3.31

L, left; NS, novelty seeking; R, right. p<0.001, uncorrected; k=100.

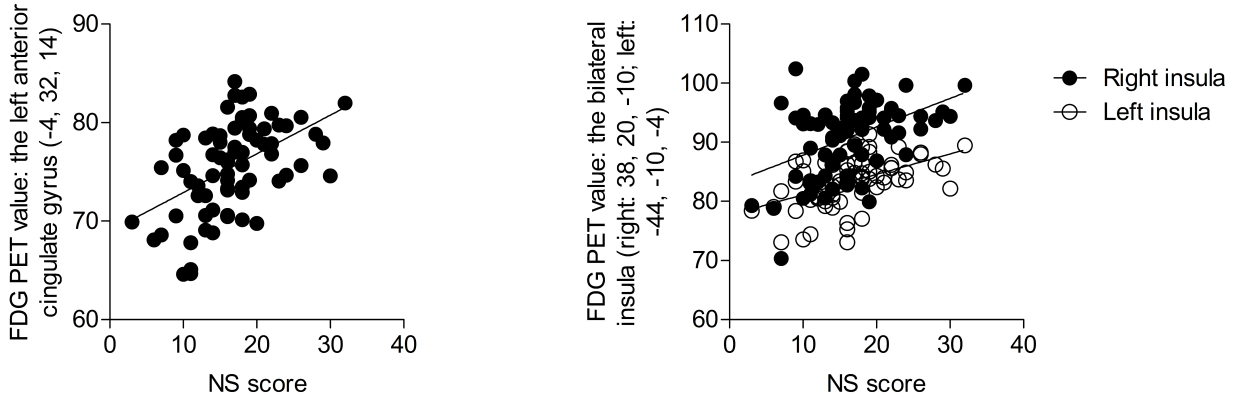

Fig. 1. Cerebral metabolism in the anterior cingulate area (Pearson r=0.49, p<0.0001) and insula (left, Pearson r=0.48, p<0.0001; right, Pearson r=0.44, p<0.0001) correlate with novelty seeking scores.

increased cerebral blood flow in the anterior cingulate gyrus and insula simultaneously [28]. A proposed model of neuronal connectivity between the anterior cingulate gyrus and the insula suggests that the insula integrates the urge of the volitional agents that is then represented in the anterior cingulate gyrus [29, 30]. Our data not only demonstrate a functional association between these areas but also implicate this association as a neural substrate for the propensity for addictive behavior. Additionally, negative correlations between metabolism in the right pallidum and putamen and NS scores also support Cloninger's hypothesis of a negative correlation between NS score and dopaminergic activity [1, 3, 5, 9] (Fig. 2). Traditionally, subcortical and limbic regions of the brain have been viewed as involved in the generation of negative feelings and behavior, whereas the frontal cortex is viewed as inhibiting and modulating these basic emotions [31].

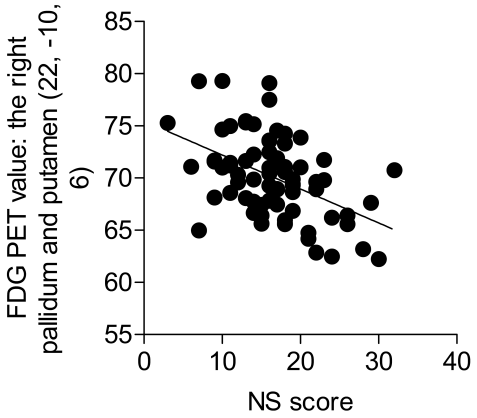

Fig. 2. Cerebral metabolism in clusters of the right pallidum and putamen (Pearson r=0.47, p<0.0001) correlate with novelty seeking scores.

Participants with ASP (13 of the 72 participants, 18%) showed significantly higher NS scores (mean±SD=21.3±3.3) than those without ASP (mean±SD=15.6±5.6; t [70]=3.464, p<0.001). However, despite high NS scorers being well represented in the ASP group, regional changes in glucose metabolism largely did not overlap between the ASP and NS groups, with the exception of the middle cingulate gyrus. Increased cerebral regional glucose metabolism was found in the left hemisphere, including in the inferior frontal gyrus (peak activation at x=-54, y=14, z=4; Z=3.02, k=156). Decreased metabolism occurred bilaterally in cortical and subcortical regions, including the right orbitofrontal gyrus (peak activation at x=26, y=42, z=-2; Z=4.00, k=814) and hippocampus (peak activation at x=40, y=-22, z=-16; Z=3.60, k=744). These results are summarized in Table 2. The present results identify neuronal abnormalities in the frontal and temporal cortical regions and the hippocampus related to ASP. In accordance with these findings, previous studies have identified abnormalities in frontal and prefrontal areas as relevant to borderline personality disorder and impulse control disorder [32-34]. It could be argued that what may be critically important in predisposing individuals to antisocial behavior is the relative balance of activity between the prefrontal and subcortical brain regions. Our findings suggest that ASP may be related to differences in level of regional glucose metabolism in specific prefrontal and subcortical brain regions.

Table 2. Brain regions with activated or deactivated regional cerebral glucose metabolism in individuals in antisocial personality categories

Region		Clusters (k)	Coordinates			Z scores
			x	y	z	
Activated regions in ASP						
L	Inferior frontal gyrus	156	-54	14	4	3.02
L	Middle cingulate gyrus	161	-2	16	32	2.99
L	Medial superior frontal gyrus	180	0	46	18	2.80
Deactivated regions in ASP						
L	Supramarginal gyrus	2211	-48	-24	26	4.53
R	Superior orbitofrontal gyrus	814	26	42	-2	4.00
L	Middle temporal gyrus	1090	-48	-44	2	3.78
R	Hippocampus	744	40	-22	-16	3.60
L	Postcentral gyrus	1115	-22	-36	58	3.50
L	Middle cingulate gyrus	245	-18	-52	38	3.43
R	Middle cingulate gyrus	159	14	18	38	3.21
L	Middle temporal gyrus	150	-36	-68	10	3.10

ASP, antisocial personality; L, left; R, right. p<0.005 uncorrected, k=100.

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Regional cerebral function in addition to neurotransmitter effects seems to play a crucial role in the prevalence of personality disorders and psychiatric disease. For example, it is known that borderline personality disorder involves typical antisocial characteristics with impulsive, irresponsible, violent, and suicidal behaviors [33, 34]. This study had some limitations. For example, once the participants had been divided according to their TCI results, only 13 were placed in the ASP group. This relatively low number prevented us from conducting a full analysis of the brain metabolism changes according to the NS trait within the ASP subgroup. Indeed, the current findings do not suggest that NS and ASP have a common neurobiological basis, which is incongruous with the literature suggesting that NS is a central trait of ASP. Further, we were limited as to the type of analyses we could do based on the number of participants in this study. In the future, we would like to utilize the new graph-theoretical approaches to assess the functional subnetworks of the anterior cingulate cortex and insula in order to more fully understand the biological substrates of NS and ASP.

In the present study, we investigated the neurobiological substrates of NS and ASP as fundamental aspects of problematic behavior. Voxel-based correlation and subtraction analysis with TCI scores and FDG PET data revealed that personality variants might be predicted by resting-state patterns of regional cerebral glucose metabolism. These data may benefit the identification of patients who are at risk for the development of psychological or psychiatric disorders.

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REFERENCES

1. Cloninger CR (1987) A systematic method for clinical description and classification of personality variants. A proposal. Arch Gen Psychiatry 44:573-588.
2. Cloninger CR, Svrakic DM, Przybeck TR (1993) A psychobiological model of temperament and character. Arch Gen Psychiatry 50:975-990.
3. Compton PA, Anglin MD, Khalsa-Denison ME, Paredes A (1996) The D2 dopamine receptor gene, addiction, and personality: clinical correlates in cocaine abusers. Biol Psychiatry 39:302-304.
4. Fishbein DH, Eldreth DL, Hyde C, Matochik JA, London ED, Contoreggi C, Kurian V, Kimes AS, Breeden A, Grant S (2005) Risky decision making and the anterior cingulate cortex in abstinent drug abusers and nonusers. Brain Res Cogn Brain Res 23:119-136.
5. Laine TP, Ahonen A, Räsänen P, Tiihonen J (2001) Dopamine transporter density and novelty seeking among alcoholics. J Addict Dis 20:91-96.
6. Cloninger CR, Svrakic DM, Przybeck TR (2006) Can personality assessment predict future depression? A twelve-month follow-up of 631 subjects. J Affect Disord 92:35-44.
7. Hansenne M, Reggers J, Pinto E, Kjiri K, Ajamier A, Ansseau M (1999) Temperament and character inventory (TCI) and depression. J Psychiatr Res 33:31-36.
8. Peirson AR, Heuchert JW, Thomala L, Berk M, Plein H, Cloninger CR (1999) Relationship between serotonin and the temperament and character inventory. Psychiatry Res 89:29-37.
9. Zald DH, Cowan RL, Riccardi P, Baldwin RM, Ansari MS, Li R, Shelby ES, Smith CE, McHugo M, Kessler RM (2008) Midbrain dopamine receptor availability is inversely associated with novelty-seeking traits in humans. J Neurosci 28:14372-14378.
10. Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH (1996) Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. Nat Genet 12:81-84.
11. Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett ER, Nemanov L, Katz M, Belmaker RH (1996) Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. Nat Genet 12:78-80.
12. Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ (1991) Allelic association of the D2 dopamine receptor gene with receptor-binding characteristics in alcoholism. Arch Gen Psychiatry 48:648-654.
13. Wiesbeck GA, Mauerer C, Thome J, Jakob F, Boening J (1995) Neuroendocrine support for a relationship between "novelty seeking" and dopaminergic function in alcohol-dependent men. Psychoneuroendocrinology 20:755-761.
14. Khan AA, Jacobson KC, Gardner CO, Prescott CA, Kendler KS (2005) Personality and comorbidity of common psychiatric disorders. Br J Psychiatry 186:190-196.
15. Hesselbrock MN, Hesselbrock VM (1992) Relationship of

family history, antisocial personality disorder and personality traits in young men at risk for alcoholism. J Stud Alcohol 53:619-625.
16. Ponce G, Jimenez-Arriero MA, Rubio G, Hoenicka J, Ampuero I, Ramos JA, Palomo T (2003) The A1 allele of the DRD2 gene (TaqI A polymorphisms) is associated with antisocial personality in a sample of alcohol-dependent patients. Eur Psychiatry 18:356-360.
17. Goyer PF, Andreason PJ, Semple WE, Clayton AH, King AC, Compton-Toth BA, Schulz SC, Cohen RM (1994) Positron-emission tomography and personality disorders. Neuropsychopharmacology 10:21-28.
18. Raine A, Meloy JR, Bihrle S, Stoddard J, LaCasse L, Buchsbaum MS (1998) Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. Behav Sci Law 16:319-332.
19. Kuruoğlu AC, Arikan Z, Vural G, Karataş M, Araç M, Işik E (1996) Single photon emission computerised tomography in chronic alcoholism. Antisocial personality disorder may be associated with decreased frontal perfusion. Br J Psychiatry 169:348-354.
20. Sung SM, Kim JH, Yang E, Abrams KY, Lyoo IK (2002) Reliability and validity of the Korean version of the temperament and character inventory. Compr Psychiatry 43:235-243.
21. Talairach J, Tournoux P (1988) Co-planar stereotaxic atlas of the human brain. Thieme, New York, NY.
22. Sugiura M, Kawashima R, Nakagawa M, Okada K, Sato T, Goto R, Sato K, Ono S, Schormann T, Zilles K, Fukuda H (2000) Correlation between human personality and neural activity in cerebral cortex. Neuroimage 11:541-546.
23. Matsuo K, Nicoletti M, Nemoto K, Hatch JP, Peluso MA, Nery FG, Soares JC (2009) A voxel-based morphometry study of frontal gray matter correlates of impulsivity. Hum Brain Mapp 30:1188-1195.
24. Goldstein RZ, Alia-Klein N, Volkow NS, Larry RS (2009) Drug addiction: neuroimaging. In: Encyclopedia of neuroscience (Squire LR, ed), pp 699-711. Academic Press, Oxford.
25. Paulus MP, Stein MB (2006) An insular view of anxiety. Biol Psychiatry 60:383-387.
26. Stein MB, Simmons AN, Feinstein JS, Paulus MP (2007) Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am J Psychiatry 164:318-327.
27. Brody AL, Mandelkern MA, Olmstead RE, Jou J, Tiongson E, Allen V, Scheibal D, London ED, Monterosso JR, Tiffany ST, Korb A, Gan JJ, Cohen MS (2007) Neural substrates of resisting craving during cigarette cue exposure. Biol Psychiatry 62:642-651.
28. Wang Z, Faith M, Patterson F, Tang K, Kerrin K, Wileyto EP, Detre JA, Lerman C (2007) Neural substrates of abstinence-induced cigarette cravings in chronic smokers. J Neurosci 27:14035-14040.
29. Sarinopoulos I, Dixon GE, Short SJ, Davidson RJ, Nitschke JB (2006) Brain mechanisms of expectation associated with insula and amygdala response to aversive taste: implications for placebo. Brain Behav Immun 20:120-132.
30. Craig AD (2009) How do you feel--now? The anterior insula and human awareness. Nat Rev Neurosci 10:59-70.
31. Weiger WA, Bear DM (1988) An approach to the neurology of aggression. J Psychiatr Res 22:85-98.
32. Goldstein RZ, Volkow ND, Wang GJ, Fowler JS, Rajaram S (2001) Addiction changes orbitofrontal gyrus function: involvement in response inhibition. Neuroreport 12:2595-2599.
33. Bolla KI, Eldreth DA, London ED, Kiehl KA, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, Cadet JL, Kimes AS, Funderburk FR, Ernst M (2003) Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. Neuroimage 19:1085-1094.
34. Soloff PH, Meltzer CC, Becker C, Greer PJ, Kelly TM, Constantine D (2003) Impulsivity and prefrontal hypometabolism in borderline personality disorder. Psychiatry Res 123:153-163.

 http://dx.doi.org/10.5607/en.2016.25.4.185