Major Depressive Disorder Shows Frequency-specific Abnormal Functional Connectivity Patterns Associated with Anhedonia

Yajing Pang
1 The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, China
2 School of Life Science and Technology, Center for Information in Medicine, University of Electronic Science and Technology of China, Chengdu, China
yajingpang@yeah.net

Qian Cui
1School of Public Administration, University of Electronic Science and Technology of China, Chengdu, China
qiancui26@gmail.com

Yifeng Wang
1 The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, China
2 School of Life Science and Technology, Center for Information in Medicine, University of Electronic Science and Technology of China, Chengdu, China
wangyif@uestc.edu.cn

Yuyan Chen
1 The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, China
2 School of Life Science and Technology, Center for Information in Medicine, University of Electronic Science and Technology of China, Chengdu, China
18227633563@163.com

Qi Yang
1 The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, China
2 School of Life Science and Technology, Center for Information in Medicine, University of Electronic Science and Technology of China, Chengdu, China
463583942@qq.com

Huafu Chen
1 The Clinical Hospital of Chengdu Brain Science Institute, MOE Key Lab for Neuroinformation, University of Electronic Science and Technology of China, Chengdu, China
2 School of Life Science and Technology, Center for Information in Medicine, University of Electronic Science and Technology of China, Chengdu, China
chenhf@uestc.edu.cn

ABSTRACT

Anhedonia is a core feature of major depression disorder (MDD), is associated with the dysfunction of the dopamine system. Here, we aimed to examine how resting-state functional connectivity (FC) within the dopamine system in MDD patients is related to anhedonia and whether this relationship relies on specific frequency bands (slow 4: 0.027—0.073 Hz and slow 5: 0.01—0.027 Hz). The regional connectivity strength and FC were evaluated. Our results revealed decreased connectivity strength in MDD in the posterior cingulate cortex and hippocampus at slow 4 and in the anterior insula and hippocampus at slow 5. Of note, increased FC in the mesocorticolimbic system was found in MDD only at slow 5. Furthermore, the altered connectivity at slow 5 contributed to predicting anhedonia symptom and depression severity. These findings suggest that dopamine system functional connectivity remains a prime target for understanding the anhedonia of MDD.

ICMHI 2019, May 17–19, 2019, Xiamen, China

ACM ISBN 978-1-4503-7199-5/19/05…$15.00
https://doi.org/10.1145/3340037.3340051

CCS Concepts
Applied computing → Health informatics

Keywords
Major depressive disorder; anhedonia; functional connectivity; dopamine system

1. INTRODUCTION

Anhedonia, the diminished ability to experience pleasure, is a core symptom and potential trait marker of major depressive disorder (MDD) [1, 2]. According to the National Institute of Mental Health （NIMH） Research Domain Criteria (RDoC) initiative (https://www.nimh.nih.gov/research-priorities/rdoc/units/behaviors/150689.shtml), the anhedonia is considered to be related to the specific neural circuit. Examining the associations across the neural circuit, clinical symptom and behavior probably contribute to understanding the pathophysiology of MDD.

The anhedonia is associated with the dopaminergic mesolimbic and mesocortical reward circuit [3, 4]. In detail, the mesolimbic circuit includes the ventral tegmental area, ventral striatum,

amygdala, and hippocampus, which involving learning, reward motivation, and reinforcement. The mesocortical circuit includes cingulate cortex, anterior insula, and prefrontal cortex, which involving work memory, attention, and inhibitory control [3]. MDD has been repeatedly reported to shows hypoactivation of these reward-related regions during processing pleasant stimuli [5, 6], as well as shows altered resting-state functional connectivity (FC) of the striatum, which was associated with patients' anhedonia and depression severity [7, 8]. Different FC patterns of dorsomedial prefrontal cortex specific to anhedonia and depression severity could provide neural targets for intervention in young people at risk of depression [9]. Thus, investigating the disrupted FC of the dopamine system in MDD patients is a promising way to clarify the neuropathology of anhedonia in MDD and to improve the treatment of MDD.

Of note, on the basis of frequency-dependent effects exist in different networks in MDD [10], the present study aimed to examine the frequency-specific anhedonia network in MDD patients using region of interest (ROI)-based approach. Especially, the slow 4 (0.027—0.073 Hz) and slow 5 (0.01—0.027 Hz) frequency bands were mainly included due to they both linked to physiological meanings [11, 12]. In detail, for each frequency band, the FC data was firstly calculated among these ROIs for each subject. The node connectivity strength and FC was evaluated for MDD and HC groups. Then, the two-sample t-test and network-based statistic (NBS) were employed to test the group effect. Last, we tested whether abnormal FC could predict anhedonia and depression severity.

2. METHODS

2.1 Participants

Thirty-six currently depressed patients with MDD were recruited from The Clinical Hospital of Chengdu Brain Science Institute. All patients were interviewed by two experienced psychiatrists using the Structured Clinical Interview for DSM–IV–TR–Patient Edition (SCID-P, 2/2001 version). MDD patients were diagnosed according to the DSM–IV criteria. The exclusion criteria included anxiety disorders, schizophrenia, mental retardation or personality disorders, any history of consciousness loss, substance abuse, and serious medical or neurological illnesses. The clinical states of the patients were evaluated using the 24-item Hamilton Depression Scale (HAMD). Thirty-six HCs who were comparable with patients regarding age, gender, education, and handedness were recruited through advertisements. The SCID (non-patient edition) was employed to ensure the lifetime absence of psychiatric illnesses in the HCs.

Written informed consent was obtained from all participants before the experiment. This study was approved by the research ethics committee of the University of Electronic Science and Technology of China in compliance with the latest revision of the Declaration of Helsinki and registered at ClinicalTrials.gov (Identifier: NCT02888509;https://www.clinicaltrials.gov/ct2/show/NCT02888509?term=NCT02888509&rank=1).

2.2 Data Acquisition

The fMRI data were acquired using the 3T GE DISCOVERY MR750 scanner (General Electric, Fairfield Connecticut, USA) equipped with a high-speed gradient and an 8 channel head coil. Foam pads and headphones were used to minimize head movement and scanner noise. The participants were instructed to simply rest with their eyes closed, not fall asleep, and remain motionless during the data acquisition. Functional images were collected using an echo-planar imaging sequence with the following parameters: repetition time/echo time = 2000/30 ms, slices = 43, matrix size = 64 × 64, flip angle = 90°, field of view = 240 × 240 mm2, voxel size = 3.75 × 3.75 × 3.2 mm3, thickness = 3.2 mm, no gap, and a total of 255 volumes. The structural image was scanned using the following parameters: TR/TE = 5.92/1.956 ms, slices = 156, matrix size = 256 × 256, FA = 12°, FOV = 256 × 256 mm2, voxel size = 1 × 1 × 1 mm3, slice thickness = 1 mm, and no gap.

2.3 Data Preprocessing

The fMRI data were preprocessed using FSL 5.0.10 and SPM12 functions through DPABI (http://rfmri.org/dpabi). The first five volumes were removed before any preprocess steps. The standard preprocessing pipeline in FSL FEAT software was conducted, which included non-brain removal, motion correction using MCFLIRT, spatial smoothing using a Gaussian kernel of full-width at half maximum (FWHM) of 6 mm, grand mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and registered to MNI-152 standard space image using FMRIB's Nonlinear Image Registration Tool (FNIRT). In addition, a state-of-the-art ICA-based denoising procedure (ICA-AROMA) was employed to remove motion-related artifacts in native space [13]. Then, DAPBI was used to regress nuisance covariance regression (Friston 24 motion parameters, white matter, cerebrospinal fluid) and linear detrended. Temporal band-pass filtering was then performed in the following two frequency bands: 0.01—0.027 Hz (termed as slow 5) and 0.027—0.073 Hz (termed as slow 4) to isolate the low-frequency fluctuations which characterize resting-state blood oxygen level dependent signals.

2.4 SHAPS: Snaith–Hamilton Pleasure Scale

The Snaith–Hamilton Pleasure Scale (SHAPS) is a self-administered instrument that was used to measure hedonic capacity [14]. The SHAPS includes 14 items, and each of the items has a set of four response categories: Definitely Agree, Agree, Disagree, and Strongly Disagree, with coded as 1, 2, 3, 4, respectively. A higher total SHAPS score indicated higher levels of present state of anhedonia.

2.5 Connectivity Analyses

ROI definition. The ROIs were defined according to RDoC and previous literature, and including reward network defined by Satterthwaite and colleagues [15], bilateral dorsolateral prefrontal cortex (dlPFC)[16], orbitofrontal cortex (OFC) [17], right inferior parietal lobule [17], bilateral amygdala, and bilateral hippocampus [4, 18]. These regions were defined by a sphere with a radius of 5 mm. Additional details are available in Table 1. Of note, as the amygdala was small, then it was created by the AAL template. Thus, totally 19 ROIs were included in our study.

Resting-state FC analysis. For each frequency band, the mean time series of each ROI was extracted. The Pearson correlation coefficient was calculated for each two ROIs' time series. Fisher's r-to-z transformation was employed to improve the normality. Thus, the 19×19 matrix was obtained for each subject. Group-level models evaluated the FC data at two levels of resolution including (a) overall connectivity strength of each node and (b) connectivity at each network edge. Node strength, defined as the sum of the connectivity strength of each network edge connected to a given node, was calculated using the Brain Connectivity Toolbox [19].

2.6 Statistical Analysis

A two-sample t-test was employed to assess the difference of whole network connectivity strength between MDD and HC. Then, the permutation t-test was calculated and repeated 5000 times to evaluate the difference of node connectivity strength between MDD and HC. The significant value was set at $p < 0.05$. Last, the differences in network connectivity between MDD and HCs were assessed using NBS approach with 5000 iterations performed to identify any variations. We reported any components that were significant at a p-value of 0.05 after family-wise error correction.

2.7 Prediction Model

To investigate the relationship between abnormal FC measurement and anhedonia and depression severity in MDD, the linear Support Vector Regression (SVR) was performed to predict SHAPS and HAMD scores for each MDD patient. Leave-one-out cross-validation method was utilized to develop the prediction model. For each cross-validation, the predictive SHAPS and HAMD score was obtained for each MDD patient to determine the correlation coefficient between the real scores and predicted the scores.

3. Results

Table 2 showed the demographics of the study population; there were no significant differences between MDD and HCs for age, gender, handedness, and education years. Figure 1 shows that MDD patients had significantly higher SHAPS scores than HCs. In line with the previous study [20], SHAPS had no correlation with HAMD in MDD ($r = -0.008$; $p = 0.97$).

Frequency-specific difference in node connectivity strength between MDD and HCs

There were no significant differences between MDD and HCs in network connectivity strength for both slow 4 and slow 5 frequency bands. However, contrast with HCs, MDD patients exhibited decreased connectivity strength in the posterior cingulate cortex (PCC) and right hippocampus at slow 4 and decreased connectivity strength in the right anterior insula and bilateral hippocampus at slow 5 (Figure 2).

Frequency-specific difference in FC pattern between MDD and HCs

Group effect of FC was only found at slow 5 but not slow 4. Compared to HCs, increased FC in MDD was found between PCC and Pre-SMA; between left anterior insula and OFC; between right anterior insula and left amygdala; between right inferior parietal lobule and left amygdala; between bilateral anterior insula and right amygdala; between Pre-SMA and right amygdala; between right anterior insula and left hippocampus; between Pre-SMA and bilateral hippocampus; between left hippocampus and right hippocampus (Figure 3).

Prediction based on connectivity measurements

The altered node connectivity strength and FC was used as features to predict anhedonia and depressive severity in linear SVR analysis. Results showed that the decreased connectivity strength and increased FC at slow 5 could predict anhedonia and depressive severity in MDD, respectively. The predicted SHAPS/HAMD scores showed significant positive correlation with real SHAPS/HAMD scores in patients with MDD (Figure 4).

4. DISCUSSION

The present study examined the frequency-specific abnormal FC related to anhedonia in MDD patients. Our results revealed (1) frequency-specific decreased connectivity strength in MDD patients compared to the HC group in the hippocampus, insula, and PCC; (2) two abnormal FC patterns in MDD patients at slow 5: increased FC among mesocortical circuit and increased FC between mesocortical and mesolimbic system; (3) the altered hippocampus connectivity patterns at slow 5 could predict anhedonia and depression severity in MDD. The findings provide new insight into the neuropathology of MDD.

Compared to HCs, the connectivity strength of PCC was decreased in MDD at slow 4. The PCC, a core region in default mode network (DMN), is implicated in self-referential processing and rumination in depression [21, 22]. The abnormal FC in DMN was related to anhedonia and depression severity in depression adolescents [9], suggesting that the DMN may play a role in the self-referential aspect of anhedonia [23]. The connectivity strength of right anterior insula was decreased at slow 5. The right anterior insula is a critical region in the salience network and involved in processing salient emotional stimuli [24]. The activation of this region and the effective connectivity between the insula and mesolimbic reward system were negatively correlated with anhedonia during music stimuli [17]. In this context, the insula was involved in regulating emotional reactivity to hedonic stimuli [25]. Moreover, the hippocampus showed decreased connectivity strength in MDD at both slow 4 and slow 5 compared to HCs. Hippocampus is also implicated in the rewarding process [4], is believed to be responsible for to reward-spatial view representations and learning [26]. Decreased neurogenesis in the hippocampus led to anhedonia and prevented the reversal of anhedonia by antidepression treatment [27]. Aberrant FC of these regions was widely reported and documented to reflect emotional and cognitive dysfunction in MDD [28-30]. Furthermore, the decreased connectivity strength of insula and hippocampus at slow 5 could predict anhedonia in MDD, whereas the altered connectivity strength at slow 4 could not. Our findings of decreased connectivity strength of these regions at different frequency bands extended previous literature, suggesting that these alterations may occur at different time scales and therefore altering different circuits in MDD.

Increased FC between the limbic region and other regions (e.g., anterior insula, SMA, and inferior parietal lobule) was found in MDD at slow 5, along with increased FC among mesocortical circuit. Among these abnormal FC patterns, we found increased hippocampus FC could predict the anhedonia and depression severity in MDD patients. This is congruent with previous literature, which reported that anhedonia in MDD was associated with altered mesocorticolimbic dopamine transmission and may be improved by dopaminergic therapies [31]. The abnormal FC of the hippocampus was widely reported in MDD [32], especially the FC between hippocampus and insula[33], which was suggested to be responsible for negative moods in MDD [34]. Extended to previous literature, our findings provided further information that hippocampus FC may underlie the anhedonia in MDD, thus probably lead to depressive states in MDD patients.

5. CONCLUSION

This study investigated the frequency-specific abnormal FC in the dopaminergic system in MDD and highlighted its role in anhedonia and depression severity. However, our study has limitations. The small sample leads to relatively low statistical

significance. Most of our MDD patients undertaking medicine, which probably results in the unstable of our results. In sum, future study with a large sample and drug-free depression patients was needed to verify our finding.

Table 1. MNI coordinates of ROIs

Regions	MNI coordinate		
	x	y	z
Left ventral striatum	-12	12	-7
Right ventral striatum	12	10	-6
VMPFC	2	46	-8
Left anterior insula	-30	22	-6
Right anterior insula	32	20	-6
Posterior Cingulate	-4	-30	36
Brainstem/VTA	-2	-22	-12
Anterior Cingulate	-2	28	28
Pre-SMA	-2	28	46
Left Thalamus	-6	-8	6
Right Thalamus	6	-8	6
Left dlPFC	-44	15	29
Right dlPFC	44	22	25
OFC	-20	40	-14
Right IPL	62	-28	32
Left amygdala	AAL		
Right amygdala	AAL		
Left hippocampus	-20	-10	-30
Right hippocampus	26	-20	-20

VMPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area; Pre-SMA, pre-supplementary motor area; dlPFC, dorsolateral prefrontal cortex; OFC, orbital frontal cortex; IPL, inferior parietal lobule; AAL, automated anatomical labeling.

Table 2. Characteristics of demographic and clinical variable

Variables	HC (36)	MDD (36)	*p*-value
Age (yrs)	29.75 ± 8.89	30.06 ± 9.65	0.89[a]
Gender (Male / Female)	17/19	16/20	0.81[b]
Education (yrs)	15.22 ± 3.33	14.19 ± 2.69	0.16[a]
Handness (Left / Right)	1/35	0/36	0.31[b]
SHAPS	24.00 ± 6.01	29.03 ± 6.67	0.001[a]
HAMD		25.61 ± 6.04	

Values are mean ± SD.

[a] Two-tailed two-sample t-test.

[b] Chi-square t-test.

HC, Healthy control; MDD, Major depressive disorder; SHAPS: Snaith–Hamilton Pleasure Scale; HAMD, Hamilton depression scale.

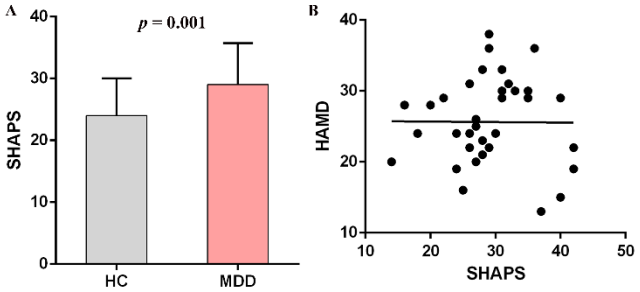

Figure 1. (A) Comparison of SHAPS between patients with MDD and HCs. (B) SHAPS has no correlation with HAMD. MDD, major depressive disorder; HC, healthy control; SHAPS: Snaith–Hamilton Pleasure Scale; HAMD, Hamilton depression scale.

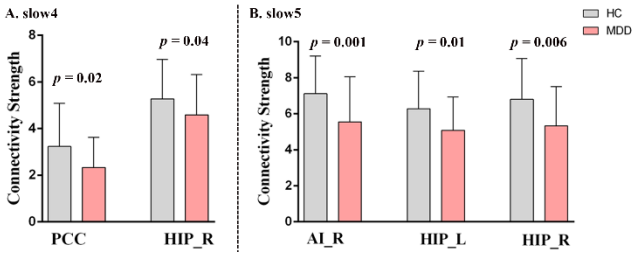

Figure 2. (A) The decreased node strength in MDD compared to HCs at slow 4. (B) The decreased node strength in MDD compared to HCs at slow 5. MDD, major depressive disorder; HCs, healthy controls; PCC, posterior cingulate cortex; AI, anterior insula; HIP, hippocampus; L, left; R, right.

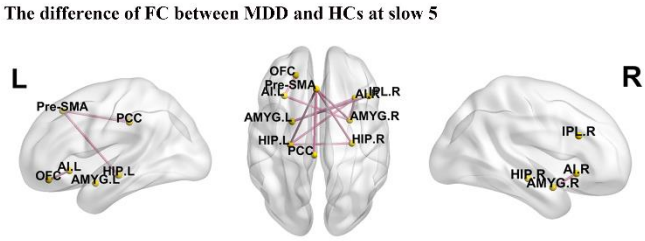

Figure 3. Increased FC in MDD patients compared to HCs at slow 5. MDD, major depressive disorder; HCs, healthy controls; AI, anterior insula; PCC, posterior cingulate cortex; OFC, orbitofrontal cortex; Pre-SMA, pre-supplementary motor area; IPL, inferior parietal lobule; AMYG, amygdala; HIP, hippocampus.

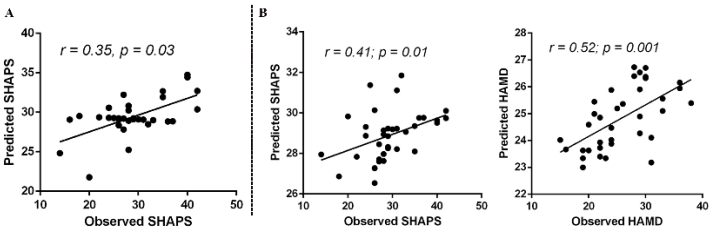

Figure 4. (A) Decreased connectivity strength in the anterior insula and hippocampus predicts anhedonia in MDD at slow 5. (B) Increased hippocampus FC predicts the anhedonia and depression severity in MDD at slow 5. FC, functional connectivity; SHAPS: Snaith–Hamilton Pleasure Scale; HAMD, Hamilton depression scale.

6. Acknowledgments

This work was supported by the Natural Science Foundation of China (61533006, U1808204, 81771919, and 31600930).

7. References

[1] Dichter, G.S., Anhedonia in unipolar major depressive disorder: a review. Open Psychiatry J., 2010. 4: p. 1-9.

[2] Guze, S.B., DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL-DISORDERS, 4TH EDITION (DSM-IV) - AMER-PSYCHIAT-ASSOC. American Journal of Psychiatry, 1995. 152(8): p. 1228-1228.

[3] Martinotti, G., et al., Anhedonia and Reward System: Psychobiology, Evaluation, and Clinical Features. International Journal of Clinical Medicine, 2012. 03(07): p. 697-713.

[4] Heshmati, M. and S.J. Russo, Anhedonia and the Brain Reward Circuitry in Depression. Current Behavioral Neuroscience Reports, 2015. 2(3): p. 146.

[5] Young, C.B., et al., Anhedonia and general distress show dissociable ventromedial prefrontal cortex connectivity in major depressive disorder. Translational Psychiatry, 2016. 6(5): p. e810.

[6] Takamura, M., et al., Patients with major depressive disorder exhibit reduced reward size coding in the striatum. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 2017. 79(Pt B): p. 317-323.

[7] Vilma, G., et al., Striatum-based circuitry of adolescent depression and anhedonia. Journal of the American Academy of Child & Adolescent Psychiatry, 2013. 52(6): p. 628-641.e13.

[8] Yang, X., et al., Anhedonia correlates with abnormal functional connectivity of the superior temporal gyrus and the caudate nucleus in patients with first-episode drug-naive major depressive disorder. Journal of Affective Disorders, 2017. 218: p. 284-290.

[9] Rzepa, E. and C. Mccabe, Anhedonia and depression severity dissociated by dmPFC resting-state functional connectivity in adolescents. Journal of Psychopharmacology, 2018. 32(10): p. 1067-1074.

[10] He, Z., et al., Frequency-specific alterations in functional connectivity in treatment resistant and -sensitive major depressive disorder. Journal of Psychiatric Research, 2016. 82: p. 30-39.

[11] Zuo, X.-N., et al., The oscillating brain: Complex and reliable. Neuroimage, 2010. 49(2): p. 1432-1445.

[12] Han, Y., et al., Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnestic mild cognitive impairment: A resting-state fMRI study. Neuroimage, 2011. 55(1): p. 287-295.

[13] Pruim, R.H.R., et al., ICA-AROMA: A robust ICA-based strategy for removing motion artifacts from fMRI data. Neuroimage, 2015. 112: p. 267-277.

[14] Snaith, R.P., et al., A SCALE FOR THE ASSESSMENT OF HEDONIC TONE - THE SNAITH-HAMILTON PLEASURE SCALE. British Journal of Psychiatry, 1995. 167: p. 99-103.

[15] Satterthwaite, T.D., et al., Common and Dissociable Dysfunction of the Reward System in Bipolar and Unipolar Depression. Neuropsychopharmacology, 2015. 40(9): p. 2258-2268.

[16] Chung, Y.S. and D.M. Barch, Frontal-Striatum Dysfunction During Reward Processing: Relationships to Amotivation in Schizophrenia. Journal of Abnormal Psychology, 2016. 125(3).

[17] Keller, J., et al., Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. Journal of Psychiatric Research, 2013. 47(10): p. 1319-1328.

[18] Lally, N., et al., Neural correlates of change in major depressive disorder anhedonia following open-label ketamine. Journal of Psychopharmacology, 2015. 29(5): p. 596.

[19] Mikail, R. and S. Olaf, Complex network measures of brain connectivity: uses and interpretations. Neuroimage, 2010. 52(3): p. 1059-1069.

[20] Schrader, G.D.J.C.P., Does anhedonia correlate with depression severity in chronic depression? 1997. 38(5): p. 260-263.

[21] Brewer, J.A., K.A. Garrison, and S. Whitfield-Gabrieli, What about the “Self” is Processed in the Posterior Cingulate Cortex? Frontiers in Human Neuroscience, 2013. 7: p. 647.

[22] Burkhouse, K.L., et al., Neural correlates of rumination in adolescents with remitted major depressive disorder and healthy controls. Cognitive Affective & Behavioral Neuroscience, 2016. 17(2): p. 1-12.

[23] Lee, J.S., et al., Neural Basis of Anhedonia and Amotivation in Patients with Schizophrenia: The role of Reward System. Current Neuropharmacology, 2015. 13(6): p. 750-759.

[24] Wang, Y., et al., Frequency dependent hub role of the dorsal and ventral right anterior insula. Neuroimage, 2017. 165: p. 112.

[25] Berridge, K.C. and M.L. Kringelbach, Affective neuroscience of pleasure: reward in humans and animals. Psychopharmacology, 2008. 199(3): p. 457-480.

[26] Rolls, E.T. and X.J.J.o.N.t.O.J.o.t.S.f.N. Jian-Zhong, Reward-spatial view representations and learning in the primate hippocampus. 2005. 25(26): p. 6167-74.

[27] Der-Avakian, A. and A. Markou, The neurobiology of anhedonia and other reward-related deficits. Trends in Neurosciences, 2012. 35(1): p. 0-77.

[28] Ramasubbu, R., et al., Reduced Intrinsic Connectivity of Amygdala in Adults with Major Depressive Disorder. 2014. 5: p. 17.

[29] Cao, X., et al., Disrupted resting-state functional connectivity of the hippocampus in medication-naïve patients with major depressive disorder. 2012. 141(2-3): p. 194-203.

[30] Pang, Y., et al., Transdiagnostic and diagnosis-specific dynamic functional connectivity anchored in the right anterior insula in major depressive disorder and bipolar depression. Prog Neuropsychopharmacol Biol Psychiatry, 2018. 85: p. 7-15.

[31] Mann, J.J. and S.J.C.N. Kapur, A Dopaminergic Hypothesis of Major Depression. 1995. 18(1): p. S57-S65.

[32] Zhu, X., et al., Aberrant functional connectivity of the hippocampus in older adults with subthreshold depression. Psych Journal, 2015. 3(4): p. 245-253.

[33] Song, Z., M. Zhang, and P. Huang, Aberrant emotion networks in early major depressive disorder patients: an eigenvector centrality mapping study. Translational Psychiatry, 2016. 6(5): p. e819.

[34] Peng, D., et al., Altered brain network modules induce helplessness in major depressive disorder - Journal of Affective Disorders. Journal of Affective Disorders, 2014. 168: p. 21-29.