Neurotransmitters in Young People with Internet and Smartphone Addiction: A Comparison with Normal Controls and Changes after Cognitive Behavioral Therapy

PURPOSE
To reveal changes in neurotransmitters in internet and smartphone addicted youth compared with normal controls and after cognitive behavioral therapy, and to identify the correlations between neurotransmitters and affective factors related to addiction.

METHOD AND MATERIALS
Institutional review board approved this prospective study and informed consents were obtained. Nineteen young persons with internet and smartphone addictions consisted of 9 males and 10 females and their mean age was 15.47±3.06 years. Nineteen gender and age-matched healthy controls were also included. Nine weeks cognitive behavioral therapy was administered to 12 addicts ages 11 to 17 years. MEGA-press MRS was used to measure GABA and glutamate-glutamine (Glx) levels in the anterior cingulate cortex. GABA and Glx levels in the addicted group were compared to controls and after 9 weeks of cognitive behavioral therapy. GABA and Glx levels were correlated to clinical scales of internet and smartphone addictions, impulsiveness, depression, anxiety, insomnia and sleep quality.

RESULTS
Brain-parenchymal and gray-matter volume adjusted GABA to creatine ratios (p=0.028 and 0.016) and GABA to Glx ratios (p=0.031 and 0.021) were significantly increased in internet and smartphone addictions. After 9 weeks of cognitive behavioral therapy, brain-parenchymal and gray-matter volume adjusted GABA to creatine ratios (p=0.034 and 0.026) and brain-parenchymal volume adjusted GABA to Glx ratio (p=0.05) were significantly decreased. Glx was not statistically significant. Most brain-parenchymal and gray-matter volume adjusted GABA to creatine ratios and GABA to Glx ratios were significantly correlated with clinical scales of internet and smartphone addictions, depression and anxiety.

CONCLUSION
The increased GABA level and disrupted balance between GABA and glutamate in the anterior cingulate cortex may contribute to understanding the pathophysiology of and treatment for internet and smartphone addictions. Correlations between neurotransmitters and psychology tests in internet and smartphone addictions may reveal the relation and solution to their psychological comorbidities.

CLINICAL RELEVANCE/APPLICATION
The increased GABA in internet and smartphone addicted youth and its decrease after cognitive behavioral therapy will be useful to reveal the neurobiology of comorbidities and treatment.
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PURPOSE
Growing evidence indicates shared and distinct emotional perception in schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MDD). The alterations of spontaneous low-frequency fluctuations have been increasingly reported in emotional perception neural system in these disorders. However, it is unknown what similarities and differences of their amplitudes (ALFF) are across SZ, BD, and MDD.

METHOD AND MATERIALS
ALFF and its signal balance between two frequency bands (slow-5 and slow-4) within emotional perception neural system were compared across 119 SZ, 100 BD, 123 MDD, and 183 healthy control (HC) participants. Exploratory analyses were performed to determine the relationship between an ALFF balance and clinical variables.

RESULTS
Commonalities in ALFF change pattern were observed across three disorders in emotional perception neural substrates, such as increased ALFF in the anterior cingulum including subcortical, limbic, paralimbic, and heteromodal cortical regions, and decreased ALFF in the posterior visual cortices. SZ, BD, and MDD showed significant decreased ALFF signal balance within emotional perception neural system in both slow-5 and slow-4, with greatest alterations in SZ, followed by BD, and then MDD. A negative correlation was shown between the ALFF balance and negative/disorganized symptoms in slow-4 across SZ, BD, and MDD.

CONCLUSION
Our findings suggest that the extent of observed commonalities herein further support the presence of core neurobiological disruptions shared among SZ, BD, and MDD. ALFF signal balance might be considered as an important neuroimaging marker for the future diagnosis and treatment in these major psychiatric disorders.

CLINICAL RELEVANCE/APPLICATION
Our major findings suggest that the extent of observed commonalities herein further support the presence of core neurobiological disruptions shared among SZ, BD, and MDD. The balance of ALFF signals within emotional perception neural system might be considered as an important neuroimaging marker for the future diagnosis and treatment in these major psychiatric disorders.

SSQ16-03 The Impact of Apolipoprotein E Gene Polymorphism on the Cerebral Blood Flow in Patients with Mild Cognitive Impairment

Thursday, Nov. 30 10:50AM - 11:00AM Room: N229

Participants
Lin Zhu, PhD, Nanjing, China (Presenter) Nothing to Disclose

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PURPOSE
We sought to investigate whether the apolipoprotein E (APOE) genotype specifically modulates cerebral blood flow in patients with amnesic mild cognitive impairment (aMCI) by using the pulsed arterial spin labeling (ASL) data.

METHOD AND MATERIALS
83 aMCI and 130 healthy controls (HC) underwent neuropsychological battery assessments, genetic screening and MRI scanning. ASL data preprocessing was carried out using the ASLtbx toolbox. A voxel-wise two-way ANOVA was performed to examine the main effects of diagnosis (aMCI vs. HC) and APOE genotype (ε2 vs. ε3ε3 vs. ε4), and the diagnosis-by-genotype interactions on CBF maps. Then, we performed multiple linear regression analyses to examine the relationships between the neuropsychological test scores and CBF values in brain areas showing significant diagnosis-by-genotype interactions.

RESULTS
(1) Significant diagnosis-by-genotype interactions on CBF were observed in the left superior frontal gyrus, right anterior cingulate/medial prefrontal cortex and bilateral superior temporal gyrus. Post-hoc pairwise analysis revealed that compared with the ε2 carriers and ε3ε3 carriers, the ε4 carriers had significant higher CBF values in the above areas in the aMCI group, but there were no significant genotype differences in the HC group. (2) APOE ε4 carriers showed significant higher CBF values in the right anterior and posterior cingulate cortex than the ε2 carriers and ε3ε3 carriers respectively; (3) Compared with HC group, the aMCI group exhibited higher CBF values primarily in the left superior and middle frontal gyrus. (4) We found that the CBF values in the right anterior cingulate/medial prefrontal gyrus and superior temporal gyrus were negatively correlated with the similarity test scores (r = -0.453, P = 0.014; r = -0.497, P = 0.006).

CONCLUSION
The APOE genotype has disease-specific effects on cerebral perfusion; the increased CBF within the lateral prefrontal and temporal cortex in the aMCI ε4 carriers may be interpreted as reflecting greater cognitive "effect" by aMCI ε4 carriers to achieve the same
level of performance as aMCI ε4 non-carriers (e.g., ε2 carriers and ε3ε3 carriers).

**CLINICAL RELEVANCE/APPLICATION**
(dealing with functional MR and cortical activation) 'fMRI may lay a foundation for the perfusion index of AD early diagnosis, disease severity, the following-up of AD and drug efficacy determination.'

**SSQ16-04  Interaction of Systemic Oxidative Stress and Mesial Temporal Network Degeneration in Parkinson’s Disease with and without Cognitive Impairment**

**Thursday, Nov. 30 11:00AM - 11:10AM Room: N229**

Participants
Pi-Ling Chiang, MD, Kaohsiung, Taiwan (Presenter) Nothing to Disclose
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**PURPOSE**
Systemic oxidative stress is the well-investigated factor and contributes to neuroinflammation of Parkinson’s disease (PD). Cognitive impairments in PD are strong-associated with mesial temporal lobe (MTL) dysfunction. In the present study, we sought to evaluate the relationship between systemic oxidative stress and MTL function by measuring the morphology and functional network alteration in PD patients with and without cognitive impairment.

**METHOD AND MATERIALS**
Forty-one patients with PD (subgrouping into 3 groups [PD-normal, PD-mild cognitive impairment, PD-dementia]) and 29 normal control volunteers underwent peripheral blood sampling to quantify systemic oxidative stress markers, and T1W volumetric and resting state functional MRI (rs-fMRI) scans. Rs-fMRI was used to derive the healthy intrinsic connectivity patterns seeded by the epicenter vulnerable to any of significant oxidative stress markers. The functional connectivity correlation coefficient (fc-CC) and gray matter volume (GMV) of the network seeded by the epicenter among groups were compared. The correlation analysis among fc-CC, GMV and cognitive impairment were performed.

**RESULTS**
The oxidative stress markers including leukocyte apoptosis and LFA-1 values were significantly higher in the PD group. Using whole brain VBM based correlation analysis, bilateral MTL were identified as the most vulnerable epicenters of lymphocyte apoptosis (p < 0.005). The following resting state functional connectivity analysis further revealed the MTL network seeded by the epicenter. The MTL network of normal connectivity profile was resembled the PD-associated atrophy pattern. The GMV of the MTL network also demonstrated the significant difference between groups. Reduced fc-CC and GMV were associated with the progressed cognitive impairment.

**CONCLUSION**
The epicenters vulnerable to lymphocyte apoptosis can be linked to an altered MTL network that modifies both architecture and functional connectivity, with relationship to cognitive impairment. The possible relations among them may represent consequent cognitive impairment processes of systemic oxidative stress and MTL network injuries in PD patients.

**CLINICAL RELEVANCE/APPLICATION**
The volumetric and re-fMR can demonstrate damages of MTL network vulnerable to oxidative stress.

**SSQ16-05  Effects of Mentally Stimulating Activities Training On Resting-State Network Functional Connectivity in Amnestic Mild Cognitive Impairment: A Pilot Controlled Trial**

**Thursday, Nov. 30 11:10AM - 11:20AM Room: N229**

**Awards**
Student Travel Stipend Award

Participants
Wenchao Cai, BMBS, PhD, Fuzhou, China (Presenter) Nothing to Disclose
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**PURPOSE**
To explore the resting-state network functional connectivity alterations in patients with amnestic mild cognitive impairment (aMCI) before and after mentally stimulating activities training.

**METHOD AND MATERIALS**
Cognitive diagnosis was made by an expert consensus panel based on previous published criteria. Thirty-eight elderly subjects with aMCI comprising of training group (18) and control group (18), with age-, sex- and MoCA score-matched participated in this study. Rest-state fMRI (rs-fMRI) and neuropsychological assessment were conducted at baseline and after 6-month following training/control program. The global functional connectivity of rs-fMRI was analysed based on the graph theoretical modeling and seed-based analysis. The changes of functional connectivity and neuropsychological scores were compared between the two groups.
RESULTS
After 6-month training/control program, the MoCA score was significantly increased in training group (25.53±2.51) compared with the control group (21.81±2.02). Based on the graph theoretical modeling, the bilateral angular gyrus presented positive connectivity with the global brain in training group. Seed-based analysis, functional connectivity between the hippocampus and a set of regions was decreased in training group, these regions are: the right angular, cingulate gyrus and praecuneus; While, the left supplement motor area showed increased connectivity to the hippocampus.

CONCLUSION
These findings would be helpful to aid our understanding of the neurofunctional mechanisms associated with effects of mentally stimulating activities training on the cognitive function in aMCI.

CLINICAL RELEVANCE/APPLICATION
The network functional connectivity analysis of resting-state fMRI maybe a potentially useful tool for exploring the mechanism of mentally stimulating activities in aMCI.

SSQ16-06 Multi-voxel Pattern Analysis with Large-scale Granger Causality to Investigate Brain Connectivity Changes in Resting-State Functional MRI of Patients with HIV-Associated Neurocognitive Disorder

Thursday, Nov. 30 11:20AM - 11:30AM Room: N229

Participants
Adora M. D’Souza, MSc, Rochester, NY (Presenter) Nothing to Disclose
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PURPOSE
To develop and evaluate a novel machine learning framework using large-scale Granger causality (lsGC) for identification of subjects with HIV-Associated Neurocognitive Disorder (HAND) by capturing differences in resting-state functional MRI (rsfMRI) connectivity.

METHOD AND MATERIALS
Resting-state fMRI scans (3T, EPI sequence, TR=1.65s, 250 acquisitions) were acquired in a cohort of 45 age-matched subjects (20 healthy, 25 HIV+ of which 16 had HAND symptoms (HAND+)). After pre-processing, data was parcellated into regions defined by the Automated Anatomical Labeling (AAL) atlas. Regions were represented by their average time-series. A novel multivariate directional extension of Granger causality, lsGC, quantified the interdependence between time-series. Generalized matrix learning vector quantization, a method that combines supervised machine learning with embedded feature selection was used to classify HAND+ and healthy subjects from the resulting connectivity matrix in a Multi-Voxel Pattern Analysis (MVPA) framework. Strict data separation (90% train/10% test) was carried out in a 100-iteration cross-validation scheme. As a standard reference method, we used conventional multivariate Granger Causality (mGC) for comparative evaluation. Area Under the Curve (AUC) for Receiver Operator Characteristics (ROC) analysis and prediction accuracy were used to quantitatively evaluate the diagnostic quality of HAND+ subject classification.

RESULTS
Our novel lsGC rsfMRI connectivity analysis approach outperformed mGC in identifying HAND+ subjects, with AUC = 0.86 ± 0.29 and accuracy = 0.88 ± 0.17% for lsGC compared to AUC = 0.70 ± 0.35 and accuracy = 0.64 ± 0.25% for the conventional mGC method, respectively. Diagnostic quality differences between both methods were statistically significant (p < 0.01, Wilcoxon signed-rank test) for both AUC and prediction accuracy.

CONCLUSION
Our results suggest that the novel lsGC analysis method significantly improves the diagnostic quality for identification of patients with HAND. We conclude that, when compared to conventional mGC analysis, our MVPA framework is better suited to capture disease-related brain network connectivity changes based on rsfMRI neuroimaging.

CLINICAL RELEVANCE/APPLICATION
Our framework identifies HAND+ subjects by revealing disease-related changes in brain connectivity patterns, which can serve as a useful diagnostic biomarker in HIV-related neurologic disease.

SSQ16-07 The Altered Resting-State Functional Connectivity and Regional Homogeneity in Type 2 Diabetes with Mild Cognitive Impairment

Thursday, Nov. 30 11:30AM - 11:40AM Room: N229

Participants
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PURPOSE
Patients with Type-2 Diabetes Mellitus (T2DM) have considerably higher risk of developing cognitive impairment and dementia. This
Patients with type-2 diabetes mellitus (T2DM) have considerably higher risk of developing cognitive impairment and dementia. This study aims to investigate the possible alterations in spontaneous neural activity of brain through resting state-functional MRI (rs-fMRI) in T2DM patients with and without mild cognitive impairment.

METHOD AND MATERIALS

Eighteen T2DM patients with mild cognitive impairment (DM-MCI) and 18 matched T2DM patients with normal cognition (DM-NC) were enrolled. On a 3 Tesla scanner, rs-fMRI data were obtained axially using a gradient-echo planar imaging sequence. Using the Brainnetome toolkit (BRAT) (www.brainnetome.org/en/brat) and SPM8 software, the regional homogeneity (ReHo) was calculated to represent spontaneous brain activity in different brain areas. ReHo changes were correlated with neuropsychological scores and disease duration. Based on the anatomically labeled (AAL) template, the whole-brain partitional analysis on functional connectivity was also applied to search for significant links.

RESULTS

Compared to DM-NC group, DM-MCI group exhibited decreased ReHo value in the right inferior, middle, and superior temporal gyrus; but increased ReHo value in the bilateral superior and medial frontal gyrus, the right orbito frontal gyrus and the inferior frontal gyrus (fig.1). In the DM-MCI group, ReHo value was negatively correlated with Montreal Cognitive Assessment scores in the left medial frontal gyrus (R=0.662, p=0.01), and positively correlated with diabetes duration in the right inferior and middle frontal gyrus (R=0.594, p=0.026)(fig.2). Correlation between ReHo and glycosylated hemoglobin A1c was not significant. The DM-MCI group showed 11 pairs of weaker functional connectivity between different brain areas (p<0.01, FDR corrected)(fig.3).

CONCLUSION

The abnormal brain activity reflected by ReHo measurements and the weaker functional connectivity of multiple brain regions could help uncover the susceptible regions of T2DM patients who progress into cognitive dysfunction, and may provide insights into the pathogenesis of T2DM related cognitive impairment.

CLINICAL RELEVANCE/APPLICATION

Resting state-fMRI may be able to track early progression of brain functional alterations, and can be an appropriate approach for studying the spontaneous brain activity in diabetes related cognitive impairment.

SSQ16-08 Early Volume Reduction of Hippocampus after Whole-Brain Radiation Therapy: Automated Brain Structure Segmentation Study

Thursday, Nov. 30 11:40AM - 11:50AM Room: N229

Participants
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PURPOSE

It is well known that cognitive decline often occurs after whole-brain radiation therapy (WBRT), especially in the long survivors. Our hypothesis was that the hippocampus is vulnerable to radiation and may become atrophic even at early stage after WBRT. Therefore, using automated segmentation of brain structures, we assessed volume changes of the various brain structures including the hippocampus within 10 months after WBRT.

METHOD AND MATERIALS

Twenty patients with lung cancer who underwent both WBRT and chemotherapy were recruited as a WBRT group. As a control group, 18 patients with lung cancer who underwent only chemotherapy were also recruited. Pre-treatment MRI was performed within one month before radiation or chemotherapy, and post-treatment MRI were performed 6 to 10 months after the radiation or chemotherapy. Contrast enhanced high-resolution 3D T1-weighted images of pre- and post-treatment were analyzed using longitudinal processing of FreeSurfer. We calculated volume reduction ratios [100 x (volume of pre-radiation - volume of after radiation)/volume of pre-radiation] for the whole-brain cortex and white matter, hippocampus, and amygdala defined by Aseg atlas in FreeSurfer.

RESULTS

In the WBRT group, the hippocampus showed significant volume reduction (5.7%, p < 0.01), while the whole-brain cortex and white matter, and amygdala did not show significant volume reduction (4.9%; p = 0.21, 1.3%; p = 0.19, 1.3%; p = 0.95, respectively). The volume reduction ratio of the hippocampus was significantly higher than those of the whole-brain cortex and white matter (p = 0.01 and 0.02, respectively). In the control group, there was no significant volume reduction in any regions (the ratios: 0.3%, 1.0%, 1.0%, and 0.9% for the hippocampus, amygdala, whole-brain cortex and white matter, respectively).

CONCLUSION

Among the whole-brain cortex and white matter, hippocampus, and amygdala, only the hippocampus showed significant volume reduction within 10 months after WBRT suggesting its vulnerability to radiation.

CLINICAL RELEVANCE/APPLICATION

Our study may support the validity of the "hippocampus-sparing" WBRT to prevent the radiation-induced cognitive impairment.

SSQ16-09 Nonlinear Modulation of Interacting Between COMT and Depression on Brain Function

Thursday, Nov. 30 11:50AM - 12:00PM Room: N229

Participants
Cancan He, Nanjing, China (Presenter) Nothing to Disclose
Liang Gong, Nanjing, China (Abstract Co-Author) Nothing to Disclose
Purpose

The catechol-O-methyltransferase (COMT) gene is related to dopamine degradation and has been suggested to be involved in the pathogenesis of major depressive disorder (MDD). However, how this gene affects brain function properties in MDD is still unclear.

Method and Materials

Fifty patients with MDD and 35 cognitively normal participants were underwent a resting-state functional magnetic resonance imaging scan. A voxel-wise data-drive global functional connectivity density (gFCD) analysis was used to investigate the main effects and interactions of disease states and COMT rs4680 on brain function.

Results

We found significant group differences on the gFCD in bilateral fusiform area (FFA), postcentral and precentral cortex, left superior temporal gyrus (STG), rectal and superior temporal gyrus, right ventrolateral prefrontal cortex (vlPFC), and the abnormal gFCDs in left STG was positively correlated with depressive severity in MDD patients. Significant disease × COMT interaction effects were found in the bilateral calcarine gyrus, right vlPFC, hippocampus, and thalamus, and left SFG and FFA. Further post-hoc tests showed a nonlinear modulation effect of COMT on gFCD in the development of MDD. Interesting, an inverted U-shaped modulation was showed in the prefrontal cortex (control system), while U-shaped modulations were found in the hippocampus, thalamus and occipital cortex (processing system).

Conclusion

Our study manifested a nonlinear modulation of interacting between COMT and depression on brain function. This findings expand our understanding of the COMT effect underlying pathophysiology in MDD patients.

Clinical Relevance/Application

The brain functional features detecting combined with COMT genotyping may provide a useful biomarker to the occurrence and development of depression.