Journal of Affective Disorders 250 (2019) 270–277

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Increased brain entropy of resting-state fMRI mediates the relationship between depression severity and mental health-related quality of life in late-life depressed elderly

Chemin Lin[a,b,c], Shwu-Hua Lee[b,d], Chih-Mao Huang[e], Guan-Yen Chen[f], Pei-Shan Ho[f], Ho-Ling Liu[g], Yao-Liang Chen[h], Tatia Mei-Chun Lee[i,j,k,l,*], Shun-Chi Wu[f,*]

[a] Department of Psychiatry, Keelung Chang Gung Memorial Hospital, Keelung City, Taiwan
[b] College of Medicine, Chang Gung University, Taoyuan County, Taiwan
[c] Community Medicine Research Center, Chang Gung Memorial Hospital, Keelung, Keelung, Taiwan
[d] Department of Psychiatry, Linkou Chang Gung Memorial Hospital, Taoyuan County, Taiwan
[e] Department of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan
[f] Department of Engineering and System Science, National Tsing Hua University, Hsinchu, Taiwan
[g] Department of Imaging Physics, University of Texas MD Anderson Cancer Center, Houston, TX, USA
[h] Department of Medical Imaging and Intervention, Chang Gung Memorial Hospital, Keelung, Taiwan
[i] Laboratory of Neuropsychology, The University of Hong Kong, Hong Kong
[j] Laboratory of Cognitive Affective Neuroscience, The University of Hong Kong, Hong Kong
[k] State Key Laboratory of Brain and Cognitive Science, The University of Hong Kong, Hong Kong
[l] Institute of Clinical Neuropsychology, The University of Hong Kong, Hong Kong

ARTICLE INFO

Keywords:
Resting-state fMRI
Entropy
Depression
Late-life
Quality of life

ABSTRACT

Background: Entropy analysis is a computational method used to quantify the complexity in a system, and loss of brain complexity is hypothesized to be related to mental disorders. Here, we applied entropy analysis to the resting-state functional magnetic resonance imaging (rs-fMRI) signal in subjects with late-life depression (LLD), an illness combined with emotion dysregulation and aging effect.

Methods: A total of 35 unremitted depressed elderly and 22 control subjects were recruited. Multiscale entropy (MSE) analysis was performed in the entire brain, 90 automated anatomical labeling-parcellated ROIs, and five resting networks in each study participant.

Limitations: Due to ethical concerns, all the participants were under medication during the study.

Results: Regionally, subjects with LLD showed decreased entropy only in the right posterior cingulate gyrus but had universally increased entropy in affective processing (putamen and thalamus), sensory, motor, and temporal nodes across different time scales. We also found higher entropy in the left frontoparietal network (FPN), which partially mediated the negative correlation between depression severity and mental components of the quality of life, reflecting the possible neural compensation during depression treatment.

Conclusion: MSE provides a novel and complementary approach in rs-fMRI analysis. The temporal-spatial complexity in the resting brain may provide the adaptive variability beneficial for the elderly with depression.

1. Introduction

Major depressive disorder, a leading cause of disability worldwide, is a devastating mental illness affecting one's mental well-being (Moussavi et al., 2007). With the trend of aging population, increasing prevalence of late-life depression (LLD) has been identified. The devastating effects of LLD on mental health of older people have been reported, including increase in suicide, hastened cognitive decline, worsening physical comorbidities, higher caregiver burden and all-cause mortality (Beekman et al., 1999; Unützer, 2007). Early and accurate diagnosis for timely intervention has immense benefit to the mental well-being of older people, let alone that it can help save resource deployment for geriatric mental health services.

Resting-state functional MRI (rs-fMRI), using correlations in the blood oxygenation level-dependent (BOLD) signal from magnetic resonance imaging (MRI) (Biswal et al., 1995), is a promising biomarker

* Corresponding authors.
E-mail addresses: tmclee@hku.hk (T.M.-C. Lee), shunchi.wu@mx.nthu.edu.tw (S.-C. Wu).

https://doi.org/10.1016/j.jad.2019.03.012
Received 11 December 2018; Received in revised form 30 January 2019; Accepted 3 March 2019
Available online 05 March 2019

in an array of neuropsychiatric disorders (Greicius, 2008) and is potentially applicable for marking LLD. Increased thalamic and subgenual cingulate resting state functional connectivity (RSFC) within the default-mode network (DMN) has been reported in major depression (Greicius et al., 2007). Furthermore, there were significant RSFC increase in the dorsal medial prefrontal cortex to three key networks, including the DMN, the cognitive control and the affective networks (Sheline et al., 2010). Meta-analysis of the rs-fMRI studies on depression have reported the cortico-limbic mood regulating dysregulation (Wang et al., 2012). However, no consistent spatially overlapping area has been reported.

Traditional approach in fMRI analysis focuses on point-to-point correlation between brain regions (such as the functional connectivity). However, the abundant information in moment-to-moment variability has been neglected (Bassett et al., 2012; Garrett et al., 2013). Here, we referred to the magnitude of the BOLD signal, including the variance (He, 2011) or the standard deviation (Garrett et al., 2010). Thus, increasing attention has been shifted to nonlinear or complex analysis of rs-fMRI data. Indeed, the BOLD signal has long been found to harbor the property of nonlinearity (Friston et al., 2000), and the brain itself is a complex organ. Thus, burgeoning studies began applying the analysis of entropy, a nonlinear statistical computation method, to the fMRI time series (Sokunbi et al., 2011; Wang et al., 2014). Conceptually, entropy measures the probability of specific patterns that run in the subsequent time frame. Lower entropy connotes more predictability and less complexity in the system, whereas higher entropy signifies more variability and more complexity. Several methods of entropy calculation have been developed. Approximate entropy (ApEn), first developed by Pincus (1991), and its variant sample entropy (SampEn) (Richman and Moorman, 2000) have been applied to different modalities in the medical field, including electroencephalogram (EEG) (Abásolo et al., 2006), electrocardiogram (ECG) (Alcaraz and Rieta, 2010), heart rate variability (Lake et al., 2002), blood pressure (Turianikova et al., 2011), and hormonal release irregularity (Pincus et al., 1996). Entropy analysis in fMRI signals has been successfully applied to different diseases such as autism (Lai et al., 2010), attention deficit hyperactivity disorder (Sato et al., 2013; Sokunbi et al., 2013), schizophrenia (Sokunbi et al., 2014), multiple sclerosis (Zhang et al., 2016), and chronic fatigue syndrome (Shan et al., 2018). A common feature of these mental disorders appears to be the loss of brain complexity (Yang and Tsai, 2013). A similar trend of decreasing complexity was also found to be replicated in BOLD fMRI signals in normal and pathological processes of aging. For example, compared with younger subjects, older people having normal cognitive function showed lower entropy of BOLD fMRI signals in DMN, which correlated with declining cognitive function (Yang et al., 2013). Relative to normal elderly, significant decline in the complexity of BOLD signals in DMN was found in subjects with Alzheimer's disease (Wang et al., 2017). However, no studies to date have examined the entropy changes using brain fMRI in subjects of late-life depression (LLD), a unique entity exhibiting both emotion dysfunction and aging process.

We aimed to examine the relationship between brain entropy and clinical features of LLD by comparing the entropy in the rs-fMRI BOLD signals between older people with LLD and their matched healthy controls. We used SampEn-based multiscale entropy (MSE) analysis for robust findings that were less susceptible to record length compared with ApEn (Richman and Moorman, 2000). Since the brain is composed of topologically different networks (Damoiseaux et al., 2006; van den Heuvel and Hulshoff Pol, 2010) subserving diversified functions (Laird et al., 2011), we calculated global entropy and regional entropy within five anatomically parcellated brain networks, including the left and right cingulo-opercular networks (CONs) and frontoparietal networks (FPNs), as well as DMN. We hypothesized that depressed elderly may have decrease entropy in these brain networks, which correlated with specific symptomatology or clinical aspects that particular network subserved.

2. Methods

2.1. Participants

A total of 35 depressed elderly subjects provided informed consent, which was approved by the institutional review board at Chang Gung Memorial Hospital. Participants were aged at least 60 years and right-handed, with DSM-IV Axis I major depressive episode confirmed by a certified geriatric psychiatrist after a diagnostic interview. No other Axis I major psychiatric diagnosis was allowed, except for anxiety disorders. All participants had a minimum score of 24 on the Mini-Mental State Examination (MMSE). Other exclusion criteria included the history of significant head trauma, stroke, major neurocognitive decline, Parkinson's disease, or other major neurological disorders. Use of psychotropics was allowed for participants with LLD due to ethical reasons; however, the same dosage must have been maintained for at least 2 months before the scan date. A total of 22 elderly control subjects free of any Axis I diagnosis were enrolled through an advertisement in the same time period. These subjects also met the same exclusion criteria.

All the participants also received the 15-item Geriatric Depressive Scale (GDS-15) (Liu et al., 1997) and the 36-Item Short Form Health Survey (SF-36) (Lu, 2003). They are both self-rated scales to measure subjective depression severity and perceived health-related quality of life. The SF-36 includes eight domains: physical functioning, role limitations due to physical problems, pain, energy and fatigue, general health, social functioning, role limitations due to emotional problem, and mental health (Ware and Sherbourne, 1992). The first four items are grouped in the physical component score (PCS), and the latter four mental component score (MCS). These two summary scores account for 80% of the variance in the original eight domains (Ware et al., 1994). We employed the Taiwanese version of the SF-36 with good validity and reliability (Tseng et al., 2003).

2.2. Data acquisition

We collected our MRI data using an 8-channel head coil on a 3T MRI scanner (Discovery MR750, GE Healthcare, Milwaukee, WI). Participants were asked to keep their eyes closed, not to think of anything, and not to fall asleep during the scan. The resting-state functional MRI data were collected using a T2*-weighted gradient- echo-planar imaging sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, flip angle = 90°, number of slices = 36, in-plane matrix size = 64 × 64, and slice thickness = 4 mm. A total of 180 dynamic volumes were acquired for each subject. The T1-weighted structural imaging was acquired with: TR = 8 ms, TE = 3 ms, flip angle = 12°, Field of view (FOV) = 250 × 250 mm^2, voxel size = 0.98 × 0.98 × 1 mm^3, slice number = 160.

2.3. Image preprocessing

The preprocessing included the following steps: slice-timing correction, motion correction by realigning images to the first volume and removing those images showing 3-mm axial displacement and 3° in rotation angle, normalization and deformation to Montreal Neurological Institute template, and reslicing to 2 × 2 × 2 isotropic voxel dimension. These procedures were implemented using SPM8 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/).Further preprocessing steps used the REST toolbox (http://restfmri.net/forum/REST_V1.8). At each voxel, the time series were detrended and bandpass-filtered (frequencies between 0.04 and 0.08 Hz) (Achard et al., 2006; Braun et al., 2012; Cordes et al., 2001; Fornito et al., 2010). We then extracted the time series of the white matter, the cerebrospinal fluid, and six motion parameters for head movement and regressed out the physiological artifacts by treating these time series as nuisance regressors.

2.4. MSE analysis

MSE analysis has the potential to reveal the signal complexity of a biological system at different temporal scales. Based on previous procedures (Costa et al., 2005), the analysis is performed as follows: To begin, an N-point data series is divided into non-overlapping segments of length τ, which are averaged to form a coarse-grained data series of length $L \approx N/\tau$. Next, the SampEn for this coarse-grained time series is calculated according to previous research (Richman and Moorman, 2000) as follows:

$$\mathrm{SampEn}(m, r, L) = -\ln \frac{\sum_{i=1}^{L-m} n_i^{m+1}}{\sum_{i=1}^{L-m} n_i^{m}}, \quad (1)$$

Where n_i^m represents the number of vectors $\mathbf{x}_m(j) = [x_j, x_{j+1}, ..., x_{j+m-1}]$ in a data series $\mathbf{x} = [x_1, x_2, ..., x_L]$ that "match" the m-point template vector $\mathbf{x}_m(i) = [x_i, x_{i+1}, ..., x_{i+m-1}]$. A template match with tolerance r is said to occur if $d[\mathbf{x}_m(i), \mathbf{x}_m(j)] < r$, with

$$d[\mathbf{x}_m(i), \mathbf{x}_m(j)] = \max\{|x_{i+k} - x_{j+k}|: 0 \le k \le m-1\} \quad (2)$$

being the maximum difference of their corresponding scalar components. The SampEn reflects the frequency with which each pattern appears in a time series and is reported to be less dependent on the record length and relatively consistent over a broad range of m, r, and L. To obtain a reasonable estimate, the value of m should lie in a range such that $L = 10\,\mathrm{m}$ to $20\,\mathrm{m}$. Furthermore, the tolerance r is generally set to be a ratio (0.6 in this study) of the standard deviation of the time series under consideration. Finally, the scale factor τ was varied from 1 to 5 in this study. The tolerance r is generally set to be a percentage of the standard deviation of the time series under consideration.

To examine the effects of LLD on distinct brain networks, we further selected five canonical networks, including DMN, the left and right CONs, and FPNs, and calculated the MSE within each network. Each network was constructed by combining selected nodes from 90 automated anatomical labeling (AAL) regions (Tzourio-Mazoyer et al., 2002) (see Table S1 for detailed composing nodes in each network).

2.5. Statistical analysis

We calculated MSE under each temporal scale within (1) the entire brain, (2) the five brain networks, and (3) the 90 brain regions identified by AAL. Two-sample t-test group comparison was conducted with the significant level set at global ($p < 0.05$), network-wise ($p < 0.05/5$, corrected), and the 90-AAL regional basis ($p < 0.05$, both uncorrected and false discovery rate (FDR) corrected). The network that demonstrated a group difference was selected to perform Pearson correlation between MSE and the clinical variables, including depression scales and SF-36. Mediation analysis was further performed to understand the causal relationships between cognitive and emotional roles of MSE in LLD. The correlation and mediation analyses were performed using SPSS v21 (SPSS, Inc., Chicago, IL, USA).

3. Results

3.1. Demographic and clinical data

No significant difference was observed in gender, age, and MMSE scores between the two groups. At the time of the scan, 34 depressed elderly subjects were taking antidepressants, which included 150–300 mg bupropion ($n = 3$), 15–45 mg mirtazapine ($n = 6$), 10–20 mg paroxetine ($n = 7$), 10–20 mg escitalopram ($n = 8$), 30–60 mg duloxetine ($n = 6$), 75 mg venlafaxine ($n = 1$), 25 mg agomelantine ($n = 1$), and a combination of bupropion and mirtazapine ($n = 2$). None of the elderly control subjects had been exposed to psychotropic drugs before. The LLD group scored significantly higher in GDS and lower in SF-36 and its subscales, reflecting the diagnosis difference (Table 1).

Table 1
Demographic data between the LLD and normal control groups.

	LLD ($n = 35$)	Control ($n = 22$)	p-value
Age (years)	68.0 ± 6.0	68.9 ± 5.6	0.78
Gender (M/F)	16/19	9/13	0.91
Mini Mental State Examination	28.1 ± 1.3	28.1 ± 1.2	0.76
Age at onset of depression	61.4 ± 5.3	N.A.	
Number of previous episodes of depression	1.7 ± 1.3	N.A.	
Geriatric depression scale	9.2 ± 2.5	N.A.	
SF-36 total scores	55.2 ± 15.2**	81.2 ± 7.0	0.00
SF-36 physical scores	52.2 ± 18.1**	77.5 ± 10.8	0.00
Physical functioning	76.9 ± 21.5	89.5 ± 9.7	0.01
Role limitations (physical health)	46.3 ± 41.3*	83.0 ± 29.3	0.00
Energy and fatigue	42.5 ± 17.3**	73.9 ± 14.3	0.00
Pain	73.1 ± 20.8	88.5 ± 12.7	0.00
SF-36 mental scores	56.7 ± 16.8**	86.3 ± 9.7	0.00
Role limitations (emotional problems)	34.3 ± 41.5**	90.9 ± 29.4	0.00
Mental health	48.4 ± 13.3**	77.2 ± 13.1	0.00
Social functioning	71.6 ± 23.3	88.8 ± 14.8	0.00
General health	42.9 ± 17.1**	63.6 ± 15.7	0.00

SF-36 = 36-Item Short Form Health Survey; **Significant levels $p < 0.001$.

3.2. Construction of the MSE parameters

We chose the MSE parameters by simulating noises of length 180 with the tolerance $0.1 \le r \le 1.5$ (with an increment of 0.1 each time) and $m = 1$ or 2. We found that SampEn tended to decrease as r increased in each data series and stabilized after $r > 0.6$. There was no distinguishable difference in noises in either parameter in m (Figure S1a). Moreover, the SampEn did not show a discernible difference in various noises under two different m's. Nevertheless, $m = 2$ is chosen for more refined reconstruction of the joint probabilistic dynamics of the time series (Pincus, 1995). Therefore, we set the parameters $m = 2$ and $r = 0.6$ in the subsequent analysis. We calculated the MSE profiles in five different scales from 1 to 5, and the results are shown in Figure S1b. The trend of the white, pink, and red noise as well as the network entropy across the time scales was similar to that reported previously (McDonough and Nashiro, 2014). In short, the entropy of the white noise was high at first but decayed fast at coarser time course, whereas the pink and red noise showed a flat and steady increase in entropy. On the other hand, the global rs-fMRI entropy showed an initial increase and then a gradual decline as the time course changed from fine to coarse. This trend was qualitatively different from those of the noises, ensuring the validity of our choices of the parameters (Ho et al., 2017).

3.3. Group comparison of MSE differences

There was also no between-group difference in the mean global entropy across the five different time scales. In the 90 AAL regions at the fine time scale, LLD group showed decreased entropy only in the right posterior cingulate cortex (PCC) ($p = 0.036$) but increased entropy in the right putamen ($p = 0.023$), the right thalamus ($p = 0.005$ at scale 2; $p = 0.013$ at scale 3), the left superior parietal gyrus ($p = 0.025$), the left fusiform gyrus ($p = 0.015$), the left paracentral lobule ($p = 0.007$), and the left Heschl's gyrus ($p = 0.007$). At the coarse time scale, we still found higher entropy in subjects with LLD in the left middle temporal pole ($p = 0.004$), the right inferior temporal gyrus ($p = 0.007$), and the left olfactory gyrus ($p < 0.05$ across scale 3–5). The following two areas demonstrated persistent higher entropy in LLD across fine to coarse time scale: the left supplementary motor area (SMA) ($p < 0.000$ at scale 2; $p = 0.005$ at scale 3; $p = 0.045$ at scale 5) and the rectus gyrus (RG) ($p = 0.008$ at scale 2 and 3 for the

Table 2
Significant MSE nodal differences from 90 AAL regions across five scales .

AAL Node	Scale 1		Scale 2		Scale 3		Scale 4		Scale 5	
	t	*p*	*t*	*p*	*t*	*p*	*t*	*p*	*t*	*p*
L SMA	–	–	4.006	0.000	2.960	0.005	–	–	2.054	0.045
L OFB	–	–	–	–	2.087	0.043	2.111	0.039	2.403	0.020
L RG	–	–	–	–	–	–	2.083	0.042	2.901	0.006
R RG	–	–	2.771	0.008	2.732	0.008	–	–	–	–
R PCC	−2.145	0.036	–	–	–	–	–	–	–	–
L FG	–	–	2.514	0.015	–	–	–	–	–	–
L SPG	–	–	2.308	0.025	–	–	–	–	–	–
L PAC	–	–	2.789	0.007	–	–	–	–	–	–
R Pu	–	–	2.334	0.023	–	–	–	–	–	–
R TH	–	–	2.916	0.005	2.575	0.013	–	–	–	–
L HG	–	–	2.789	0.007	–	–	–	–	–	–
L MTP	–	–	–	–	–	–	–	–	3.048	0.004
R ITG	–	–	–	–	–	–	2.794	0.007	–	–

L = left; *R* = Right; SMA = supplementary motor area; RG = rectus gyrus; PCC = posterior cingulate cortex; FG = fusiform gyrus; SPG = Superior parietal gyrus; PAC = paracentral lobule; Pu = Putamen; TH = thalamus; HG = Heschl gyrus; MTP = middle temporal pole; ITG = inferior temporal gyrus; OFB = olfactory cortex.

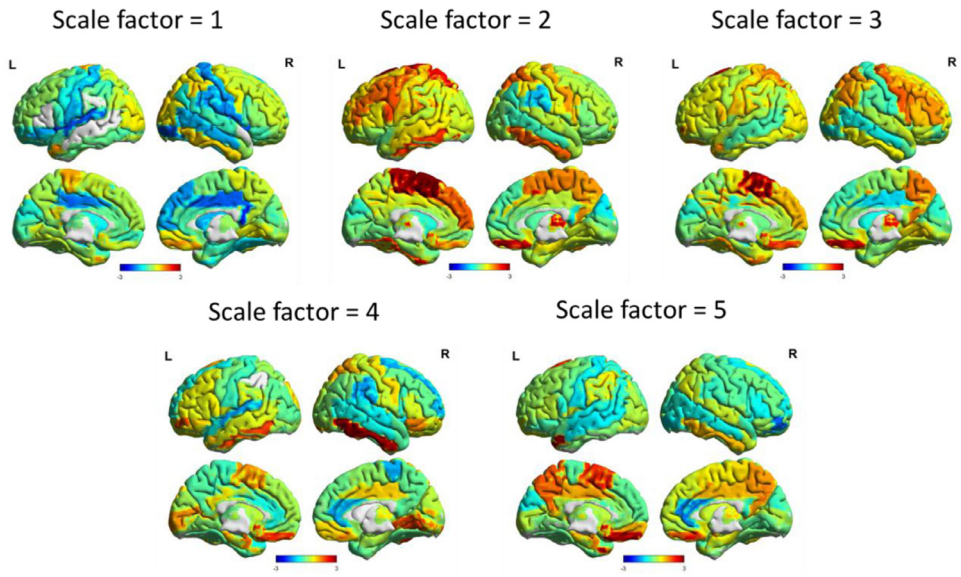

Fig. 1. Group difference in MSE of 90 AAL ROIs across five time scales. The *t*-test results rendered with BrainNet Viewer (https://www.nitrc.org/projects/bnv/) with warm color representing higher MSE in LLD than controls.

right RG; $p = 0.042$ at scale 4 and $p = 0.006$ at scale 5 for the left RG) (Table 2 and Fig. 1).

Among the five networks, we found significantly higher left FPN entropy in the LLD group when the time scale was set to 2 (LLD = 0.63 ± 0.05, control = 0.59 ± 0.05, $t = 2.94$, $p = 0.005$, corrected; Fig. 2 for representation of the nodes in the left FPN). It is to be noted that only SMA at scale 2 passed FDR correction for multiple comparisons, and the rest of the nodes from the 90-AAL regions were uncorrected for multiple comparisons. There was no significant group difference in the other four different time scales.

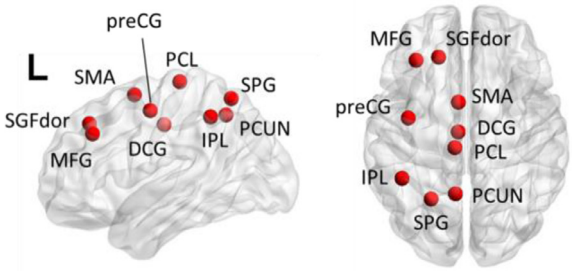

Fig. 2. Composing nodes from 90 AAL ROIs in the left fronto-parietal network, rendered with BrainNet Viewer (https://www.nitrc.org/projects/bnv/).

3.4. Correlation and mediation results in LLD

The entropy in the left FPN negatively correlated with the level of GDS ($r = -0.405$, $p = 0.016$) and positively correlated with total score of SF-36 ($r = 0.420$, $p = 0.014$) and with the following subscales of SF-36: social functioning ($r = 0.414$, $p = 0.015$), role limitation due to emotional problems ($r = 0.427$, $p = 0.012$), energy and fatigue ($r = 0.451$, $p = 0.007$), and the mental component summary scores ($r = 0.431$, $p = 0.011$). Moreover, the level of GDS negatively correlated with social functioning ($r = -0.512$, $p = 0.002$), role limitation due to emotional problems ($r = -0.427$, $p = 0.012$), and the mental component summary scores ($r = -0.465$, $p = 0.006$). None of the abovementioned correlations was significant in the elderly control subjects.

As the level of depression severity (GDS) negatively correlated with both MSE in the left FPN and SF-36, and the better health status (i.e., a higher score of SF-36) was coupled with a lower level of depression severity, we performed a mediation analysis to test the hypothesis that

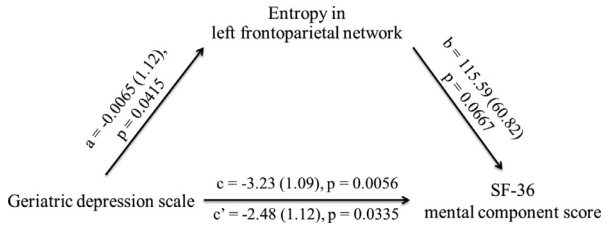

Fig. 3. Path diagram of mediation analysis showing entropy of the left frontoparietal network (FPN) partially mediates the effect of depression severity (measured by geriatric depression scale, GDS) on the mental health-related quality of life (measured by mental component scores in SF-36). Path b controls for the entropy in left FPN, and path c' controls for GDS.

entropy in the left FPN would mediate the association between the level of depression severity (GDS) and the mental aspect of subjective quality of life (i.e., the mental component summary scores of SF-36). After controlling for the variance associated with age, the analysis revealed that the entropy in the left FPN was a partial mediator of the relationship between depression severity and mental health (Fig. 3), with greater entropy in the left FPN associated with better mental aspect of subjective quality of life ($a = -0.0065$, SE = 1.12, $p < 0.05$; $b = 115.59$, SE = 60.82, $p = 0.067$), suggesting the possible neural compensatory adaptation occurring during depression treatment.

4. Discussion

We used the MSE-based analysis of BOLD signal fluctuations in subjects with LLD and observed significant differences in entropy between subjects with LLD and the controls. LLD showed brain entropy increase in various regions, except that lower entropy was found in right posterior cingulate gyrus. Within the resting-state network, we observed an inverse relationship between entropy in the left FPN and level of severity of depression and also that between entropy and health-related quality of life. Specifically, entropy in the left FPN partially mediated the negative correlation between depression severity and the mental health-related quality of life in subjects with LLD.

Instead of the expected lower brain entropy in LLD, we found general brain entropy increase, including the left FPN, but not DMN or CON. This may seem to be at odds with previous RSFC finding in midlife MDD where heightened FC in DMN and decreased FC in anterior salience network (ASN) and FPN were found (Kaiser et al., 2015b). Despite the tempting hypothesis stipulating triple network dysfunction in depression (Menon, 2011), there exists some variation. For example, a recent study using serial rs-fMRI scans to track the network changes across antidepressant treatment in LLD has found concomitant increase and decrease of connectivity in DMN and executive control network, whereas the FC in ASN stayed unchanged across treatment (Karim et al., 2017). This suggests that the connectivity changes in the resting brain of the LLD are most complex than expected. More importantly, multi-scale entropy analysis is fundamentally different from previous analytic methods. It has been showed that functional connectivity was positively correlated with brain entropy at coarse scale but negatively at fine scale (McDonough and Nashiro, 2014). Brain entropy has been further shown to correlate with cerebral blood flow and fractional amplitude of low-frequency fluctuations in only a small numbers of brain regions (Song et al., 2018). Therefore, our study could provide novel findings of rs-fMRI changes in LLD which previous studies have yet to detect.

4.1. Regional entropy changes in LLD

We found decreased complexity in the right PCC, an area associated with increased metabolism, altered functional connectivity, and treatment response in depression (Leech and Sharp, 2013). These earlier findings were from fMRI studies that were not based on nonlinear analysis. Interestingly, in the MSE analysis of rs-fMRI, a decreased complexity in PCC was also found in cognitively normal elderly subjects positive for the apolipoprotein E4 (APOE4) genotype (Yang et al., 2014). As LLD has been postulated to be the harbinger of future dementia (Butters et al., 2008), our result may suggest this link through evidence from complexity analysis. We also found an increased complexity in the right thalamus and putamen, two areas within the limbic-cortical-striatal-pallidal-thalamic (LCSPT) loop implicated in mood regulation (Sheline, 2003). A meta-analysis on LLD has indicated volumetric reduction, especially in the thalamus and putamen (Sexton et al., 2013). Within the LCSPT loop, reduction in the thalamic volume is the most robust finding in subjects with LLD (Bora et al., 2012). A decreased functional connectivity between cortical regions and the thalamus from both resting and negative emotions provoking fMRI paradigms suggests the important role of the thalamus in the mood regulation of depression (Anand et al., 2005). On the other hand, increased putaminal white matter hyperintensity has been reported in subjects with LLD (Tupler et al., 2002). Apparently, earlier studies and current results using different modalities and analytic techniques converge at overlapping regions implicated to be dysfunctional in depression.

Besides the LCSPT loop, we also found increased complexity in the olfactory gyrus (olfactory), the Heschl's gyrus (auditory), the inferior temporal gyrus (visual), as well as the temporal pole, which acts to integrate these perceptual inputs with emotion (Olson et al., 2007). Speculatively, increased complexity in a node is related to higher connectedness and information processing within its module (Pedersen et al., 2017). As these nodes collectively work in the sensory network, our findings of the increased complexity in these sensory nodes were consistent with the notion of “hyper-attention” hypothesis where increased sensory perception and processing is related to the emotional or cognitive bias in mood disorders (Drevets et al., 2008). In addition, increased complexity in the rectus gyrus was also found, which coincided with the previous finding of decreased volume of rectus gyrus in subjects with LLD (Ballmaier et al., 2004). It is worth noting that the increased complexity in the gyrus rectus remained significant across the fine to coarse time scale, suggesting the involvement from local to distributed information processing(McIntosh et al., 2014; Vakorin et al., 2011). This area merits further research to reveal its functional significance.

Almost all the nodes showing complexity difference in the current study could be found to have a volumetric reduction in previous research on LLD (Andreescu et al., 2008). In terms of functional studies, we must be cautious to infer previous resting-state fMRI studies to interpret our results. A recent study has demonstrated that at the fine time scale, functional connectivity negatively correlated with complexity, and vice versa at the coarse time scale (McDonough and Nashiro, 2014). However, using centrality measures (i.e., the connections of a node) from graph theory, it was found that the functional connectivity correlated with complexity, ranging over multiple time scales, although weaker at the fine time scale (Misic et al., 2011). A more nuanced interpretation is that the complexity result in the fine time scale, such as most of the regional nodes in our results showing increased complexity, reflects neural interconnectivity at a more local level, whereas that in the coarse time scale suggests neural connection in more distributed areas (McIntosh et al., 2014; Vakorin et al., 2011). As no evidence exists regarding the physiological underpinning of the complexity in different time scales, further research is needed in this context. Nevertheless, our results demonstrated the need for multiscale analysis in entropy as different time scales entail different nodal changes in complexity.

4.2. Entropy changes within resting-state networks

Besides regional entropy differences, we also found increased left

FPN in subjects with LLD, mediating the negative relationship between depression severity and mental health-related quality of life. This finding is congruent with our regional entropy increase in the left paracentral gyrus, the supplementary motor area, and the left superior parietal gyrus as they are all constituent nodes in left FPN. Reduced RSFC in FPN has been reported to be associated with affective symptoms (especially apathy) in subjects with mild cognitive impairment (Munro et al., 2015) and also with higher depressive symptoms in subjects with LLD (Alexopoulos et al., 2012). A meta-analytic large-scale network analysis reported hypoconnectivity within FPN and hyperconnectivity between FPN and DMN in depression, which was postulated to be associated with a cognitive bias toward internal self-reference attention other than external attention in depression (Kaiser et al., 2015a). Previous findings have shown that dysfunctional FPN is critical in the formation of depressive symptoms, while our results complement this finding by demonstrating that increased complexity in FPN is associated with lower depressive symptoms (measured by GDS) and higher mental health-related quality of life (measured by mental component of SF-36). It has long been held that a system must maintain certain entropy to be adaptive, the so-called "Chaotic flexibility" (Pool, 1989), and to be ready for unpredictable stimuli (Saxe et al., 2018). A "balanced" nonlinear instability endows the brain with certain entropy to stay healthy (Breakspear, 2017). On the other hand, loss of the complexity in the brain is one of the signatures in various mental illness, and rumination on negative events is suggestive of low entropy in the depressed brain (Yang and Tsai, 2013). Therefore, we hypothesize that the restored complexity in FPN in our result reflects an adaptive process during treatment in subjects with LLD. A similar finding that increased global entropy was associated with successful ketamine treatment in adolescent treatment-resistant depression has been reported recently (Roy et al., 2018). In fact, the FPN is responsible for the goal-directed behavior and the cognitive flexibility in information processing (Dosenbach et al., 2007). Moreover, the tendency of the healthy brain to wander and not to remain fixed in any specific state (Friston et al., 2012) confers flexibility in thinking and allows the brain to explore other possibilities, which are essential in the reduction of depression (Dennis and Vander Wal, 2010; Deveney and Deldin, 2006) and possibly in improving subjective well-being. A recent study also found that increased entropy in the brain of people with chronic fatigue syndrome was associated with better health-related quality of life, measured using either the mental or the physical component of SF-36 (Shan et al., 2018).

4.3. Limitation and conclusion

Our study has a few limitations. First, due to ethical concerns, all the participants were receiving pharmacotherapy at the time of data collection. Hence, it is difficult to disentangle variances contributed by the trait/state in LLD or the medication effect. Although findings of our mediation analysis suggest that the increased entropy in FPN may result from some compensatory change, future longitudinal studies that incorporate pre- and post-treatment scans for patients with LLD will help verify if this change occurs before or after the treatment (i.e. either as self-adaptive changes to counter against depression or as adaptive effects induced by medication). Second, we found it difficult to compare our findings with that reported in previous studies that used MSE analysis in major depression because there were different time scales embedded in each modality (ECG, EEG, or MEG). Third, our sample size was small, which lead to insufficient statistical power. Still, we are able to find increase entropy in left FPN and left SMA in LLD group passing the correction of multiple comparisons. However, since all the rest of our findings were uncorrected, we cannot determine whether this is due to false positive or due to insufficient power secondary to low sample size. Although we should be cautious about the conclusions here, as neuroimaging studies using MSE are scare at this point, further validation in different studies with larger sample size is urgently needed. Last, but not the least, we used MSE analysis to unravel the difference in complexity across different time scales. However, even though the complexity in different time scales may reflect information processing at different ranges (McDonough and Nashiro, 2014), the exact neurophysiological basis is not known, which greatly limits how we may interpret our findings. Also, the limitation of MSE analysis, especially at higher scale, is the reduction in the availability of the data length (Wang et al., 2014) and hence, the decrease in statistical power (Smith et al., 2015). Nevertheless, our MSE analysis could provide more accurate results at different scale as noise will be filtered out due to lack of f^{-1} property during the "coarse-graining" process in MSE analysis (Smith et al., 2014). Also, group differences in entropy have been found beyond the original time scale, justifying the multi-scale exploration in this kind of analysis.

In conclusion, this study reveals that applying MSE analysis in rs-fMRI BOLD signals provides a complementary and novel approach to those from the traditional linear analysis in rs-fMRI. Our findings are also important for understanding the biological meaning of entropy within rs-fMRI as higher entropy in left FPN is associated with lower depression severity and higher mental health-related quality of life in patients of LLD. The temporal-spatial complexity in the resting brain could provide adaptive variability beneficial for the elderly with depression.

Conflict of interest

All authors declare no conflict of interest including any financial, personal or other relationships with other people or organizations within 3 years of beginning the work submitted that could inappropriately influence, or be perceived to influence, this work.

Acknowledgments

Supported by medical research grants CMRPG3C0041/42 and CRRPG2G0061 from Chang Gung Memorial Hospital and NRRPG2H0031 from Ministry of Science and Technology, Taiwan to Chemin Lin and the KKHo Charitable International to Tatia Lee. The authors report no financial relationships with commercial interests. The funding sources had no role in the design of this study and had no role during its execution, analyses, interpretation of the data, or decision to submit results.

Contribution

C. Lin and S.W. Lee. carried out the experiment. C. Lin. wrote the manuscript with support from C.M. Huang, P.S. Ho, and G.Y. Chen; Y.L. Chen helped supervise the project. T. Lee and S.C. Wu. conceived the original idea. H.L. Liu, T. Lee and S.C. Wu. supervised the project. All authors critically examined the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2019.03.012.

References

Abásolo, D., Hornero, R., Espino, P., Alvarez, D., Poza, J., 2006. Entropy analysis of the EEG background activity in Alzheimer's disease patients. Physiol. Meas. 27 (3), 241.

Achard, S., Salvador, R., Whitcher, B., Suckling, J., Bullmore, E., 2006. A resilient, low-frequency, small-world human brain functional network with highly connected association cortical hubs. J. Neurosci. 26, 63–72.

Alcaraz, R., Rieta, J.J., 2010. A novel application of sample entropy to the electrocardiogram of atrial fibrillation. Nonlinear Anal. Real World Appl. 11 (2), 1026–1035.

Alexopoulos, G.S., Hoptman, M.J., Kanellopoulos, D., Murphy, C.F., Lim, K.O., Gunning, F.M., 2012. Functional connectivity in the cognitive control network and the default mode network in late-life depression. J. Affective Disord. 139, 56–65.

Anand, A., Li, Y., Wang, Y., Wu, J., Gao, S., Bukhari, L., Mathews, V.P., Kalnin, A., Lowe, M.J., 2005. Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. Biol. Psychiatry 57, 1079–1088.
Andreescu, C., Butters, M.A., Begley, A., Rajji, T., Wu, M., Meltzer, C.C., Reynolds III, C.F., Aizenstein, H., 2008. Gray matter changes in late life depression—a structural MRI analysis. Neuropsychopharmacology 33, 2566.
Ballmaier, M., Toga, A.W., Blanton, R.E., Sowell, E.R., Lavretsky, H., Peterson, J., Pham, D., Kumar, A., 2004. Anterior cingulate, gyrus rectus, and orbitofrontal abnormalities in elderly depressed patients: an MRI-based parcellation of the prefrontal cortex. Am. J. Psychiatry 161, 99–108.
Bassett, D.S., Nelson, B.G., Mueller, B.A., Camchong, J., Lim, K.O., 2012. Altered resting state complexity in schizophrenia. Neuroimage 59, 2196–2207.
Beekman, A.T., Copeland, J., Prince, M.J., 1999. Review of community prevalence of depression in later life. Br. J. Psychiatry 174, 307–311.
Biswal, B., Zerrin Yetkin, F., Haughton, V.M., Hyde, J.S., 1995. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn. Reson. Med. 34 (4), 537–541.
Bora, E., Harrison, B., Davey, C., Yücel, M., Pantelis, C., 2012. Meta-analysis of volumetric abnormalities in cortico-striatal-pallidal-thalamic circuits in major depressive disorder. Psychol. Med. 42, 671–681.
Braun, U., Plichta, M.M., Esslinger, C., Sauer, C., Haddad, L., Grimm, O., Mier, D., Mohnke, S., Heinz, A., Erk, S., Walter, H., Seiferth, N., Kirsch, P., Meyer-Lindenberg, A., 2012. Test–retest reliability of resting-state connectivity network characteristics using fMRI and graph theoretical measures. NeuroImage 59, 1404–1412.
Breakspear, M., 2017. Dynamic models of large-scale brain activity. Nat. Neurosci. 20, 340.
Butters, M.A., Young, J.B., Lopez, O., Aizenstein, H.J., Mulsant, B.H., Reynolds III, C.F., DeKosky, S.T., Becker, J.T., 2008. Pathways linking late-life depression to persistent cognitive impairment and dementia. Dialogues Clin. Neurosci. 10, 345.
Cordes, D., Haughton, V.M., Arfanakis, K., Carew, J.D., Turski, P.A., Moritz, C.H., Quigley, M.A., Meyerand, M.E., 2001. Frequencies contributing to functional connectivity in the cerebral cortex in “resting-state” data. Am. J. Neuroradiol. 22, 1326–1333.
Costa, M., Goldberger, A.L., Peng, C.-K., 2005. Multiscale entropy analysis of biological signals. Phys. Rev. E. 71, 021906.
Damoiseaux, J.S., Rombouts, S.A.R.B., Barkhof, F., Scheltens, P., Stam, C.J., Smith, S.M., Beckmann, C.F., 2006. Consistent resting-state networks across healthy subjects. Proc. Natl. Acad. Sci. 103 (37), 13848–13853.
Dennis, J.P., Vander Wal, J.S., 2010. The cognitive flexibility inventory: instrument development and estimates of reliability and validity. Cognit. Ther. Res. 34, 241–253.
Deveney, C.M., Deldin, P., 2006. A preliminary investigation of cognitive flexibility for emotional information in major depressive disorder and non-psychiatric controls. Emotion 6, 429.
Dosenbach, N.U., Fair, D.A., Miezin, F.M., Cohen, A.L., Wenger, K.K., Dosenbach, R.A., Fox, M.D., Snyder, A.Z., Vincent, J.L., Raichle, M.E., Schlaggar, B.L., Petersen, S.E., 2007. Distinct brain networks for adaptive and stable task control in humans. Proc. Natl. Acad. Sci. U S A 104, 11073–11078.
Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct. Funct. 213, 93–118.
Fornito, A., Zalesky, A., Bullmore, E.T., 2010. Network scaling effects in graph analytic studies of human resting-state FMRI data. Front. Syst. Neurosci. 4, 22.
Friston, K.J., Mechelli, A., Turner, R., Price, C.J., 2000. Nonlinear responses in fMRI: the Balloon model, Volterra kernels, and other hemodynamics. NeuroImage 12 (4), 466–477.
Friston, K., Breakspear, M., Deco, G., 2012. Perception and self-organized instability. Front. Comput. Neurosci. 6, 44.
Garrett, D.D., Kovacevic, N., McIntosh, A.R., Grady, C.L., 2010. Blood oxygen level-dependent signal variability is more than just noise. J. Neurosci. 30 (14), 4914–4921.
Garrett, D.D., Samanez-Larkin, G.R., MacDonald, S.W.S., Lindenberger, U., McIntosh, A.R., Grady, C.L., 2013. Moment-to-moment brain signal variability: a next frontier in human brain mapping? Neurosci. Biobehav. Rev. 37, 610–624.
Greicius, M.D., Flores, B.H., Menon, V., Glover, G.H., Solvason, H.B., Kenna, H., ... Schatzberg, A.F., 2007. Resting-state functional connectivity in major depression: abnormally increased contributions from subgenual cingulate cortex and thalamus. Biol. Psychiatry 62 (5), 429–437.
Greicius, M., 2008. Resting-state functional connectivity in neuropsychiatric disorders. Curr. Opin. Neurol. 21 (4), 424–430.
He, B.J., 2011. Scale-free properties of the functional magnetic resonance imaging signal during rest and task. J. Neurosci. 31 (39), 13786–13795.
Ho, P.-S., Lin, C., Chen, G.-Y., Liu, H.-L., Huang, C.-M., Lee, T.M.-C., Lee, S.-H., Wu, S.-C., 2017. Complexity analysis of resting state fMRI signals in depressive patients, Engineering in Medicine and Biology Society (EMBC). In: 2017 39th Annual International Conference of the IEEE. IEEE, pp. 3190–3193.
Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015a. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72, 603–611.
Kaiser, R.H., Andrews-Hanna, J.R., Wager, T.D., Pizzagalli, D.A., 2015b. Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. JAMA Psychiatry 72, 603–611.
Karim, H., Andreescu, C., Tudorascu, D., Smagula, S., Butters, M., Karp, J., Reynolds, C., Aizenstein, H., 2017. Intrinsic functional connectivity in late-life depression: trajectories over the course of pharmacotherapy in remitters and non-remitters. Mol. Psychiatry 22, 450.
Lai, M.C., Lombardo, M.V., Chakrabarti, B., Sadek, S.A., Pasco, G., Wheelwright, S.J., ..., MRC AIMS Consortium, 2010. A shift to randomness of brain oscillations in people with autism. Biol. Psychiatry 68 (12), 1092–1099.
Laird, A.R., Fox, P.M., Eickhoff, S.B., Turner, J.A., Ray, K.L., McKay, D.R., ..., Fox, P.T., 2011. Behavioral interpretations of intrinsic connectivity networks. J. Cognit. Neurosci. 23 (12), 4022–4037.
Lake, D.E., Richman, J.S., Griffin, M.P., Moorman, J.R., 2002. Sample entropy analysis of neonatal heart rate variability. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 283 (3), R789–R797.
Leech, R., Sharp, D.J., 2013. The role of the posterior cingulate cortex in cognition and disease. Brain 137, 12–32.
Liu, C., Wang, S., Teng, E., Fuh, J., Lin, C., Lin, K., Chen, H., Lin, C., Wang, P., Yang, Y., 1997. Depressive disorders among older residents in a Chinese rural community. Psychol. Med. 27, 943–949.
Lu, J., 2003. Assessment of health-related quality of life in Taiwan (I): development and psychometric testing of SF-36 Taiwan version. Taiwan J. Public Health 22, 501–511.
McDonough, I.M., Nashiro, K., 2014. Network complexity as a measure of information processing across resting-state networks: evidence from the Human Connectome Project. Front. Hum. Neurosci. 8, 409.
McIntosh, A.R., Vakorin, V., Kovacevic, N., Wang, H., Diaconescu, A., Protzner, A.B., 2014. Spatiotemporal dependency of age-related changes in brain signal variability. Cerebral Cortex (New York, N.Y. : 1991) 24, 1806–1817.
Menon, V., 2011. Large-scale brain networks and psychopathology: a unifying triple network model. Trends Cognit. Sci. 15, 483–506.
Misic, B., Vakorin, V.A., Paus, T., McIntosh, A.R., 2011. Functional embedding predicts the variability of neural activity. Front. Syst. Neurosci. 5, 90.
Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., Ustun, B., 2007. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. The Lancet 370 (9590), 851–858.
Munro, C.E., Donovan, N.J., Guercio, B.J., Wigman, S.E., Schultz, A.P., Amariglio, R.E., Rentz, D.M., Johnson, K.A., Sperling, R.A., Marshall, G.A., 2015. Neuropsychiatric symptoms and functional connectivity in mild cognitive impairment. J. Alzheimer's Dis. 46, 727–735.
Olson, I.R., Plotzker, A., Ezzyat, Y., 2007. The Enigmatic temporal pole: a review of findings on social and emotional processing. Brain 130, 1718–1731.
Pedersen, M., Omidvarnia, A., Walz, J.M., Zalesky, A., Jackson, G.D., 2017. Spontaneous brain network activity: analysis of its temporal complexity. Network Neurosci. 1, 100–115.
Pincus, S.M., 1991. Approximate entropy as a measure of system complexity. Proc. Natl. Acad. Sci. 88 (6), 2297–2301.
Pincus, S., 1995. Approximate entropy (ApEn) as a complexity measure. Chaos 5, 110–117.
Pincus, S.M., Mulligan, T., Iranmanesh, A., Gheorghiu, S., Godschalk, M., Veldhuis, J.D., 1996. Older males secrete luteinizing hormone and testosterone more irregularly, and jointly more asynchronously, than younger males. Proc. Natl. Acad. Sci. 93 (24), 14100–14105.
Pool, R., 1989. Is it healthy to be chaotic? Science 243, 604–607.
Richman, J.S., Moorman, J.R., 2000. Physiological time-series analysis using approximate entropy and sample entropy. Am. J. Physiol. Heart Circulatory Physiol. 278, H2039–H2049.
Roy, A., Mueller, B., Klimes-Dougan, B., Schreiner, M., Thai, M., Lim, K., Cullen, K., 2018. T121. Increased resting state fMRI entropy associated with clinical response to ketamine for treatment resistant depression in adolescents. Biol. Psych. 83, S175.
Sato, J.R., Takahashi, D.Y., Hoexter, M.Q., Massirer, K.B., Fujita, A., 2013. Measuring network's entropy in ADHD: a new approach to investigate neuropsychiatric disorders. Neuroimage 77, 44–51.
Saxe, G.N., Calderone, D., Morales, L.J., 2018. Brain entropy and human intelligence: a resting-state fMRI study. PLOS ONE 13, e0191582.
Sexton, C.E., Mackay, C.E., Ebmeier, K.P., 2013. A systematic review and meta-analysis of magnetic resonance imaging studies in late-life depression. Am. J. Geriatric Psychiatry 21, 184–195.
Shan, Z.Y., Finegan, K., Bhuta, S., Ireland, T., Staines, D.R., Marshall-Gradisnik, S.M., Barnden, L.R., 2018. Brain function characteristics of chronic fatigue syndrome: a task fMRI study. NeuroImage 19, 279–286.
Sheline, Y.I., 2003. Neuroimaging studies of mood disorder effects on the brain. Biol. Psychiatry 54, 338–352.
Sheline, Y.I., Price, J.L., Yan, Z., Mintun, M.A., 2010. Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. Proc. Natl. Acad. Sci. 107 (24), 11020–11025.
Smith, R.X., Jann, K., Ances, B., Wang, D.J.J., 2015. Wavelet-based regularity analysis reveals recurrent spatiotemporal behavior in resting-state fMRI. Hum. Brain Mapping 36, 3603–3620.
Smith, R.X., Yan, L., Wang, D.J.J., 2014. Multiple time scale complexity analysis of resting state FMRI. Brain Imaging Behav. 8, 284–291.
Sokunbi, M.O., Staff, R.T., Waiter, G.D., Ahearn, T.S., Fox, H.C., Deary, I.J., ..., Murray, A.D., 2011. Inter-individual differences in fMRI entropy measurements in old age. IEEE Trans. Biomed. Eng. 58 (11), 3206–3214.
Sokunbi, M.O., Fung, W., Sawlani, V., Choppin, S., Linden, D.E., Thome, J., 2013. Resting state fMRI entropy probes complexity of brain activity in adults with ADHD. Psychiatry Research: Neuroimaging 214 (3), 341–348.
Sokunbi, M.O., Gradin, V.B., Waiter, G.D., Cameron, G.G., Ahearn, T.S., Murray, A.D., ..., Staff, R.T., 2014. Nonlinear complexity analysis of brain FMRI signals in schizophrenia. Plos one 9 (5), e95146.
Song, D., Chang, D., Zhang, J., Ge, Q., Zang, Y.-F., Wang, Z., 2018. Associations of brain entropy (BEN) to cerebral blood flow and fractional amplitude of low-frequency fluctuations in the resting brain. Brain Imaging Behav.
Tseng, H.M., Lu, J.F.R., Tsai, Y.J., 2003. Assessment of health-related quality of life in Taiwan (II): norming and validation of SF-36 Taiwan version. Taiwan J. Public

Health 22, 512–518.
Tupler, L.A., Krishnan, K.R.R., McDonald, W.M., Dombeck, C.B., D'Souza, S., Steffens, D.C., 2002. Anatomic location and laterality of MRI signal hyperintensities in late-life depression. J. Psychosomatic Res. 53, 665–676.
Turianikova, Z., Javorka, K., Baumert, M., Calkovska, A., Javorka, M., 2011. The effect of orthostatic stress on multiscale entropy of heart rate and blood pressure. Physiol. Meas. 32 (9), 1425.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15, 273–289.
Unützer, J., 2007. Late-life depression. N. Engl. J. Med. 357, 2269–2276.
Vakorin, V.A., Lippé, S., McIntosh, A.R., 2011. Variability of brain signals processed locally transforms into higher connectivity with brain development. J. Neurosci. 31, 6405–6413.
Van Den Heuvel, M.P., Pol, H.E.H., 2010. Exploring the brain network: a review on resting-state fMRI functional connectivity. Eur. Neuropsychopharmacol. 20 (8), 519–534.
Wang, L., Hermens, D., Hickie, I., Lagopoulos, J., 2012. A systematic review of resting-state functional-MRI studies in major depression. J. Affective Disord. 142, 6–12.
Wang, Z., Li, Y., Childress, A.R., Detre, J.A., 2014. Brain entropy mapping using fMRI. PLoS One 9, e89948.
Wang, B., Niu, Y., Miao, L., Cao, R., Yan, P., Guo, H., ..., Xiang, J., 2017. Decreased complexity in Alzheimer's disease: resting-state fMRI evidence of brain entropy mapping. Front. Aging Neurosci. 9, 378.
Ware, J.E., Keller, S.D., Kosinski, M., 1994. SF-36 Physical and Mental Health Summary Scales. Health Assessment Lab, Boston.
Ware Jr, J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Med. Care 473–483.
Yang, A.C., Huang, C.C., Yeh, H.L., Liu, M.E., Hong, C.J., Tu, P.C., ..., Tsai, S.J., 2013. Complexity of spontaneous BOLD activity in default mode network is correlated with cognitive function in normal male elderly: a multiscale entropy analysis. Neurobiol. Aging 34 (2), 428–438.
Yang, A.C., Huang, C.C., Liu, M.E., Liou, Y.J., Hong, C.J., Lo, M.T., Huang, N.E., Peng, C.K., Lin, C.P., Tsai, S.J., 2014. The APOE ε4 allele affects complexity and functional connectivity of resting brain activity in healthy adults. Hum. Brain Mapping 35, 3238–3248.
Yang, A.C., Tsai, S.-J., 2013. Is mental illness complex? From behavior to brain. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 45, 253–257.
Zhang, Y., Lu, S., Zhou, X., Yang, M., Wu, L., Liu, B., ..., Wang, S., 2016. Comparison of machine learning methods for stationary wavelet entropy-based multiple sclerosis detection: decision tree, k-nearest neighbors, and support vector machine. Simulation 92 (9), 861–871.