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Research Article

A Comparison of Resting Regional Cerebral Glucose Metabolism in Patients with Suicidal Attempts with and without Having a Major Depressive Disorder

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ABSTRACT

Background: Individuals with suicidal behaviors are increasingly recognized as having impairments in brain metabolism. However what differentiates those who attempt suicide while having diagnosable depression versus those who attempt suicide without depression, in terms of neurobiology is still largely unknown.

Aims: Using the F-18 FDG brain positron emission tomography to:

1. To evaluate differences in resting Cerebral Glucose Metabolism (rCMglu) between depressed and non-depressed suicidal subjects.

2. To translate a suicide attempt, which is a behavioral construct (NSSI or otherwise) into neurobiological constructs.

Methods: Patients with suicide attempt with diagnosable Depression and those with suicide attempt without diagnosable depression (NSSI) were included. Brain metabolism was assessed using [18F] Fluoro Deoxy-Glucose Positron Emission Tomography (FDG-PET). The brain PET scans were analyzed using the NEUROQ software.

Results: Of 33 subjects, eighteen had major depressive disorder. Comparison using brain FDG PET scan showed hypermetabolism in the components of the Default Mode Network (self-referential ruminations), the Salience network (modulating emotional behaviour) and hypometabolism in the Dorso lateral prefrontal cortex (cognition, executive functioning), visual association (visual memory) in those with Major Depressive disorder only and not in those with Non Suicidal Self Injury (NSSI).

Conclusion: Significant differences exist in rCMglu of suicidal individuals with and without depression. Understanding these would help us formulate treatment strategies. Our study shows that even those individuals who may not fulfil DSM or ICD criteria for Major Depressive disorder should be treated as a case of MDD if they have negative self-referential ruminations, impaired information processing and cognition.

Keywords: Deconstructing suicide; Neurobiologically vis-a-vis clinical features

INTRODUCTION

Suicide is derived from the Latin word for 'self-murder'. It is a fatal act that represents the person's wish to die. There is a range, however, between thinking about suicide, planning it and attempting it. All mental disorders carry an increased risk of suicide, the highest being major depression (30–31%). The mortality risk for suicide in major depression is 20 times that expected, and 15- to 20-fold in all affective disorders. This accounts for suicide and Major Depressive Disorders being intricately connected to each other.

However not all patients having major depressive disorder attempt suicide and not all those with suicide attempt have MDD. When we say that the patient does not have MDD, we very often mean that the patient does not fulfill the diagnostic criteria to qualify for MDD, but we do know that these two separate groups have

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overlapping clinical features. Then again how valid is a label of NSSI (Non Suicidal Self Injury) that we use frequently for the latter group of patients? We need to know the neurobiological footprints that actually differentiate these two clinical and behavioral constructs.

Hence brain PET scan studies have been employed for a better understanding of both the conditions and it has been found that depression is commonly associated with frontal hypo metabolic activity accompanied to hyper metabolism in certain limbic regions. Also, functional brain imaging studies of subjects with Major Depressive Disorder (MDD) have suggested that decreased dorsolateral (DLPFC) and increased ventrolateral (VLPFC) prefrontal cortical activity mediate the depressed state [1]. Affective illness can be explained as the consequence of a loss of top-down control (especially mPFC) over limbic structures such as the amygdala; or alternatively, the consequence of disinhibited limbic drive which overrides cortical regulation [2].

However all the brain PET scan studies done choose the regions of interest in a patient with reference to that patients occipital glucose metabolism considering that the occipital cortical metabolism would be similar in patients and controls; but to assume that would not be foolproof as this assumption would influence the thus obtained regions of interest. Thus we have studied the glucose metabolism using Neuro Q software, which compares the glucose metabolism area for area between any 2 groups of subjects, making it one of a kind.

Purpose of the study

Whilst studying, and in an attempt to understand the neurobiological underpinnings of patients with suicide attempts; with and without major depressive Disorder, most of the studies have looked individually at the rCMglu of certain brain regions and then looked at the function of that particular region in an attempt to explain the various constructs of depression and suicidal behaviour. This has largely been the way we have understood neurobiological correlates of depression and suicidal behaviour.

However as a result of this region for region comparison of rCMglu, the understanding of the dysfunction of the basic underlying basic brain network has been lost and not all the differences between the two overlapping constructs have been understood.

However in our study, a direct comparison was made was between those patients with suicidal attempts with depression versus those with suicide attempts without depression. Hence similarities cancel out and only the difference in terms of standard deviations was obtained (where >2 standard deviations was considered significant).

RESEARCH METHODOLOGY

The study, approved by the Institutional Ethics Committee. Subjects were recruited from a specialty out-patient service "Suicide prevention clinic" that runs weekly exclusively for patients with suicidal behaviors, where all patients with attempted suicide who present to the medical/emergency/surgical services are referred. For the purpose of this study, consecutive sampling was used. Inclusion criteria for the subjects were age group of 18-60, either gender with attempted suicide in the last 72 hours, not on psychotropic medication since at least 6 month, willing and cognitively stable to give consent. Written informed consent was taken from all subjects prior to inclusion in the study. Females not known to be pregnant/lactating were included. Subjects with mild to severe depressive disorder, anxiety disorders and personality disorders were also included in the study. Subjects who were already receiving pharmacotherapy/psychotherapy for their index episode, having catatonia or psychosis, severe cognitive impairment, active suicidal ideations who clinically require medication, requiring electroconvulsive therapy, medically unstable, having active substance abuse (except nicotine) were excluded. For this study, suicidal behavior was defined as "an act with nonfatal outcome that the individual, expecting to, inflict bodily harm or die, initiated and carried out with the purpose of bringing about wanted changes".

Setting

Clinical assessment by a qualified psychiatrist using International Classification of Diseases (ICD-10) criteria to evaluate for psychiatric disorders and to rule out severe depression with psychotic symptoms, psychotic disorders, substance use disorders (except nicotine) and severe cognitive impairment.. A socio-demographic and clinical proforma that has been specially devised and used in the specialty clinic was used to record the subjects' demographics, social situation and clinical details including stressors and details regarding the attempt.

Pet imaging

Assessment of brain metabolism was done using F-18 Fluoro-Deoxy-Glucose Positron Emission Tomography (FDGPET): 18F-FDG, a radio-labeled glucose analogue was injected and the regional brain distribution was detected with a PET camera. Participants were fasting for at least 6 hours prior to the scan, had not consumed/ smoked tobacco for the last 8 hours and had a blood glucose level of <150 $mgdl^{-1}$.

The patients were made to lie under the scanner and positioned with head straight and hands down in the supine position. Head movement was minimized by strapping the head of the patient on a custom made brain cushion. A Philips TOF (Time of Flight) Gemini series PET/CT scanner with 16 slice CT (with a resolution of approximately 4 mm) acquired a 5 min emission scan in 3D mode as a single frame. CT was used for attenuation correction. An average dose of 185 MBq (111–222) of 18F, 2-fluoro, 2-deoxy-glucose (18F- FDG) was injected. Acquisition was carried out approximately 45 minutes to 1 hour after the injection. Emission scans of 70 slices were obtained parallel to the cantho-meatal line from vertex to the neck. The images were reconstructed with CT attenuation correction and elastic spatial reformatting into a standard volumetric space with 35 trans-axial slices of 4.25 mm thickness.

Image analysis

Regional glucose metabolism was examined in reference to the whole brain uptake. The regional activity in 47 clusters were expressed as average of counts per second per pixel. A ratio of these counts with reference to the whole brain was calculated and the regions compared with the data base of those patients who had suicide attempts without having Major Depressive Disorder. A standard deviation of greater than 2 was considered to be significant.

Statistical analysis

PET images were processed using NEUROQ software which was provided with the system for Brain analysis.

The program quantifies mean pixel values lying within standardized regions of interest and provides quantified comparisons with brain scans derived from FDG-PET of 18 patients with suicidal attempt and Major depressive disorder against 15 patients with suicidal

attempt, without a Major Depressive Disorder. The Program provides automated analysis of brain PET scans, with output that includes relative activity in 240 different regions of brain as well as measures magnitude and statistical significance with which activity in each region differs from mean activity values of brain in the comparison database.

The operator initiates an elastic spatial reformatting or normalization of patients scan into a standardized volumetric space. A rigid registration is used to match the reference brain slice in case of excessive tilt. Reformatting of the slices is performed for 10 iterations to match the reference slices in the database. The program determines uptake in 240 ROIs and compares with database values. Any region with an uptake of 2 SD of the mean established from normal database is considered abnormal.

RESULTS

Socio-demographic profile

As shown in Table 1, the overall mean age of the sample was 25.33 (Standard deviation (SD):9.94), with mean age in the depressed group being 28 years (SD: 11.72) and for the non-depressed group was 22.13 years (SD 6.26). Overall, there were 11 males and 22 females in our sample and the male: female ratio in both the groups was 1:2. Around 70% of our sample was unemployed but this group includes housewives as well. Eighty percent of the subjects belonged to the upper-lower socio economic class as per Kuppuswamy classification of socio economic status.

The Neuro Q software provides with regions of the brain with a difference in glucose metabolism of 2 or more Standard Deviations (more=hyper & less=hypo metabolism) from the mean of the metabolism of the depressed group as compared to the mean of the glucose metabolism of the non-depressed group of patients.

DISCUSSION

While comparing those depressed versus the non-depressed, with suicidal attempts, we often find overlapping clinical symptoms, even though they are very separate groups, especially when it comes to treatment, prevention and prophylaxis. Let us now look at region specific neurobiological differences between these 2 very separate groups.

In recent times, more weightage is given to brain/neural networks, for understanding the neurobiology of any psychiatric illness, rather than rigidly narrowing down the focus on specific brain regions to explain the signs and symptoms of psychiatric disorders. This is because the different regions of the brain do not work independently of each other, but work in specific circuits or specific networks (also called connectomics).

Let us keep in mind that depression is a syndrome. It has, apart from the affective component, rumination of thoughts, negative self-evaluation, vegetative, executive and cognitive dysfunction.

In the depressed group with suicide attempt

1. Our study shows hyper metabolism in -- the Posterior Cingulate Cortex (PCC), Ventromedial Prefrontal Cortex (VMPFC) and Medial Temporal Cortex (MTC) (Table 2).

Our study shows, in keeping with other studies; a significant increase in the rCMglu in the Posterior Cingulate cortex (PCC), Ventro-Medial Prefrontal Cortex (VMPFC) (specifically responsible for blunted affect and anhedonia) and the Medial Temporal Cortex (MTC) [3].

These together are components of a network called the Default Mode Network (DMN) [4].

Translation in terms of functional networks: The Default Mode Network (DMN)

The dominant functional characterization of the PCC arises out of its central role within the DMN [5,6]. In addition to the PCC, the main nodes in the DMN are the Ventromedial Prefrontal Cortex (VMPFC), lateral Inferior Parietal Lobes (LIPL) and Medial Temporal Cortex (MTC) [7].

Thus our study shows significant hyper-metabolism in the Default Mode Network, during the resting state. Now what does this mean?

As per a study done by Hamilton, resting state brain FDG-PET provides information about the default mode network, a group of brain regions that are activated during self-referential mentation [8].

Also, relative dominance of the default-mode network activity on BOLD fMRI in the resting state is associated with increased maladaptive and ruminative thinking. Elevated rCMRglu in default mode network is also associated with ruminative thinking and is closely associated with suicidal ideation and behavior [9].

Information processing

Not only do the Ventro-medial Prefrontal Cortex (VMPFC), Posterior Cingulate Cortex (PCC) and Medial Temporal Cortex (MTC) govern free-wheeling (resting state) thinking, that is the DMN, they play a key role in information processing. Diffusion Tensor Imaging Tractography and Graph-theoretic analyses of structural connectivity show how highly connected the PCC, VMPFC and MTC are, relative to other brain regions, providing evidence for a role as a hub for information processing [10].

Our study shows significant hyper metabolism in the Anterior Cingulate Cortex and Medial Temporal Cortex, in the group with MDD with suicide attempt.

Salience network

A salience network comprises bilateral insula (in the Medial Temporal region) and anterior cingulate cortex (ACC). [11] It is thought to play a role in recruiting relevant brain regions for the processing of sensory information and modulating emotional behaviour. Also a study showed significantly increased rCMglu in the ACC in the depressed group compared with the non-depressed group. On follow- up, the metabolic activity was elevated in the ACC in the depressed relative to the remitted phases of the same MDD subjects, and effective antidepressant treatment was associated with a reduction in rCMglu ACC activity [12].

Our study shows significant hyper-metabolism in bilateral Visual Association Cortices (VAC), Hypo-metabolism in the Dorsal and Lateral Prefrontal Cortex (DLPFC) and Left Inferior Prefrontal Cortex (LIPFC). These areas (VAC, DLPFC, LIPFC) sum up to form the Association and Cognitive network.

Association and cognitive networks

Visual task information was given to a group of patients with MDD (with suicide attempts) and then withdrawn, in spite of which persistent activation in the Visual Association Cortex (VAC) was associated with greater rumination and depressive symptoms [13].

Also a partial failure in visual working memory updating mechanism was seen due to persistent activity of the visual association areas,

Table 1: Socio-demographic details of the sample.

Socio-demographic parameters	Total Sample	Depressed group Mean (SD)/N (%)	Non-depressed group Mean (SD)/N (%)
Total number of subjects	33	18	15
Mean age (in years)	25.33 (9.94)	28.0 (11.72)	22.13 (6.26)
Gender			
Male	11 (33.3%)	6 (33.3%)	5 (33.3%)
Female	22 (66.7%)	12 (66.7%)	10 (66.7%)
Marital Status			
Single	20 (60.61%)	10 (55.6%)	10 (66.7%)
Married	13 (39.39%)	8 (44.5%)	5 (33.3%)
Religion: Hindu	31 (93.93%)	18 (100%)	13 (86.7%)
Education			
Illiterate -primary school	2 (06.06%)	2 (11.11%)	0 (0%)
Middle- high school	14 (42.42%)	6 (33.33%)	8 (53.33%)
Post high school diploma/ graduation	17 (51.52%)	10 (55.56%)	7 (46.67%)
Employment status			
Unemployed	23 (69.69%)	13 (72.2%)	10 (66.7%)
Employed	10 (30.3%)	5 (27.8%)	5 (32.4%)
Income			
Below Rs 10,000/month	10 (30.3%)	6 (33.33%)	6 (33.33%)
Above Rs 10,000/month	23 (69.7%)	12 (66.7%)	11 (73.33%)
Family type			
Nuclear	20 (60.6%)	10 (55.6%)	10 (66.7%)
Joint	13 (39.39%)	8 (44.5%)	5 (33.3%)

affecting their connectivity with the (DLPFC) and the Left Inferior Prefrontal Cortex (LIPFC). Now persistent activity of the Association cortex, coupled with hypo-metabolism of the DLPFC and LIPFC (as is seen in our study), accounts for the core feature of cognitive dysfunction seen in patients with MDD with suicide attempt. [13] This however is not seen in the group with suicidal attempt, without MDD.

Assessment of the severity of depression based on neurobiological findings the severity of depression was associated with decreased rCBF in Inferior Prefrontal Cortex of left hemisphere (LIPFC), and increased rCBF of right Associative Visual Cortex (although our study shows increased rCMglu in bilateral VAC) and that rCBF SPECT/CT may provide an objective assessment for MDD severity and could be used for monitoring therapeutic efficacy in the management of MDD [14].

Our study showed significant hyper metabolism in the Cerebellum.

Cerebellum and lethality of suicide

Our study shows increased rCMglu in bilateral Cerebellum in those with suicide attempt with depression versus those without depression. A study done by Oquendo et al. found increased rCMRglu in cerebellum bilaterally in high-lethality compared with low-lethality attempters [15]. It has been suggested that the cerebellum, which has reciprocal connections with various limbic

Table 2: Areas showing hyper metabolism in those patients having MDD with suicide attempt.

Region		Mean (ND)	SD (ND)	Mean (Dep)	#SD (Dep)
Frontal cortex (medial)	left	1.180	0.04220	0.07430	1.763
	Right	1.033	0.04530	0.1061	2.342
Frontal cortex (lateral)	Left	0.7408	0.05750	0.09660	1.680
Frontal cortex (inferior)	Left	1.015	0.03270	0.1346	4.110
	Right	1.073	0.03720	0.06240	1.678
Temporal cortex (medial)	Left	0.9631	0.02030	0.04780	2.358
	Right	0.6859	0.02700	0.07420	2.748
Temporal cortex (lateral)	Left	0.8895	0.06480	0.1138	1.757
	Right	0.9524	0.02600	0.04400	1.694
Superior parietal Cortex	Left	0.8245	0.02710	0.08380	3.093
	Right	0.8910	0.03730	0.06530	1.750
Sensorimotor Cortex Sensorimotor cortex	Left	0.8388	0.03770	0.1073	2.849
	Right	0.9415	0.02980	0.09040	3.029
Anterior Cingulate cortex	Left	1.133	0.04560	0.08200	1.799
	Right	1.107	0.02320	0.05630	2.425
Posterior Cingulate Cortex		1.123	0.01810	0.06440	3.557
Associative visual cortex	Left	1.046	0.04010	1.196	3.759
	Right	1.028	0.03260	0.06660	2.043
Thalamus		1.007	0.05000	0.1206	2.413
Lentiform nucleus	Right	0.9041	0.05190	0.08950	1.725
Caudate nucleus	Left	0.9215	0.04560	0.09230	2.023
	Right	0.8807	0.03740	0.1235	3.299
Cerebellum	Left	0.9138	0.04830	0.1487	3.081
	Right	0.8676	0.03660	0.1151	3.144
Midbrain		0.7167	0.02500	0.08310	3.319

structures, may play a role in the regulation of emotion [16].

Our study showed significant hyper metabolism in the Thalamus.

The thalamus and treatment resistant depression

Yamamura in 2016, showed evidence of an association between the thalamus and MDD has been reported. For instance, in the context of resting-state neural activity, previous studies have suggested an association between spontaneous neural activity in the thalamus and Treatment resistant depression. Patients with MDD have been reported to exhibit greater neuronal density in the thalamus, greater regional cerebral blood flow therein. Thalamic metabolism decreases along with remission of depression [17].

Our study showed significant hyper metabolism of the Caudate nucleus in the depressed group [18]. However most of the literature shows otherwise. Patients with unipolar depression showed a significantly lower ratio of the metabolic rate of the caudate nucleus, divided by that of the hemisphere as a whole, when compared with normal controls [19].

Studies show that hypermetabolism in the Caudate nucleus is associated with recovery from depression and OCD [20]. Our study showed significant hypo metabolism in Left Superior Temporal Gyrus (STG) also showed significant hyper metabolism in the sensorimotor cortices and sensor motor network-the social processing network (Table 3).

Table 3: Areas showing hypo metabolism in those patients having MDD with suicide attempt.

Region		Mean (ND)	SD (ND)	M (Dep)	#SD (Dep)
Frontal cortex (lateral)	Left	1.041	0.02650	-0.06150	-2.320
	Right	1.041	0.02650	-0.05330	-2.013
Frontal cortex (dorsal)	Left	0.7785	0.05470	-0.1742	-3.182
Frontal cortex (inferior)	Right	1.219	0.04750	-0.1292	-2.718
Temporal cortex (lateral)	Left	1.096	0.02450	-0.06010	-2.457

Social cognition

We know that the superior temporal gyrus has a functional role in auditory processing and short-term memory, facial related emotional perception and also social cognition processing through its connection with the prefrontal cortex and amygdala [21]. Another study showed positive correlation between hyperactivity in Superior Temporal Gyrus (STG) and cognitive performing scores, suggesting an association between higher frequency resting-states activity in STG and successful task execution [22]. Thus, this also means that decreased rCMglu in the STG would be associated with declining cognitive performance. Our study shows significantly increased rCMglu in bilateral Sensorimotor Cortices.

Our sensorimotor system has evolved to function beyond purely motor control. They form a part of the Mirror Neuron System and are found to be involved in resonating, imitating, and/or simulating the actions of others. They perform higher order social processes, such as motor learning, action understanding, imitation, perspective taking, understanding facial emotions, and empathy and hence called the resonance system [23-44].

CONCLUSIONS

When comparing neurobiological footprints of patients with suicide attempt with MDD versus without MDD, the neurobiology of patients with MDD are significantly different from those without MDD, in the following

1. There is significantly increased rCMglu in PCC, Medial Temporal Cortex, Left Inferior Parietal Cortex and bilateral Ventromedial Prefrontal Cortex. This group of Cortices is form the Default Mode Network (DMN).

2. Elevated rCMRglu in default mode network is associated with, self-referential mentation, maladaptive and ruminative thinking and is closely associated with suicidal ideation and behavior.

3. Our study shows significant hyper metabolism in the Anterior Cingulate Cortex and Medial Temporal Cortex. These form the Salience Network

4. Elevated metabolic activity in the Salience Network is seen in depressed patients, relative to those in the remission phase of the same MDD subjects. Also reduction in rCMglu in the ACC is a predictor of effective antidepressant treatment.

5. Hypo-metabolism in the Dorsal and Lateral Prefrontal Cortex (DLPFC) and Left Inferior Prefrontal Cortex (LIPFC), are responsible for cognitive dysfunction, poor working memory, and executive dysfunction.

Additionally the increased rCMglu in the Visual Association Cortex adds to the greater rumination and depressive symptoms along with impairment in visual memory.

6. Increase in the rCMglu in the Cerebellum was found to be directly proportional to the lethality of suicide.

7. The rCMglu was significantly increased in the Thalamus. Thalamic rCMglu is directly proportional to the treatment resistance.

8. Our study showed increased rCMglu in the Caudate Nucleus. No other evidence backing this was found.

9. Increased rCMglu in the superior temporal gyrus was found which has a functional role in auditory processing, short-term memory and facial related emotional perception. This coupled with hypometabolism in the Superior Temporal Gyrus is a potential reason for executive task dysfunction

10. Increased rCMglu in the Sensorimotor Cortices which are a part of the mirror neuron system, playing a higher order social processes, empathy and perspective taking.

11. The neurobiological findings tell us that even in cases of NSSI, if there is impaired information processing, cognition, working memory and ruminations, these patients still have a neurobiological print in accordance with those who have Depressive Disorder.

Thus we have traced and differentiated the neurobiological footprints between patients with suicide attempts with MDD and without MDD. Thereafter we have translated these neurobiological findings into clinically relevant phenomena with clinical implications.

CLINICAL RELEVANCE

1. The entire phenomenology of suicide with and without MDD has been explained by translating symptoms into neurological origins, makes our understanding and diagnosis of the two separate, but overlapping constucts easier.

2. Resting state glucose metabolism can be used as an indicator to correlate treatment response and/or resistance, on follow up.

3. The region and its resting state glucose metabolism, can determine lethality of the suicide attempt.

4. We now also have neurobiological markers for clinical

improvement and remission.

5. There is no universal, fool proof way of determining whether a given suicide attempt is a Non Suicidal Self Injury (NSSI) or otherwise. In spite of this, our treatment is biased when it comes to patients with NSSI. Our study recommends treating patients with NSSI as we would for a depressive disorder, if they have impaired information processing, cognition, working memory and ruminations, even if they may not fulfill diagnostic criteria for Major Depressive Disorder.

REFERENCES

1. Torgersen SO ldham JM, Skodol AE, Bender DS. Textbook of Personality Disorders. Arlington: American Psychiatric Publishing, USA. 2005; 129-141.
2. Links PS, Heslegrave RJ. Prospective studies of outcome. Understanding mechanisms of change in patients with borderline personality disorder. Psychiatr Clin North Am. 2000; 23:137-150.
3. Sublette ME, Milak MS, Galfalvy HC. Regional brain glucose uptake distinguishes suicide attempters from non-attempters in major depression. Archives of Suicide Research: Official Journal of the International Academy for Suicide Research. 2013; 17:434-447.
4. Greicius, MD, Supekar K., Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. Cerebral cortex. 2009;19:72–78.
5. Daniel S, Margulie S, Ghosh S, Goulas A, Falkiewic M, Julia M, et al. Principal gradient of cortical organization. Proceedings of the National Academy of Sciences Nov 2016; 113:12574-12579.
6. Leech R, Braga R, Sharp DJ. Echoes of the brain within the posterior cingulate cortex. The Journal of neuroscience: the official journal of the Society for Neuroscience. 2012; 32:215–222.
7. Raichle Marus, MacLeod Ann, Snyder Abraham, Powers William, Gusnard Debra, Shulman Gordon. A default mode of brain function. Proceedings of the National Academy of Sciences of the United States of America. 98; 676-82.
8. Hamilton J, Paul & Farmer, Madison & Fogelman, Phoebe & Gotlib, Ian. Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. Biological Psychiatry. 2018; 78.
9. O'Connor, Rory & Noyce, Rosie. Personality and cognitive processes: Self-criticism and different types of rumination as predictors of suicidal ideation. Behaviour Research and Therapy. 2008; 46:392-401.
10. Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, et al. Mapping the structural core of human cerebral cortex. PLoS Biol. 2008; 6(7): e159.
11. Uddin L Q. Salience processing and insular cortical function and dysfunction. Nature Reviews Neuroscience, 2014; 16:55 61.
12. Hamilton JP, Glover GH, Bagarinao E, Chang C, Mackey S, Sacchet MD & Gotlib I H. Effects of salience-network-node neurofeedback training on affective biases in major depressive disorder. Psychiatry research. Neuroimaging. 2016; 249:91–96.
13. Le TM, Borghi JA, Kujawa AJ, Klein DN, Leung H. C. Alterations in visual cortical activation and connectivity with prefrontal cortex during working memory updating in major depressive disorder. NeuroImage. Clinical. 2017; 14:43–53.
14. Li J, Yang Y, Zhu Y, Zhou L, Han Y, Yin T, Cheng Z, Zhang G, Shen Y & Chen J. Towards characterizing the regional cerebral perfusion in evaluating the severity of major depression disorder with SPECT/CT. BMC psychiatry. 2018; 18:70.
15. Oquendo MA, Placidi GPA, Malone KM. Positron Emission Tomography of Regional Brain Metabolic Responses to a Serotonergic Challenge and Lethality of Suicide Attempts in Major Depression. Arch Gen Psychiatry. 2003; 60:14–22.
16. Schutter DJL, Van Honk J. The Cerebellum in Emotion Regulation: A Repetitive Transcranial Magnetic Stimulation Study. Cerebellum. 2009;8:28–34 (2009).
17. Yamamura T, Okamoto Y, Okada G, Takaishi Y, Takamura M, Mantani A, Kurata A, Otagaki, Y, Yamashita H & Yamawaki S. Association of thalamic hyperactivity with treatment-resistant depression and poor response in early treatment for major depression: a resting-state fMRI study using fractional amplitude of low-frequency fluctuations. Translational Psychiatry. 2016; 3:e754.
18. Holthoff VA, Beuthien-Baumann B, Zündorf G, Triemer A, Lüdecke S, Winiecki P, Koch R, Füchtner F & Herholz K. Changes in brain metabolism associated with remission in unipolar major depression. Acta Psychiatrica Scandinavica. 2004; 110:184-94.
19. Krishnan KR, McDonald WM, Escalona PR, Doraiswamy PM, Na C, Husain MM, Figiel GS, Boyko OB, Ellinwood EH & Nemeroff CB. Magnetic resonance imaging of the caudate nuclei in depression. Preliminary observations. Arch Gen Psychiatry. 1992; 49:553-7.
20. Baxter LR, Schwartz JM, Bergman KS. Caudate Glucose Metabolic Rate Changes with Both Drug and Behavior Therapy for Obsessive-Compulsive Disorder. Arch Gen Psychiatry. 1992; 49:681–689.
21. Radua J, Phillips ML, Russell T, Lawrence N, Marshall N, Kalidindi S, El-Hage W, McDonald C, Giampietro V, Brammer MJ, David AS & Surguladze SA. Neural response to specific components of fearful faces in healthy and schizophrenic adults. Neuroimage. 2010; 49:939-946.
22. Tadayonnejad R, Yang S, Kumar A & Ajilore O. Clinical, cognitive and functional connectivity correlations of resting-state intrinsic brain activity alterations in unmedicated depression. Journal of affective disorders. 2015; 172:241–250.
23. Pineda J. A. Sensorimotor cortex as a critical component of an 'extended' mirror neuron system: Does it solve the development, correspondence, and control problems in mirroring? Behavioral and brain functions: BBF. 2008;4: 47.
24. Podchufarova EV, Razumov DV. Pain behavior in patients with chronic back pain. News of Medicine and Pharmacy. 2011; 370:50-55.
25. Weinstein PR. Diagnosis and management of lumbar spine stenosis. Clin Neurosurg. – 1983; 30:677-697.
26. Veyn AM, Voznesenskaya TG, Danilov AB. Pain syndromes in neurological practice. Moscow: MEDpress. 2001; 368.
27. Danilov AB, Veyna AM. Complex regional pain syndrome. Vegetative Disorders. 1998; 604-615.
28. Popova TI, Ustyuzhanina VO. Postisometric muscle relaxation in manual medicine: Textbook method. Handbook 11th International Congress of Manual Medicine. Vienna. 1995; 26-29.
29. Meyers WC, Foley DP, Garrett WE, Lohnes JH, Mandlebaum

BR. Management of severe lower abdominal or inguinal pain in high-performance athletes. PAiN (Performing Athletes with Abdominal or inguinal Neuro -muscular Pain Study Group). Am J Sports Med. 2000; 28:2-8.

30. Morales-Conde S, Socas M, Barranco A. Sportsmen hernia: What do we know? Hernia 2010; 14: 5-15.

31. Kinlyan K, Bakakireva M. Back pain. A new approach to treatment and prevention in adults and children. 1999; 77.

32. Bonica JJ. General Considerations of pain in the chest. J. Bonica. The Management of Pain. Ed. Lea & Febiger, Philadelphia, USA. 1990; 2:959.

33. Gavronski G, Veraksits A, Vasar E, Maaroos J. Evaluation of viscoelastic parameters of the skeletal muscles in junior triathletes. Physiol Meas. 2007; 28:625–637.

34. Agyapong-Badu S, Warner M, Samuel D, Stokes M. Practical considerations for standardized recording of muscle mechanical properties using a myometric device: Recording site, muscle length, state of contraction and prior activity. J Musculoskelet Res. 2018; 21:1850010.

35. Nair K., Masi AT, Andonian BJ, Barry AJ, Coates BA, Dougherty J, et al. Stiffness of Resting Lumbar Myofascia in Healthy Young Subjects Quantified Using a Handheld Myotonometer and Concurrently with Surface Electromyography Monitoring. J Body Mov Ther. 2016; 20:388–396.

36. Wu Z, Zhu Y, Xu W, Liang J, Guan Y, Xu X. Analysis of Biomechanical Properties of the Lumbar Extensor Myofascia in Elderly Patients with Chronic Low Back Pain and That in Healthy People. BioMed Res. Int. 2020; 2020:7649157.

37. White A, Abbott H, Masi AT, Henderson J, Nair K. Biomechanical Properties of Low Back Myofascial Tissue in Younger Adult Ankylosing Spondylitis Patients and Matched Healthy Control Subjects. Clin. Biomech.2018; 57:67–73.

38. Hosmer DW, Lemeshow S, Sturdivant RX. Assessing the Fit of the Model. In Applied Logistic Regression; Wiley-Blackwell: Hoboken, NJ, USA. 2013; 153–226.

39. Manvelov LS. Vertebral pain syndromes. Atmosphere. Nervous Diseases. No. 3. 2004; 42-44.

40. Nizar AJ, Chen CK. Myofascial pain syndrome in chronic back pain patients. Korean J. Pain. 2011; 24:100–104.

41. Shorin GA. Kinesotherapy in traumatology and orthopedics: Textbook/GA. Shorin N.I. Erofeeva. – Chelyabinsk. 2001; 94.

42. Shevtsov AV. Technology for relieving myofascial pain syndrome using an individual corrector of disorders in the spine/Shevtsov AN. Fomin // Family health - XXI century: materials of the VI International. Scientific. Conf., May 1-3, 2002, Dubai, UAE. - Perm - Dubai, 2002; 166-167.

43. Shevtsov AV. The functional state of the visceral systems of the body of athletes with a non-drug method for correcting the muscle-tonic asymmetry of the paravertebral zone: Abstract of the thesis. Dr. Biol. Sciences: 03.03.01/ChGPU. – Chelyabinsk. 2012; 38.

44. Korolyova VV. Correction of biomechanical disorders in the spinal motion segments as a way to regulate cerebral blood flow in athletes-kickboxers/A.V. Shevtsov, V.V. Korolyova. Manual Therapy. - №1. - Obninsk, 2007; 67-73.