Relationship between defense styles and neurochemical variables of the hippocampus in patients with obsessive-compulsive disorder

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Abstract

Objectives: This study aims to assess the correlation between NAA (N-acetyl-l-aspartate), CHO (choline), and CRE (creatine) levels in the hippocampus regions of individuals suffering from obsessive-compulsive disorder (OCD) and defensive styles of the ego.

Methods: The study group was composed of twenty patients with OCD and twenty healthy controls. NAA, CHO, and CRE values in the hippocampal region using proton magnetic resonance spectroscopy (1H-MRS) were measured. Participants' defense styles were ascertained by administering the Defense Style Questionnaire-40.

Results: The patient group's NAA levels were considerably lower than the control group's on both sides of the hippocampus. The levels of CHO and CRE did not significantly differ between the two groups. The following statistically significant correlations were discovered: in the comparison group, there were negative correlations between the scores of mature defense styles and the right and left CHO levels, as well as between the immature defense mechanism scores and the right NAA levels in both the patient and control groups. In the patient group, there were also negative correlations between the left NAA values and the scores of mature defense styles.

Conclusion: OCD patients have lower levels of NAA in the hippocampus. To validate and extend the current findings, more research involving a greater sample size is required.

Keywords: MRS; defense syles; N-acetylaspartate; OCD; Choline

Significant Outcomes

- Mature defense styles are used less in OCD patients compared to healthy controls.
- OCD patients' right and left hippocampus have noticeably reduced NAA levels.
- Immature defense style scores and right NAA levels are negatively correlated.

Limitations

Our study had several limitations. Neurochemical changes should be taken cautiously due to the cross-sectional character of the study and require validation in additional research. Second, because the hippocampus was the only brain region examined in this study, it is impossible to generalize our findings to other brain regions. Third, our study may not have had the statistical ability to detect tiny changes in the metabolite concentrations due to the small sample size. Finally, since the defense mechanisms are unconscious processes and defense styles may be influenced by the severity of the illness, it should be acknowledged the limitations of the DSQ-40 as an instrument that evaluates defense mechanisms.

1. Introduction

With a lifetime prevalence of 2-3% worldwide, obsessive-compulsive disorder (OCD) is typified by intrusive unwanted thoughts, ideas, or images that cause distress, as well as the impulse to engage in ritualistic actions or mental activities in an attempt to ease this pain (Weissman et al., 1994). Several studies conducted over the past two to three decades have strongly suggested that anomalies in frontal—subsortical circuitry are implicated in the pathophysiology of OCD, even if the exact cause of the disorder is still up for debate. Expanding neuroimaging research could contribute to our daily understanding of the relationship between the neurobiological and clinical characteristics of OCD. Magnetic resonance spectroscopy (MRS), which is efficient in assessing in vivo different chemical metabolites of the human brain, has been used more and more in psychiatric research. According to this availability, a number of MRS investigations have looked into the brain metabolite levels of patients with mental illnesses. Perhaps the most distinctive and important feature of MRS is that it can provide in vivo neurochemical information about the brain's metabolic and information processing infrastructure that cannot be accessed by current methods and cannot be accessed by any other means. The physical principles underlying MRS differ in many ways from the fundamental physical principles underlying magnetic resonance imaging (MRI). Thanks to efforts to develop MRS, physical instrumentation, pulse sequences, and post-processing methods have been continuously improved, allowing reliable

measurement of an expanding group of important brain metabolites, facilitating our in vivo understanding of the neurobiological dynamics underlying psychiatric disorders. MRS is a safe, non-invasive method for studying brain chemistry and metabolism in vivo that is becoming more and more popular in neuroimaging research. Its main application has been in the measurement of metabolite concentrations in brain tissue, including myo-inositol, creatine (CRE; a marker of cellular energy), combined glutamate and glutamine, choline (CHO; a diagnostic of cell membrane turnover), and N-acetyl-l-aspartate (NAA; a marker of neuronal survival). It has been shown that N-acetyl aspartate (NAA) is primarily found in neurons. A decrease in NAA is thought to indicate neurological malfunction or the death of neurons and axons (De Stefano et al., 1995). Myelin degradation is associated with a rise in choline (CHO), a marker of the membrane phospholipids. One indicator of cellular energy is creatine-phosphocreatine or CRE. Abnormalities in frontostriatal-thalamic-cortical networks have been highlighted in the most recent functional and structural neuroimaging results. However, the hippocampus-amygdala complex is one of the other potential structures. Studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) highlighted hippocampal and amygdalar abnormalities, and the authors noted that the region may play a significant role in the pathophysiology of OCD (McGuire et al., 1994). However, structural research has indicated that changes in the structure of the hippocampus may contribute to the pathophysiology of obsessive-compulsive disorder (OCD) (Adler et al., 2000). Moreover, it has been demonstrated that medications that effectively treat OCD (such as serotonergic reuptake inhibitors and anti-anxiety medications) act on receptors in (Gonzalez et al., 1996; Nagy et al., 1979). Based on this correlation, we have assessed NAA, CHO, and CRE in the hippocampus regions of eighteen OCD patients and an equal number of healthy controls using proton magnetic resonance spectroscopy (1H-MRS). In that investigation, we found that individuals with OCD had lower hippocampal NAA/CRE and NAA/CHO ratios than did healthy control participants. Based on these findings, we hypothesized that OCD may be associated with neuronal degeneration (Atmaca et al., 2009).

The link and interplay between the neurobiological and psychoanalytic aspects of psychiatric diseases are so rarely examined in the literature. According to Willick's review of recent advances in neurobiological research during that period, the most pathognomonic feature of schizophrenia, the deficit or negative syndrome, may be linked to functional abnormalities in the brain's frontal lobe that are correlated with those conceptualized by psychoanalytic theories of withdrawal of libido and loss of mental representation (Willick,

1993). Concerning OCD, a limitation is so obvious. Albucher et al. looked at defense mechanism alterations in a brief report using the Defense Style Questionnaire following OCD patient therapy (Albucher et al., 1998). They discovered that following behavioral therapy, the patients showed significant improvements in the use of more adaptive defense mechanisms without changing the categories of maladaptive defense mechanisms. They concluded that contrary to what was previously thought, personality, as characterized by defense mechanisms, might be more responsive to brief behavioral treatment. The patients also showed remarkable decreases in Y-BOCS scores (Albucher et al., 1998). On the other hand, in one of the limited investigations, Katz proposed a 5-HT function model in which violent or libidinal impulses were regularly suppressed and filtered. This model seemed to at least partially align with Freud's concept of ego-id interactions, raising the possibility that a Freudian metaphor may be medically supported (Katz, 1991). In this issue, another effort has come from Cath et al. (Cath et al., 2001). They assessed self-rated and clinician-rated indices of psychopathology and personality in fifteen Gillette de la Tourette syndrome (GTS) without OCD subjects, twenty-one tics with (+) OCD individuals, fifteen OCD without tic subjects, and twenty-six controls (all without serotonergic medication). They also compared blood serotonin levels between OCD (without tics) and GTS. They found interaction effects on the neuroticism scores of the Eysenck Personality Questionnaire, platelet MAO, 5-HT, Y-BOCS severity, and trait anxiety (Cath et al., 2001).

As can be observed, all available historical data regarding the relationship between the neurobiological and psychoanalytic aspects of OCD nearly perfectly matches the previously provided information. In this context, our goal was to assess the correlation between the hippocampus regions of OCD patients' NAA, CHO, and CRE values and the defensive styles, which include immature, mature, and neurotic defenses.

2. Materials and methods

Participants

Patients with OCD diagnoses and healthy individuals made up the two age and sex-matched groups. There were twenty subjects in each group, all of them right-handed. The Turkish version of the Structured Clinical Interview for DSM-5 (SCID-5) was used to get the diagnoses from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Elbir et al., 2019). After age and gender adjustments, eighteen patients out of a total of thirty patients were included in our other study, which involved the patient group. The patients were recruited from the Department of Psychiatry at Firat University School of

Medicine and invited to have their proton magnetic resonance spectroscopy (1H-MRS) imaging performed (Atmaca et al., 2009). For the previous two weeks, they had either stopped taking their medicine or used no psychoactive substances at all. Twenty of the thirty patients accepted to be included in the study, out of the patients who could be reached by phone based on age and sex adjustments. Normal volunteers were selected from among the patients who were recruited by the hospital personnel and invited to participate in proton magnetic resonance spectroscopy (1H-MRS) imaging for the aforementioned investigation. In this study, a total of thirty controls and eighteen patients were included to adjust for gender and age. For the previous two weeks, they had either stopped taking their medicine or used no psychoactive substances at all. Twenty of the thirty controls—adjusted for age and sex—were phoned, and they all agreed. Every participant received comprehensive information about the study and signed consent forms indicating their voluntary participation in the research. Every research subject's right to confidentiality was rigorously upheld. The protocols adhered to were in compliance with the 1975 Helsinki Declaration, as amended in 1983.

Any past or present comorbid psychiatric disorder, ongoing medical issues, or alcohol or drug addiction during the six months before the study are among the exclusion criteria. In addition to not having any current medical issues, neurologic or psychiatric history, or use of psychoactive medicine within two weeks of the study, healthy control volunteers also did not have any DSM-5 Axis I disorders in themselves or a first-degree relative, as assessed by the SCID-5.

The severity of OCD was evaluated by using the Y-BOCS, while for examining the severity of depressive symptoms, the Hamilton Depression Rating Scale (HDRS) was used (Goodman et al., 1989; Hamilton, 1960). Defense styles of self were detected by using the Defense Style Questionnaire (DSQ)-40 (Andrews et al., 1993; Yılmaz et al., 2007).

MRI procedure

MRI and MRS images were acquired using a 1.5-Tesla GE Signa Excite high-speed scanner (Milwaukee, USA). A high-resolution structural image of the entire brain was created using sagittally acquired 3D spiral fast spin-echo high-resolution images (repetition time [TR] = 2000 ms, field of view [FOV] = 240 mm, echo time [TE] = 15.6 ms, flip angle = 200, bandwidth = 20.8, slice thickness = 2.4 mm, echo spacing = 15.6 ms, 8 echoes, matrix size = 240, resolution = 0.9375×0.9375×2.4 mm). On a sophisticated workstation computer, anatomic measurements were gathered using the GE Volume Viewer voxtool 4.2 application.

Standard anatomic atlases were used as a reference while drawing the hippocampus area (Duvernoy, 1999; Fitzgerald et al., 2000; Rosenberg et al., 2001).

We looked into the neurochemical indicators CHO, CRE, and NAA. NAA, CHO, and CRE peaks were automatically identified for every voxel. Three 18x18 metabolite signal arrays were created by integrating the signal strength surrounding the NAA, CHO, and CRE signal sites. Figure 1 displays the location of the sample magnetic resonance spectrum and hippocampus voxels.

Statistical analysis

The SPSS for Windows program, version 22.0 (SPSS, Armonk, NY: IBM Corp.), was used to conduct statistical analyses. One-way analysis of variance (ANOVA) was used to evaluate the differences between patients and controls for each metabolite ratio, defense style score, and hemisphere (left or right) as the within-group factor and diagnosis as the between-group component. To perform post hoc analysis, Tukey's honestly significant difference test was used. Using continuous data, group differences in demographic characteristics were calculated using an independent t-test. The chi-square test was used to evaluate categorical data between-group comparisons. The Spearman's correlation test was used to evaluate correlations.

3. Results

There was no difference in the intracranial volume (ICV), whole-brain volume, age, gender, or volumes of gray or white matter between the patients and the controls ($p>0.05$). Table 1 lists the clinical and demographic characteristics of OCD patients as well as age- and sex-matched healthy comparator participants. The mean HDRS scores were 7.35±3.44.

Based on the psychoanalytic function, defense mechanisms were divided into three groups; the mature factor scores for patients and control individuals were, respectively, 30.65±10.86 and 42.75±7.90 ($t=-4.028$, $df=38$, $P<0.001$). In comparison to healthy comparisons, the neurotic factor ratings in the patient group were substantially higher (47.40±13.09 for patients and 38.05±79.57 for control individuals, respectively) ($t=2.579$, $df=38$, $P=0.014$). Regarding the immature factor scores, the patients' scores (80.00±16.29) ($t=5.000$, $df=38$, $P<0.001$) were similarly statistically substantially higher than the control subjects' scores.

Table 1 lists the hippocampal metabolite concentrations of OCD patients and healthy controls. NAA levels of the right hemisphere of the OCD patients (6.97±0.89 mmol/kg)) were significantly lower than those of healthy controls (8.72±1.59 mmol/kg)) ($t = -4.284$, df=38, $P<0.001$). Likewise, the left hippocampus of the patient group showed a significantly lower NAA concentration compared to healthy controls (8.48±1.28 mmol/kg)for patients and 9.67±1.42 mmol/kg) for control subjects; $t=-2.779$, df=38, $P= 0.008$). CHO levels of right and left hippocampus of the OCD patients were statistically insignificantly higher when compared to those of healthy controls (for right hippocampus 2.72±0.33 mmol/kg and 2.58±0.28 mmol/kg for patients and controls, respectively, $P>0.05$; and for left hippocampus 2.82±0.37 mmol/kg and 2.69±0.40 mmol/kg for patients and controls, respectively, $P>0.05$). Concerning CRE levels, as can be seen for CHO values, no difference was found for both right and left hippocampus (for the right hippocampus, 6.52±0.95 mmol/kg and 6.48±0.94 mmol/kg for patients and controls, respectively, $P>0.05$; and for left hippocampus 6.23±1.23 mmol/kg and 6.78±1.27 mmol/kg for patients and controls, respectively, $P>0.05$). The patient group's mature defense style scores and appropriate NAA levels did not significantly differ from one another (P>0.05, Spearman's rho=0.251). Immature defense mechanism scores had a negative correlation with the right NAA levels (r=-0.381, P=0.049), but neurotic defense mechanism scores did not correlate with the right NAA values (r=0.054, P>0.05). There was a statistically significant correlation between the left NAA values and the mature defense scores (r=-0.374, P=0.05). On the other hand, no correlation was observed between the left NAA levels and the neurotic or immature defense style scores (r=--0.270, P>0.05 for the former and r=0.048, P>0.05 for the latter). Apart from the significant association between the right NAA values and the scores of immature defense styles (r=-0.526, P<0.009), no relationship was found for the right and left hippocampal NAA values and the defense style scores for the healthy comparison group (r=-0.049, $P>0.05$ for the right NAA-mature styles; r=0.021, $P>0.05$ for the right NAA-neurotic styles**;** r=-0.200, $P>0.05$ for the left NAA-mature styles**;** r=-0.028, $P>0.05$ for the left NAA-neurotic styles**;** and r=-0.045, $P>0.05$ for the left NAA-immature styles). Regarding CHO levels, no correlation was observed for the patient group between the appropriate CHO values and the immature, neurotic, or mature defense style ratings (r=0.214, $P>0.05$ for the mature styles; r=0.103, $P>0.05$ for neurotic styles; and r=-0.264, $P>0.05$ for immature styles). In the comparison group, there was no link found for the neurotic (r=-0.117, P>0.05) or immature (r=-0.176, P>0.05) defense styles, but there was a significant negative correlation between the right CHO levels and mature defense styles (r=-0.569, P=0.009). In the comparison group, left CHO values were also correlated

with the mature defense styles (r=-0.478, *P*=0.033) but not with the neurotic and immature styles (r=-0.117, *P*>0.05 for neurotic and r=-0.194, *P*>0.05 for the immature styles). No correlation was found between the right CRE levels and any defense styles in the patient group (r=0.143, *P*>0.05 for mature, r=0.324, *P*>0.05 for neurotic, and r=0.170, *P*>0.05 for the immature styles) and controls (r=-0.389, *P*>0.05 for mature, r=0.032, *P*>0.05 for neurotic, and r=-0.373, *P*>0.05 for the immature styles). The left CRE values were also not correlated with any defense styles in both groups (for the patient group, r=0.422, *P*>0.05 for mature, r=-0.267, *P*>0.05 for neurotic, and r=-0.079, *P*>0.05 for the immature styles; and for the control group, r=-0.232, *P*>0.05 for mature, r=-0.138, *P*>0.05 for neurotic, and r=0.004, *P*>0.05 for the immature styles).

4. Discussion

The present study may provide preliminary findings to be able to perform in the study area which consists of both neurochemical variables and psychoanalytical data. Even with all types of mental disorders, such as depression and schizophrenia, this field is remarkably novel. So, let us start the work by giving our important findings obtained from the present study: First of all, compared to healthy controls, OCD patients had lower mature defense style scores, but their neurotic and immature defense style scores were significantly higher in the patient group. Second, CHO levels in the right and left hippocampus of OCD patients were statistically insignificantly higher than those in the healthy control group, with no difference observed for CRE values. In contrast, NAA levels in the patient group's hippocampus were found to be significantly lower than those of the healthy controls. Thirdly, the following statistically significant correlations were found: (i) negative correlations between immature defense mechanism scores and right NAA levels both in the patient and control groups and between the left NAA values and the scores of mature defense styles in the only patient group (ii) concerning CHO values, for the comparison group, negative correlations between both the right and left CHO levels and the scores of mature defense styles. The first discovery that the OCD patients' scores for mature defense styles were lower than those of healthy controls, while the patient group's ratings for neurotic and immature defense styles were much higher than those of the healthy comparisons, was predicted. This finding is supported by Albucher et al. (Albucher et al., 1998). They examined how a 7-week group behavior therapy program affected the patients' defense mechanisms. They discovered that the patients' use of more adaptive defense mechanisms increased significantly after behavior therapy, while their Y-BOCS scores significantly decreased. However, there were

no significant changes in the categories of maladaptive defense mechanisms. These findings led the researchers to the conclusion that personality, as defined by defense mechanisms, may be more amenable to brief behavioral treatment than previously believed. Our finding revealing that CHO levels in the right and left hippocampus of OCD patients were statistically insignificantly higher than those in the healthy control group seems to be a finding that needs to be studied in larger samples. Greater sample can help us reach clearer results about statistical significance. Our findings of decreased right and left NAA may suggest decreased hippocampal neuronal density or at least neuronal dysfunction in patients with OCD, as noted in our previous study because NAA is thought to be a measure of neuronal integrity. However, it is unclear whether this decrease is due to a neurodegenerative process or to a trait characteristic of the disorder (Atmaca et al., 2009). However, in this investigation, we discovered that the CHO levels in the right and left hippocampus of OCD patients were statistically not substantially greater than those in the healthy controls. The left and right medial thalamus, but not the lateral thalamus, showed localized functional neurochemical marker changes, according to recent proton magnetic resonance spectroscopy imaging (1H MRSI) studies (Albucher et al., 1998; Steingard et al., 2000). Eleven pediatric OCD patients who had not received therapy were found to have thalamus concentrations of CHO that were considerably higher in another investigation. According to a paper, the CHO signal that appears may be a significant biomarker in particular neuropsychiatric illnesses, which confirms our earlier observation on potential neurodegeneration (Fitzgerald et al., 2000; Rosenberg et al., 2001). Nonetheless, additional research involving more individuals and across more brain regions is necessary to provide compelling proof. Our most significant finding, which is likely the most significant finding overall, is the negative correlations between the scores of immature defense mechanisms and the right NAA levels in both the patient and control groups, as well as the left NAA values and the scores of mature defense styles in the single patient group. This is significant because it implies that changes in brain NAA function as a functional neurochemical marker may be a potentially helpful neurobiological marker in identifying patients who use immature and mature defense styles, adding to our understanding of their pathophysiology. The use of immature defense styles for both the patient and control groups, and mature styles for the patient group, may be associated with this neurochemical consequence, given that, as previously mentioned, it is thought that NAA levels are sensitive to pathological processes affecting the neuronal functioning, and its reduction is considered to reflect a loss of neurons and axons and/or neural dysfunction. This is especially true given that all correlations found in the present

study for NAA are negative (Deicken et al., 2003). To confirm this finding, replication, and comparisons of NAA values with other mental conditions are required. Furthermore, to more fully identify the specificity of NAA alterations in the larger context of psychiatric disorders, additional research including numerous brain regions is needed. Further investigation is necessary to clarify the significance of the association between the scores of mature defense styles and the left NAA values in the single patient group, as well as the relationship between immature defense styles and the right NAA but not the left. Making some educated guesses about these hemispheric effects is challenging. First of all, we have to acknowledge that favorable outcomes could be a fabrication. Secondly, at this point, it is important to account for the meaning of lower NAA levels. Lower NAA indicates a loss of neurons and/or axons, a decrease in interneuronal neuropil, a metabolic malfunction of the neurons or axons, or complexity of these processes because NAA is only found in neurons and axons and not in glial cells (Deicken et al., 2003). Furthermore, it was suggested that reduced hippocampus NAA may result from cellular alterations brought on by stress and mediated by elevated glucocorticoid levels, rendering neurons more susceptible to ischemia and excitatory amino acid toxicity (McEwen, 1999). Conversely, alterations in neurotrophic or neuroprotective factors can be linked to a decrease in NAA levels. So, stress that may underlie the defense mechanisms seems to reduce the expression of brain-derived neurotrophic factor (BDNF) and lead to loss of hippocampal neurons (Lima Giacobbo et al., 1995). So, these disabling processes may lead to activating a cascade in the right hemisphere for immature defense styles and in the left hemisphere for mature ones. Our last finding that for the comparison group, negative correlations between both the right and left CHO levels and the scores of mature defense styles but not those of neurotic or immature styles led us to consider that CHO might be important in the neurobiochemical basis of the mature defense styles in healthy subjects. Our findings, especially regarding NAA, reveal the importance of neuronal survival in OCD and, suggest that treatment approaches that will increase NAA activity may be useful. Perhaps the search for treatment on this issue may be important in terms of satisfactory results.

There were various shortcomings in our study. Neurochemical changes should be taken cautiously due to the cross-sectional character of the study and require validation in additional research. Second, because the hippocampus was the only brain region examined in this study, it is impossible to generalize our findings to other brain regions. Third, our studies may not have had the statistical ability to detect tiny changes in the metabolite concentrations due to the small sample size. Finally, since the defense mechanisms are unconscious

processes and defense styles may be influenced by the severity of the illness, it should be acknowledged the limitations of the DSQ-40 as an instrument that evaluates defense mechanisms.

5. Conclusions

Together, our data indicate that OCD patients had reduces right and left hippocampal NAA and statistically insignificantly higher CHO levels in OCD patients than in healthy controls, with no discernible difference in CRE values. We also find negative correlations between the scores of immature defense mechanisms and right NAA levels in both the patient and control groups, between left NAA values and the scores of mature defense styles in the only patient group, and between both right and left CHO levels and the comparison group's scores of mature defense styles for CHO values. To validate and extend the current findings, more research involving a greater sample size is required.

6. Financial support

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7. Statement of interest

There is no conflict of interest between the authors.

8. Ethical statement

This study was approved by the Firat University School of Medicine Local Ethics Committee. All participants were informed in detail about the study and written consent documents were obtained stating that they wished to participate in the study voluntarily. Confidentiality was strictly taken into consideration for all study subjects. The procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 1983.

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Table 1. Clinical and demographic characteristics of normal control subjects and patients with OCD

	Patients with OCD (n=20)	Controls (n=20)	p
Age	28.4±4.3	29.2±4.1	>0.05
Gender (F/M)	12/8	12/8	>0.05
Age at onset (years)	22.9±4.4	-	
Handedness (right)	20	20	>0.05
Y-BOCS score	16.1±2.8	-	
Hippocampus Volume (mm^3)			
Left	2310.2±209.3	2620.4±321.6*	<0.05
Right	2298.4±191.5	2688.8±300.1*	<0.05
NAA (mmol/kg)			
Left	8.48±1.28	9.67±1.42 **	<0.01
Right	6.97±0.89	8.72±1.59 **	<0.01
CHO (mmol/kg)			
Left	2.82±0.37	2.69±0.40	>0.05
Right	2.72±0.33	2.58±0.28	>0.05

CRE (mmol/kg)			
Left	6.23±1.23	6.78±1.27	>0.05
Right	6.52±0.95	6.48±0.94	>0.05

No significant differences exist between groups in age, handedness, and gender composition.

ICV, Intracranial volume; Y-BOCS, Yale Brown obsession compulsion scale; NAA, *N*-acetyl aspartate; CHO, choline; CRE, creatine

*$p<0.05$

**$p<0.01$

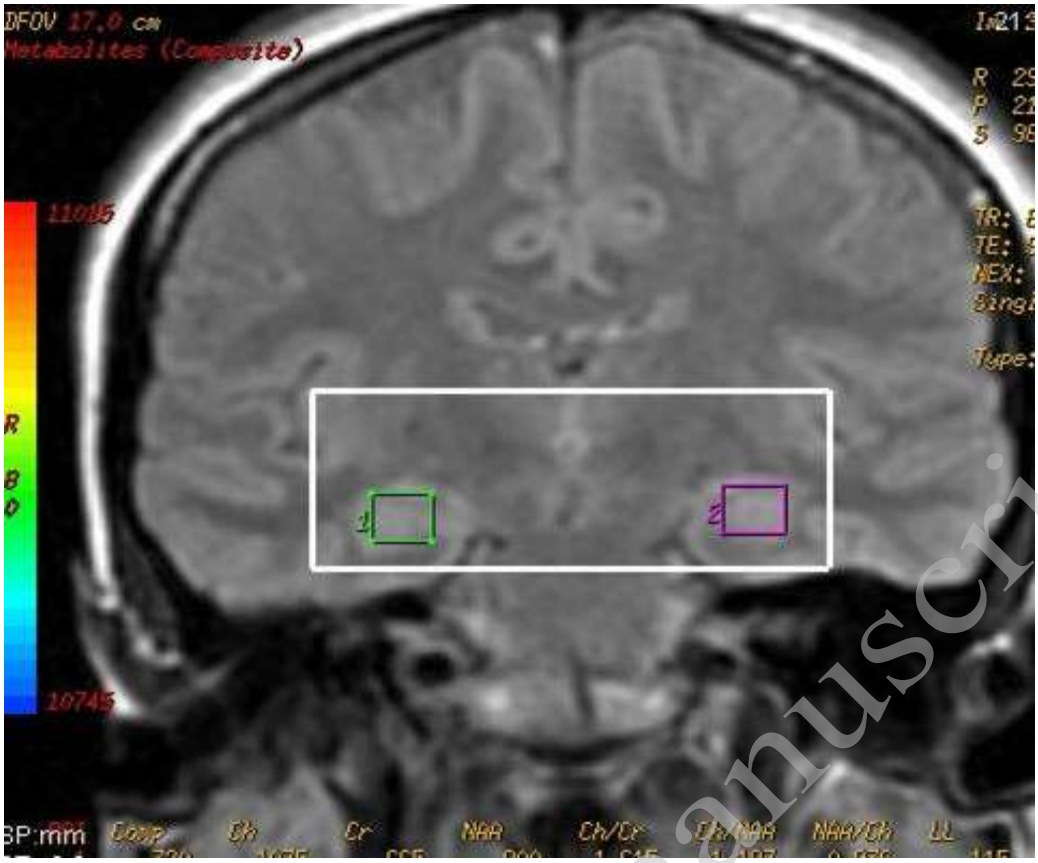

Figure 1. Position of hippocampal voxels and sample magnetic resonance spectrum