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Gray Matter Volume Deficits are Associated with Motor and Attentional Impairments in Adolescents with Schizophrenia

Sanjiv Kumra, MD, Manzar Ashtari, PhD, Jinghui Wu, BA, Donaya Hongwanishkul, MA, Tonya White, MD, Kelly Cervellione, MA, John Cottone, PhD, and Philip R. Szaszko, PhD
University of Minnesota, Department of Psychiatry, Minneapolis, MN; Feinstein Institute for Medical Research, Manhasset, NY; Zucker Hillside Hospital, Department of Psychiatry Research, Glen Oaks, NY; Albert Einstein College of Medicine, Bronx, NY

Abstract

Cognitive deficits have been well described in adolescents with schizophrenia, but little is known about the neuroanatomical basis of these abnormalities. The authors examined whether neuropsychological deficits observed in adolescents with schizophrenia were associated with cortical gray matter volume deficits. Volumes of the superior frontal gyrus, anterior cingulate gyrus and orbital frontal lobe were outlined manually from contiguous MR images and automatically segmented into gray and white matter in 52 patients and 48 healthy volunteers. Subjects received a comprehensive neuropsychological test battery, assessing five different functional domains: executive, attention, verbal memory, motor and sensory motor. Children and adolescents with schizophrenia were found to have lower total cortical and lower superior frontal gyrus gray matter volumes and lower test scores across all functional domains compared to healthy volunteers. Among patients, lower total cortical gray matter volume was associated with worse functioning on the attention and motor domains. Our findings point to widespread, perhaps multifocal, pathology as contributing to cognitive dysfunction in adolescents with schizophrenia.

Keywords

adolescents; schizophrenia; MRI; frontal lobes; cortical parcellation

Introduction

The prefrontal cortex is hypothesized to be an important site of dysfunction in schizophrenia and developmental changes in the connectivity of the prefrontal cortex may be critical for the appearance of the clinical features and cognitive impairments associated with the disorder (Lewis et al 2004). Post-mortem studies of adults with schizophrenia have reported the presence of structural abnormalities in the dorsolateral prefrontal cortex, but not in ventral regions of the prefrontal cortex (e.g., Broca's area 44) that are consistent with a reduction of neuropil (Selemon et al., 2003). This work was conducted, however, in adults with long-standing mental illness who had a substantial medication history, raising concerns about confounding variables that could partially account for these findings.

In adolescence there is considerable ongoing cortical development (Gogtay et al., 2004). Normative studies of adolescents have reported a postpubertal loss in cortical gray matter during adolescence, particularly in prefrontal areas involved in executive function, attention and motor coordination (Gogtay et al., 2004). Adolescents with early-onset schizophrenia

(EOS; onset of psychotic symptoms by 18 years of age) provide a unique subgroup of patients with schizophrenia to examine neurodevelopmental hypotheses of the disorder. For example, they may have a more severe form of the disorder and may be less affected by environmental factors that could potentially affect brain morphometry such as long-term antipsychotic exposure, substance abuse and chronic illness relative to their adult counterparts (Rapoport et al., 1999).

Anatomic brain magnetic resonance imaging abnormalities of the prefrontal cortex have been reported both in adolescents with childhood-onset schizophrenia (COS; onset of psychotic symptoms by age 13 years) (Rapoport et al., 1999) and adolescents with EOS (James et al., 2004). However, the findings have been inconsistent in that some studies have not reported group differences in the volume of the prefrontal cortex (Kumra et al., 2000; Sowell et al., 2000). This discrepancy may, in part, reflect methodological difficulties associated with using arbitrary internal landmarks and examining a large frontal region that may be insensitive to subtle neuromorphometric abnormalities (e.g., Kumra et al., 2000). To address these problems, we examined volumes of prefrontal subregions given that the frontal lobes are both structurally and functionally heterogeneous (Fuster 2002).

Few studies have examined the regional specificity of gray matter structural alterations in the prefrontal cortex of patients with COS or EOS. In one study that included 12 severely ill, treatment-refractory children with COS who were referred for an inpatient trial of clozapine examined the distribution of cortical gray matter deficits in the prefrontal cortex in adolescents with schizophrenia (Thompson et al., 2001). This study reported abnormalities primarily in dorsal frontal regions, but did not examine the neurocognitive correlates of these abnormalities. Also, the long-term effects of clozapine treatment on brain morphology remain unknown. Thus, additional studies in larger and more representative samples of adolescents with schizophrenia are needed.

In this study, we examined whether adolescents with EOS had volumetric abnormalities in discrete frontal lobe subregions representing the archicortical (superior frontal gyrus, anterior cingulate gyrus) and paleocortical systems (orbital frontal gyrus) (Sanides, 1969) as measured from MR images using methods for cortical parcellation adapted from Rademacher and colleagues (1992). Second, we examined relationships between prefrontal volumetric measures and neuropsychological test performance. Based on post-mortem (Selemon et al., 2003) and prior neuroimaging studies of adolescents with childhood-onset schizophrenia (Bertolino et al., 1998; Thompson et al., 2001) and adults with schizophrenia (Gur et al., 2000), we hypothesized that cortical gray matter deficits would be present in the superior frontal gyrus and anterior cingulate gyrus and that these would be associated with worse functioning on tests of attention and executive functioning in patients (Gur et al., 2000; Szeszko et al 2000).

Methods and Materials

Subjects

One-hundred children and adolescents (52 early-onset schizophrenia, 48 healthy comparison subjects) were included in this study. All patients had been treated with antipsychotic medication at the time of scanning including: quetiapine (n=4), olanzapine (n=8), risperidone (n=9), ziprasidone (n=2), clozapine (n=5) and aripiprazole (n=4). Four subjects were being treated with multiple antipsychotics. Six patients received prior treatment with conventional antipsychotics.

Recruitment and diagnostic procedures have been described in detail elsewhere (Kumra et al., 2004, 2005). In brief, patients were ascertained by means of screening consecutive

admissions to the inpatient units of three large children's psychiatric facilities. Psychiatric diagnoses were based on clinical and structured interviews (Kaufman et al., 1997) with children and their parents, and supplemented by chart review and discussion with treatment teams. Inclusion criteria included: (1) diagnosis of schizophrenia (n=34), schizoaffective disorder (n=16) or schizophreniform disorder (n=2) based on DSM-IV criteria; (2) age 10 to 19 years; (3) absence of a documented history of mental retardation prior to onset of psychotic symptoms; (4) absence of any history of a neurological disorder that could produce psychotic-like symptoms and (5) a negative toxicology screen at the time of scanning. Patients' mean age at onset of psychotic symptoms was 13.8 years (SD=3.0), and their mean duration of psychosis was 2.4 years (SD=2.0) at the time of the scan. Eighteen of 52 patients developed the onset of their psychotic symptoms prior to their thirteenth birthday and were classified as having childhood-onset schizophrenia.

Healthy volunteers matched for age, sex, and handedness were recruited from the community through medical clinics, churches, libraries, and community and recreation centers. Any physical or neurological disorder that could potentially affect brain development or a lifetime history of any Axis I psychiatric disorder in the probands was exclusionary. A diagnosis of schizophrenia or bipolar disorder in a first-degree relative was also exclusionary. Demographic characteristics for the entire subject pool are presented in Table 1. After complete description of the study to the subjects and their parents, written assent and informed consent was obtained. The Institutional Review Board at the North Shore-Long Island Jewish Health System approved this study.

Magnetic Resonance (MR) Imaging Procedures

The details of the MR imaging acquisition protocols (Kumra et al., 2005), image analysis methods and anatomical definitions for the measured brain regions (Szeszko et al., 1999, 2004) have been detailed elsewhere. In brief, MR exams were conducted at the Long Island Jewish Medical Center on a 1.5T GE Neuro Vascular Interactive (NV/I) system. MR images were acquired in the coronal plane using a three-dimensional spoiled gradient echo pulse sequence prepped with an inversion pulse of 600 msec, flip angle of 20 degrees, minimum TR and TE (default settings of the MR system), FOV = 220 mm, and matrix size of 256×192. This sequence produced 124 contiguous coronal slices (slice thickness=1.5mm) through the whole head with nominal in-plane resolution of 0.859×1.146 mm. For routine clinical purposes, an axial T2-weighted/proton density and FLAIR images were obtained to exclude visually detectable structural abnormalities on MRI scans.

Measurements were completed in the MEDx program (Sensor Systems, Inc., Sterling, Virginia) after alignment along the anterior and posterior commissures (AC-PC) for purposes of standardization. To remove laterality bias all 3D images were flipped randomly in the right-left axis. The action of rotation and the group status of the subjects were not annotated on any of the images. A well-trained and reliable operator completed all measurements (JW). The operator was blind to the subject's group membership during measurement. Using the Brain Extraction Tool (Smith, 2002), MEDx (Sensor Systems, Inc., Sterling, Virginia), and an in-house program, intracranial volume was calculated for each subject.

Measurement Delineation Criteria

Detailed methods for measuring the anterior cingulate gyrus, superior frontal gyrus and orbital frontal cortex have been described previously (Szeszko et al., 1999). The boundaries of the anterior cingulate gyrus were (anterior, posterior, ventral, dorsal): the tip of the cingulate sulcus, the connection of the superior and precentral sulci, the callosal sulcus, and the cingulate sulcus. The boundaries of the superior frontal gyrus were (anterior, posterior,

lateral, medial): the tip of the cingulate sulcus, the connection of the superior and precentral sulci, the superior frontal sulcus, and the cingulate sulcus. The boundaries of the orbital frontal region were (anterior, posterior, ventral, dorsal): anterior horizontal ramus of the Sylvian fissure, olfactory sulcus, anterior horizontal ramus (anteriorly) and inferior segment of the circular sulcus of insula (posteriorly), and the olfactory sulcus. Numbers for the orbital frontal region measurements vary because in some subjects the anterior horizontal ramus was not present (Ono et al., 1990) in either the left (8 patients, 1 healthy volunteer), right (5 patients, 6 healthy volunteers), or both hemispheres (5 patients, 1 healthy volunteer). Based on our previous work (Szeszko et al., 2004), frontal regions of interest were segmented by using a thresholding algorithm that was generated from gray-level histograms (Otsu, 1979). The interrater reliabilities (intraclass correlation coefficients) for each structure for 10 cases in each frontal lobe subregion for gray and white matter ranged from 0.90 to 0.97. The intraclass correlation for intracranial contents was 0.99.

Statistical Analyses

Group differences in demographic variables were examined using independent groups *t* tests and chi-square tests. All statistical analyses were performed using SPSS (version 14). Repeated measures analysis of covariance was used to compare brain structure volumes of frontal lobe subregions across groups. Analyses were conducted separately for the anterior cingulate, superior frontal gyrus, and orbital frontal lobe because of their neuroanatomical heterogeneity. For each of the 3 frontal regions the statistical model included group (patient versus healthy comparison subject) as the between subjects factor and tissue type (gray versus white) as the repeated measure. Intracranial volume was included as a covariate to control for nonspecific differences in brain size among individuals. Because the group-by-hemisphere interaction was not significant for any of the frontal lobe subregions, right and left hemisphere volumes were pooled for the analyses. In addition, given that the group-by-sex interaction was not significant for any of the frontal lobe subregions, sex was not included in the statistical models. Analyses of brain structure volumes were conducted using two-tailed tests with alpha set at 0.05.

A standardized neuropsychological test battery was administered as described previously (Rhinewine et al., 2005). Full-scale IQ scores were estimated from the Vocabulary, Similarities, Picture Completion, Block Design, Arithmetic and Coding subscales (Donders, 1997) of the Wechsler Intelligence Scale for Children -Third Edition (WISC-III; Wechsler, 1991), or the Similarities, Picture Completion, Block Design, Arithmetic, Coding, Information and Digit Span subscales (Axelrod, et al., 2001), of the Wechsler Adult Intelligence Scale -Third Edition (WAIS-III; Wechsler, 1997) for subjects over the age of 16. In addition to the intelligence scales, the test battery included the California Verbal Learning Test, Child Version or Adult Version (>17 years of age) (Delis et al., 1987), Fingertapping (Reitan, 1979), Grooved Pegboard (Matthews and Klove, 1964), the Wisconsin Card Sorting Test, Computer Version 2 (WCST; Heaton et al., 1993), and the Continuous Performance Test, Identical Pairs Version (CPT-IP; Cornblatt et al., 1997). Reliability and validity data for each test are provided in the appropriate references.

To reduce the possibility of Type I error due to the large number of test measures we formed 5 neuropsychological test domains based on theoretical reasons and principal components analysis: attention, executive, memory, motor, and sensory motor (Cervellione et al., 2007) similar to previous published work in adults with schizophrenia (Gur et al., 2000). For correlational analyses, z-scores for each of these domains (based on the test performances of the healthy controls included in this study) were created. Pearson's product-moment partial correlations ($p \leq 0.01$) were used to test relationships between brain structure volumes that differed between patients and controls and indices of neuropsychological test performance.

Results

Adolescents with schizophrenia and comparison subjects did not differ from each other significantly in distributions of age, handedness, race, or parental socioeconomic status ($p > 0.05$). For descriptive purposes, mean unadjusted brain structure volumes for the patient group and healthy comparison subjects are presented in table 2, along with the 95% confidence intervals for the difference between group means.

Compared to healthy volunteers, patients differed significantly in terms of overall cortical gray matter volume ($t = -2.95$, $df = 98$, $p = 0.004$), but showed no significant abnormality in white matter. The main findings that distinguished the groups in terms of the frontal lobe subregions were a significant group-by-tissue type interaction for the superior frontal gyrus ($F_{1,97} = 4.11$, $p = 0.045$) and anterior cingulate gyrus regions ($F_{1,97} = 4.58$, $p = 0.035$). Follow-up analyses revealed that patients had significantly less gray matter in the superior frontal gyrus ($t_{1,98} = -2.23$, $p = 0.028$), but not in the anterior cingulate gyrus region ($t_{1,98} = -2.23$, $p = 0.09$) compared to healthy subjects. Neither the main effect of group nor group-by-tissue type interaction were statistically significant for the orbital frontal lobe region (all $p > .05$). We also investigated group-by-age interactions for the frontal subregions, but none of these was statistically significant (all $p > .05$).

As expected, patients had lower neuropsychological test performance across all 5 domains of cognitive function (Table 3). Correlations of brain structure volumes and individual neuropsychological domains are provided in Table 4. There were significant associations of less total cortical gray matter volume with worse attention ($r = 0.39$, $n = 45$, $p = 0.008$) and motor ($r = 0.44$, $n = 45$, $p = 0.003$) functioning.

To examine the possible confounding effect of antipsychotic medication on brain morphometric measures, we tested for possible associations between brain volumetric measures where we found significant group differences and measures of prior medication exposure. We did not find a significant relationship between brain volume measures (i.e., total gray, superior frontal total gray matter) and the following potential confounding variables at time of scan: antipsychotic medication (chlorpromazine equivalents), lifetime chlorpromazine equivalents, duration of psychosis, and symptom ratings ($p > 0.05$).

Discussion

Adolescents with schizophrenia were found to have a robust cortical tissue volume deficit selective to gray matter as well as a large generalized neurocognitive deficit of 1 to 1.5 SDs across multiple domains compared to healthy volunteers. Using well-defined and reliable methods for identification of cerebral sulci to subdivide the frontal lobes into functionally homogeneous subregions, a similar pattern of gray as opposed to white matter volumetric deficits was observed in the superior frontal gyrus and anterior cingulate regions. Post-hoc analyses revealed, however, that gray matter volumes were significantly lower in patients in the superior frontal gyrus region only.

This pattern of results, particularly the involvement of gray matter as opposed to white matter, is generally consistent with prior anatomic brain MRI studies of adolescents with childhood-onset schizophrenia (Rapoport et al., 1997; Thompson et al., 2001). The finding of a cortical gray matter deficit in the superior frontal gyrus region is also in keeping with a multislice proton magnetic resonance spectroscopic imaging study that found that adolescents with childhood-onset schizophrenia had smaller than normal regional N-acetylaspartate relative signals suggesting neuronal damage or malfunction in the dorsolateral prefrontal cortex (Bertolino et al., 1998). Together, these neuroimaging data in adolescents with schizophrenia are consistent with the post-mortem studies in adults with

schizophrenia that have found increased neuronal density and reduced neuropil in the cerebral cortex of patients (Selemon and Goldman-Rakic, 1999). It has been hypothesized that this lack of exuberance and redundancy of connections in patients with schizophrenia would represent a barrier for the brain to function at full capacity (Selemon and Goldman-Rakic, 1999).

The volumetric findings from the frontal lobe subregions observed in this study in adolescents with schizophrenia appear to have some diagnostic specificity because psychotropic drug-naïve children with obsessive-compulsive disorder were found to have more total gray matter in the anterior cingulate gyrus but not the superior frontal gyrus region compared to healthy volunteers using the same methodology (Szeszko et al., 2004). However, similar findings of prefrontal gray matter volumetric deficits have been reported in the left dorsolateral prefrontal cortex using voxel-based morphometry in euthymic children and adolescents with narrow-phenotype bipolar disorder relative to controls (Dickstein et al., 2005). These data could suggest that reduced dorsolateral prefrontal cortical gray matter volume may be a key region in the pathophysiology of childhood-onset psychotic disorders (ie., schizophrenia and bipolar disorder). Further research is needed, however, to delineate the precise manner in which prefrontal dysfunction contributes to the pathophysiology of schizophrenia and bipolar disorder in both children and adolescents.

The observed global gray matter volume deficit was significantly correlated with motor and attentional impairments in patients. Contrary to what we expected, however, the attentional and executive function domain scores did not show the expected relationships with gray matter volumes in the superior frontal gyrus region. These data would favor a hypothesis that a disruption of widespread cortical networks underlies the neuropsychological deficits in adolescents with schizophrenia, similar to what has been observed in adults with chronic schizophrenia (Sullivan et al., 1996). It may also be noteworthy that motor and attentional impairments are considered to be risk indicators for the development of schizophrenia based on data from genetic high-risk studies (Kimling et al., 2000).

There are several possible explanations for the group volumetric differences in total and superior frontal gyrus gray matter volume that we observed. The lower gray matter volume in patients may reflect an interaction between the underlying pathophysiological processes involved in EOS and normative maturational changes affecting frontal lobe gray matter during adolescence (Gogtay et al., 2004). The volumetric deficits in cortical gray matter in the superior frontal gyrus region are compatible with findings of postmortem studies in schizophrenia that have reported a decrease in cortical neuropil relative to tissue from healthy controls (Selemon and Goldman-Rakic, 1999), perhaps driven by excessive synaptic pruning in schizophrenia during adolescence (Gogtay et al., 2004). On the other hand, there is increasing evidence from animal (Dorph-Petersen et al., 2005) and clinical studies (Lieberman et al., 2005) that exposure to antipsychotic medications, particularly conventional antipsychotics, is associated with a reduction in cortical gray matter volume particularly in the frontal and parietal areas possibly secondary to alterations in blood flow (Miller et al., 1997) and/or brain metabolism (Molina et al., 2003). Parameters of prior medication exposure were not associated with either total or superior frontal gyrus gray matter volumes, however, and the majority of adolescents were treated only with second-generation antipsychotic medications.

There were several study limitations that should be acknowledged. Due to the cross-sectional design we were not able to examine progression of structural brain matter abnormalities in adolescents with schizophrenia. In addition, all of the patients included in this study had received prior antipsychotic treatment and the effects of second-generation antipsychotics on adolescent brain development for the particular brain volumetric measures

included in this study remain unknown. In addition, replication of these findings in other groups of patients exposed to antipsychotic medications are needed to examine whether the observed volumetric deficits are specific to schizophrenia and/or are seen in other adolescents with psychotic disorders. Although the sample size of this study is rather modest, early-onset schizophrenia is a relatively rare variant of the disorder perhaps accounting for 5% of all cases of schizophrenia (Cannon et al., 1999) and the sample size included in this report is comparable to other published MRI volumetric studies in this population (James et al., 2004; Thompson et al., 2001).

In sum, our data support the hypothesis of gray matter deficits and generalized neuropsychological dysfunction in the pathophysiology of EOS. Investigation of structure-function relations involving total cortical gray matter deficits and worse attention and motor functioning support the hypothesis of widespread pathology as a contributing factor to cognitive dysfunction in EOS.

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Table 1
Subject Demographics

Sample Characteristic	Healthy Comparison Subjects (N = 48)		Schizophrenia Spectrum Disorders (N = 52)	
Sex (M, F)	30	18	29	23
Mean Age (years, SD)	16.38	2.91	16.02	2.15
Handedness (dextral, nondextral) ^a	44	4	48	4
Parental social class (high, low) ^b	45	1	42	8
Race (Caucasian, Non-caucasian)	13	35	23	29

^aThe patient group had 1 ambidextrous person

^bHollingshead Redlich Score (Hollingshead and Redlich, 1958) where 1 = highest and 5 = lowest are dichotomized into High (1, 2, 3) and Low (4, 5)

Table 2
Unadjusted Brain Region Volumes in Early-Onset Schizophrenia Compared to Healthy Adolescents

Brain Regions	Volume (cm³)						Analyses
	Healthy Comparison Subjects (N=48)		Schizophrenia Spectrum Disorders (N=52)				
	Mean	SD	Mean	SD	95% CI of Difference Between Groups	t(98)	
Whole Brain							
Gray matter total	740.78	70.13	692.61	84.5	16.69 to 79.64	2.95	.004
White matter total	462.94	50.33	469.83	74.95	-31.90 to 18.12	-0.55	.57
Superior Frontal Gyrus							
Gray matter	30.87	4.13	29.17	3.79	0.19 to 3.28	2.23	.03
White matter	24.99	3.77	24.09	3.40	-0.42 to 2.40	1.39	.17
Anterior Cingulate Gyrus							
Gray matter	7.00	1.75	6.43	1.23	-0.09 to 1.12	1.69	.10
White matter	4.88	1.28	4.55	.95	-0.15 to 0.73	1.29	.20
Orbital Frontal Gyrus ^a							
Gray matter	10.17	2.83	9.72	2.38	-0.85 to 1.59	.61	.55
White matter	7.96	2.07	7.64	1.95	-0.71 to 1.16	.48	.63

^aThere were total (right + left hemisphere) volumetric data available for 34 patients and 40 healthy controls

Table 3
Neuropsychological Test Scores

Domain and Individual Test Variables	Patient Group		Healthy Control Group	
	Mean (SD)	N	Mean (SD)	N
Verbal Memory	-1.14 (1.03)	48	0.00 (0.96)	40
CVLT, total trials 1-5	38.79 (13.20)	48	53.00 (9.57)	40
CVLT, delayed recall	8.33 (3.08)	48	11.35 (2.82)	40
Attention	-1.40 (1.07)	46	0.01 (0.79)	35
WISC/WAIS-III				
Digit Span (scaled)	7.51 (3.35)	51	10.05 (2.39)	41
Arithmetic (scaled)	6.80 (3.30)	51	11.56 (3.10)	41
CPT-IP, d-prime (2-digit)	2.14 (1.04)	46	3.17 (0.57)	37
Executive/Reasoning	-1.34 (1.89)	44	0.17 (1.33)	40
WCST, perseverative resp	96.45 (76.31)	48	57.36 (27.56)	41
Sensory Motor	-1.5(1.5)	49	0.00 (0.43)	39
Groove Pegboard				
Dominant	106.04 (38.24)	49	69.97 (11.24)	39
Nondominant	125.82 (51.88)	49	77.33 (14.05)	39
Motor	-0.55	49	0.00 (0.92)	39
Finger Tapping				
Dominant	41.25 (10.02)	49	46.16 (9.15)	39
Nondominant	37.56 (8.94)	49	42.17 (8.09)	39
Premorbid Functioning	-0.89 (1.20)	48	0.00 (1.00)	40
WRAT-3 reading score (scaled)	93.81 (15.85)	48	105.55 (13.23)	40

Table 4

Structure/Function Correlations within Patient Group

Brain Region	Verbal Memory	Attention	Executive/Reasoning	Sensory Motor	Motor
Gray Matter Total					
Whole brain	0.13	0.39**	-0.08	-0.01	0.42**
Superior Frontal Gyrus	0.19	-0.02	-0.07	0.03	0.15
Anterior Cingulate Gyrus	-0.07	0.02	0.24	0.02	-0.10
Orbital Frontal Gyrus	0.16	0.19	0.11	0.13	-0.07
White Matter Total					
Whole brain	-0.17	-0.09	0.29	0.29*	0.23
Superior Frontal Gyrus	0.03	-0.12	0.07	0.07	0.26
Anterior Cingulate Gyrus	-0.13	-0.05	0.33*	0.12	0.01
Orbital Frontal Gyrus	0.08	0.12	0.15	0.21	0.03

*
p < 0.05**
p < 0.01