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The 5-HT$_{2A}$ receptor and serotonin transporter in Asperger's Disorder: a PET study with [^{11}C]MDL 100907 and [^{11}C]DASB

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Abstract

Evidence from biochemical, imaging, and treatment studies suggest abnormalities of the serotonin system in autism spectrum disorders, in particular in frontolimbic areas of the brain. We used the radiotracers [^{11}C]MDL 100907 and [^{11}C]DASB to characterize the 5-HT$_{2A}$ receptor and serotonin transporter in Asperger's Disorder. 17 individuals with Asperger's Disorder (age = 34.3 ± 11.1 yr) and 17 healthy controls (age = 33.0 ± 9.6 yr) were scanned with [^{11}C]MDL 100907. Of the 17 patients, eight (age = 29.7 ± 7.0 yr) were also scanned with [^{11}C]DASB, as were eight healthy controls (age = 28.7 ± 7.0 yr). Patients with Asperger's Disorder and healthy control subjects were matched for age, gender, and ethnicity, and all had normal intelligence. Metabolite-corrected arterial plasma inputs were collected and data analyzed by 2 tissue-compartment modeling. The primary outcome measure was regional binding potential BP$_{ND}$. Neither regional [^{11}C]MDL 100907 BP$_{ND}$ nor [^{11}C]DASB BP$_{ND}$ were statistically different between the Asperger's and

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Statement of Interest

Dr. Girgis has received research support from Janssen and Lilly through APIRE and a travel stipend from Lilly, Forest, and Elsevier Science through the Society of Biological Psychiatry. In the last three years, Dr. Slifstein has served as a consultant for Amgen, Inc. and GlaxoSmithKline, and has received research support from Intracellular Therapies, Inc. Dr. Wasserman, Ms. Pepa, Dr. Xu, and Dr. Laruelle have nothing to disclose. Over the last three years, Dr. Kolevzon has received research support from Neuropharm, Bristol-Myers Squibb, Johnson & Johnson, and Curemark, LLC. Dr. Frankle is a consultant for Sepracor, Inc. Dr. Anagnostou has non-paid consultations to Neuropharm and Proximagen. In the last two years, Dr. Abi-Dargham has been a speaker for BMS-Otsuka and Sunovion, received research support from Forest and GSK, and served as a consultant for Lundbeck and Boehringer Ingelhein. Dr. Hollander has applied for patents for the use of oxytocin and memantine in autism.

healthy subjects. This study failed to find significant alterations in binding parameters of 5-HT_{2A} receptors and serotonin transporters in adult subjects with Asperger's Disorder.

Keywords

autism spectrum disorders; 5-HT_{2A} receptor; Asperger's Disorder; positron emission tomography; serotonin transporter; serotonin

1. Introduction

Asperger's Disorder is a pervasive developmental disorder (PDD), or autism spectrum disorder (ASD), characterized by impairments in social interactions and restricted, repetitive patterns of behavior, interest, and activity (American Psychiatric Assocation, 1994). In order to meet DSM-IV criteria for Asperger's Disorder, in contrast to Autistic Disorder, clinically significant delays in language development should not be present (American Psychiatric Assocation, 1994), although diagnostic criteria for ASD are currently undergoing revision for the DSM-V.

Findings from challenge, treatment, biochemical, and imaging studies have suggested deficiencies in the serotonin system in ASD. In particular, early support for a role of serotonin in ASD came from challenge studies. Administration of fenfluramine, an indirect serotonin agonist, to seven adults with autism resulted in blunted prolactin release compared to controls subjects, suggesting a decreased responsivity of the serotonin system (McBride et al., 1989). When 20 adults with autism were exposed to tryptophan depletion, they demonstrated a global worsening of symptoms as well as an exacerbation of behaviors such as whirling, flapping, pacing, banging and hitting themselves, rocking and anxiety (McDougle et al., 1996).

The most direct evidence to date of central nervous system serotonergic abnormalities in autism comes from imaging studies. Chugani and colleagues used positron emission tomography (PET) imaging and the radiolabelled alpha[^{11}C]methyl-L-tryptophan to demonstrate decreased synthesis of serotonin in frontal cortex and thalamus (Chugani et al., 1997). In a single photon emission computed tomography (SPECT) study using [^{123}I]-5-I-R91150 of eight adults with Asperger's Disorder, decreased 5-HT_{2A} receptor availability in patients compared to controls was observed in several cortical regions (Murphy et al., 2006). Similar results were found in a PET study using [^{18}F]setoperone to label 5-HT_{2A} receptors in parents of children with ASD (Goldberg et al., 2009). Makkonen et al. (Makkonen et al., 2008) used SPECT and the radiotracer [^{123}I] nor-beta-CIT to study the serotonin transporter (SERT) in 15 children and adolescents with autism and 10 non-autistic comparison subjects. They found decreased SERT capacity in medial frontal cortex, consistent with previous reports of decreased capacity to synthesize serotonin in autism (Makkonen et al., 2008).

In this study, we used PET and the radiotracer [^{11}C]MDL 100907 to compare the availability of the 5-HT_{2A} receptor in adults with Asperger's Disorder to healthy control subjects. [^{11}C]MDL 100907 is selective for the 5-HT_{2A} receptor (versus 5-HT_{2C}) (Lundkvist et al., 1996) and therefore has advantages over other tracers targeted towards this receptor. Initial characterization in humans confirmed the excellent properties of [^{11}C]MDL 100907 as a PET radiotracer to label 5-HT_{2A} receptors in humans (Ito et al., 1998; Talvik-Lotfi et al., 2000). We hypothesized that individuals with Asperger's Disorder would demonstrate greater availability of the5-HT_{2A} receptor in cortical regions, as a compensatory response to the central nervous system deficiency observed in ASD.

In a subset of patients, we used PET and the radiotracer [^{11}C]DASB (Houle et al., 2000; Wilson et al., 2000) to compare the availability of the SERT in adults with Asperger's Disorder and healthy control subjects. [^{11}C]DASB has excellent selectivity for the SERT, and appropriate quantitative methods have been developed for use with this tracer (Frankle et al., 2006). We hypothesized that there would be decreased availability of SERT in individuals with Asperger's Disorder.

2. Methods

2.1. Subjects

All procedures were approved by Institutional Review Boards at both the New York State Psychiatric Institute and Mount Sinai School of Medicine. Informed consent was obtained for all subjects after a complete description of study procedures.

Individuals with Asperger's Disorder (N=17) were recruited as per *DSM-IV* criteria (American Psychiatric Association, 1994) from a larger study of fluoxetine treatment for ASD. All subjects who participated in this study did so before receiving fluoxetine as part of the larger study. Inclusion criteria were: age 18 to 50, IQ>85, a capacity to give informed consent, and an unremarkable brain MRI. Patients did not take psychotropic medications for at least 21 days before the study (3 months for fluoxetine, one year for depot neuroleptic drugs). Exclusion criteria included: any other lifetime axis I disorder, including alcohol or substance abuse or dependence (with the exception of nicotine), history of violent or dangerous behavior, pregnancy, past or present medical or neurological conditions, including seizure disorder, and presence of metallic objects in the body precluding MRI scan.

Healthy control subjects (N=17) were recruited as a comparison group. Inclusion criteria included: age 18 to 50 years, absence of current or lifetime psychiatric diagnosis, absence of a psychotic illness or mood disorder or pervasive developmental disorder in any first degree relative, ability to give written informed consent, and an unremarkable brain MRI. Exclusion criteria included: pregnancy, past or present significant medical or neurological condition, and presence of metallic objects in the body precluding an MRI.

2.2. Radiochemistry

[^{11}C]MDL 100907 and [^{11}C]DASB were prepared according to the modified procedures from Lundkvist et al. (Lundkvist et al., 1996) and Wilson et al (Wilson et al., 2000), respectively, using their desmethyl precursors and [^{11}C]methyl triflate.

2.3. PET Scanning

PET scans with [^{11}C]MDL 100907 and [^{11}C]DASB were acquired on the same day whenever possible, so that only one arterial catheter placement was needed. Of the 17 patients who received [^{11}C]MDL 100907, eight were also scanned with [^{11}C]DASB, as were eight healthy controls. Catheters were inserted into an antecubital vein for radiopharmaceutical injection and into the radial artery of the other arm (nondominant side) for collection of arterial blood samples. This was done following Allen's test and the administration of local anesthesia with lidocaine. A polyurethane head immobilization system was used (Soule Medical, Tampa, FL) to reduce head motion during scanning (Mawlawi et al., 2001a).

For both compounds, the maximal injected dose was 20 mCi. PET imaging was performed on the ECAT EXACT HR+ (Siemens Medical Systems, Iselin, NJ). Following completion of a transmission scan (10 min), the radiotracer was administered as an i.v. bolus over 45

seconds by a computer-operated pump, synchronized with the camera. Emission data were collected in the 3D mode as successive frames of increasing duration. Total acquisition time for [^{11}C]MDL 100907 was 120 minutes for 14 of the scans and 90 minutes for the remaining 20. To ensure the comparability of these data, data from the 120 minute [^{11}C]MDL 100907 scans were truncated to 90 minutes. Total acquisition time for [^{11}C]DASB scans was 100 minutes. Subjects were allowed to relax out of the gantry for 60 minutes between sessions.

2.4. Input Function Measurement

Arterial access was available for all subjects. Following radiotracer injection, arterial samples were collected and radioactivity measured as described previously (Abi-Dargham et al., 1999). Six plasma samples (collected at 2, 16, 30, 50, 70, 90 minutes) were processed by HPLC to measure the fraction of plasma radioactivity representing unmetabolized parent tracer for both radioligands. A three-exponential-fitted input curve for kinetic analyses was generated as described previously (Abi-Dargham et al., 1999). Total input function clearance was computed as the ratio of the injected activity to the total area under the curve of the input function (CL, L/hr). The fraction of radiotracer in arterial plasma not bound to protein was measured by adding a small aliquot of radiotracer to a separate sample of arterial plasma, using an ultrafiltration method (f_P, unitless).

2.5. MRI Scans

MRI scans were acquired orthogonal to the anterior commissure - posterior commissure (AC-PC) plane on GE 1.5 T or 3 T Signa Advantage systems at the New York State Psychiatric Institute. Following a sagittal scout, performed to identify the AC-PC plane (1 min), a transaxial T1-weighted sequence with 1.5 mm slice thickness orthogonal to the AC-PC was acquired over the whole brain with the following parameters: 3-dimensional SPGR (Spoiled Gradient Recalled Acquisition in the Steady State), TR 34 msec, TE 5 msec, flip angle of 45 degrees, slice thickness 1.5 mm, zero gap, 124 slices, FOV 22 × 16 cm, with 256 × 192 matrix, reformatted to 256 × 256, yielding a voxel size of 1.5 mm × 0.9 mm × 0.9 mm, time of acquisition: 11 min.

2.6. PET Data Analysis

Images were reconstructed by filtered-backprojection to a 128 × 128 × 63 matrix (voxel size of 1.7 × 1.7 × 2.4 mm) with attenuation correction using the transmission data and a Shepp 0.5 filter. Reconstructed image files were then processed with the image analysis software MEDx (Sensor Systems, Inc.). All frames were realigned to a frame of reference, using the realignment tool in the SPM2 software package (Ashburner and Friston, 1997). After frame-to-frame registration, the 21 frames were summed to generate a single data volume, which was co-registered to the MRI dataset using maximization of mutual information, as implemented in SPM2. The spatial transformation derived from the summed PET registration procedure was then applied to each registered frame. Thus, each PET frame was re-sampled in the coronal plane to a voxel volume of 1.5 × 0.9 × 0.9 mm^3.

Region of interest (ROI) and region of reference (cerebellum) boundaries were drawn on the MR image according to previously described criteria (Abi-Dargham et al., 2000; Mawlawi et al., 2001b).

Data were analyzed using a two-tissue compartment model (2TCM) with arterial input function (C_P). The total regional distribution volume (V_T, mL cm^{-3}), defined as the ratio of the total tracer concentration in the region (C_T) to the metabolite corrected plasma concentration at equilibrium (Innis et al., 2007), was derived from rate constants estimated by nonlinear least-squares fitting of the data to the compartment model. BP_{ND} was estimated indirectly in each ROI according to the formula $BP_{ND} = V_T(ROI)/V_T(cerebellum) – 1$.

BP_{ND} is equivalent to $f_{ND}B_{MAX}/K_D$ where B_{MAX} (nM) is the concentration of receptors or transporters available for binding, K_D (nM) is the equilibrium dissociation constant of the radiotracer for the receptor or transporter and f_{ND} is the free fraction of free + non-specifically bound radiotracer in brain. Analyses were performed using in-house developed software on the Matlab programming platform (Mathworks, Natick, MA).

2.7. Statistical Analysis

Group means are presented as average ± standard deviation (SD). We do not report data from ROIs for which BP_{ND} was <0.5, which indicates an extremely low concentration of either the 5-HT_{2A} receptor or SERT. A linear mixed model across all cortical regions for [^{11}C]MDL 100907 with regional BP_{ND} as the dependent variable and ROI as repeated measure was performed to test for a global effect of a diagnosis of Asperger's Disorder on BP_{ND}. A 2-tailed probability value of 0.05 was selected as the significance level.

3. Results

3.1. [^{11}C]MDL 100907 Demographic and Scan Characteristics

No significant differences were observed between the Asperger's Disorder and healthy control groups on any demographic or scan variable, including age, gender, ethnicity, injected activity, specific activity, injected mass, f_P, CL, or cerebellar V_T (Table 1).

3.2. [^{11}C] MDL 100907 Receptor Availability

Group mean [^{11}C]MDL 100907 BP_{ND} was larger in the Asperger's Disorder group in every ROI, but these differences failed to reach significance (Table 2). We also performed a linear mixed model analysis to investigate the possibility of a global effect; this analysis also failed to reach significance (F=1.375; p=0.25). No volumetric differences were observed between the two groups in any of the ROIs.

3.3. [^{11}C]DASB Demographic and Scan Characteristics

No significant differences were observed between the Asperger's Disorder and healthy control groups on any demographic or scan variable, including age, gender, ethnicity, injected activity, specific activity, injected mass, f_P, CL, or cerebellar V_T (Table 3).

3.4. [^{11}C]DASB Receptor Availability

Group means of [^{11}C]DASB BP_{ND} were smaller in the Asperger's Disorder group in every ROI, but these differences failed to reach significance (Table 4).

4. Discussion

The present study compared the availability of the 5-HT_{2A} receptor in the brains of adults with Asperger's Disorder and matched healthy controls. 5-HT_{2A} receptor availability was numerically, but not statistically, greater in the Asperger's Disorder group in every ROI. In addition, there were no significant differences in availability of the SERT in a subset of patients when compared to healthy controls, although individuals with Asperger's Disorder had numerically decreased SERT availability in every ROI.

This study failed to demonstrate significant differences in 5-HT_{2A} receptor availability in patients with Asperger's Disorder and matched healthy controls. Based on results of treatment, imaging, biochemical, and challenge studies that suggest deficiencies of central nervous system serotonin in ASD, the study hypothesis was that 5-HT_{2A} receptor availability might be increased in patients with Asperger's Disorder, reflecting a

compensatory upregulation of these receptors. While the group average of [^{11}C]MDL 100907 BP_{ND} was indeed found to be numerically increased in patients in every ROI, this increase failed to reach statistical significance. Since the regional data were suggestive of a global effect, we performed a mixed model analysis to explore the possibility that the difference in 5-HT_{2A} receptor availability was global. However, group differences in this analysis were also non-significant.

These results are discrepant with one previous SPECT study of the 5-HT_{2A} receptor in ASD (Murphy et al., 2006). In the previous study, Murphy et al. used the radiotracer [^{123}I]-5-I-R91150 with eight adults with Asperger's Disorder and found decreased 5-HT_{2A} receptor availability in patients compared to 10 healthy controls in anterior and posterior cingulate, frontal and superior temporal cortex bilaterally, and in the left parietal cortex (Murphy et al., 2006). Differences between the previous study and the current results may be the result of differences in sample size, as well as the use of SPECT versus PET. PET generally has greater spatial resolution than SPECT, is more sensitive, and provides for more accurate attenuation correction. An additional strength of our study is the use of arterial input with full kinetic analysis. The contribution of each of these differences to the discordant findings is unclear.

The primary limitation of our study of the 5-HT_{2A} receptor is that we used adults with Asperger's Disorder with normal intellectual functioning, as opposed to children, individuals with other ASDs (e.g., autistic disorder), or individuals with ASD and cognitive delays. It would be interesting to investigate the 5-HT_{2A} receptor in these other groups of individuals with PDD. However, ethical concerns preclude the administration of radioactivity to children and adolescents (i.e., due to their age), and to individuals who are more severely affected with psychiatric illness (i.e., due to capacity considerations). Therefore, the findings from this study may not be generalizable to the full spectrum of PDDs.

We also investigated the availability of the SERT in a subset of patients and compared them with matched controls. We found group averages of BP_{ND} were lower in the Asperger's group than controls in every region, but none of these were statistically significant. It is possible that the [^{11}C]DASB sample size (N=8) was too small to detect smaller differences in SERT availability between individuals with Asperger's Disorder and healthy control subjects. A larger sample would provide more power to detect possible group differences. Therefore, these results should be considered preliminary and replication studies are warranted.

Previous imaging studies reported decreased SERT levels in ASD. In particular, Nakamura et al. studied 20 adults with high-functioning autism and 20 matched healthy control subjects and used [^{11}C] (+)McN-5652 to label the SERT (Nakamura et al., 2010). They found global decreases in the availability of the SERT in patients (Nakamura et al., 2010), as well as correlations between reductions in SERT in anterior and posterior cingulate and measures of social cognition and between reductions in SERT in thalamus and severity of repetitive/obsessive compulsive behaviors. However, the study of Nakamura et al. (Nakamura et al., 2010) reported distribution volumes, rather than binding potentials. Distribution volume measures both specific and non-specific binding and is dependent on the input to the compartment of interest, among other components (Innis et al., 2007). Furthermore, Nakamura et al. (Nakamura et al., 2010) demonstrated differences in cerebellar distribution volumes, a region in which there is essentially no specific binding with [^{11}C] (+)McN-5652, as well as differences in distribution volumes in cortical regions, areas in which the signal from [^{11}C] (+)McN-5652 binding is too low to be accurately measured (Parsey et al., 2000). This suggests that the distribution volumes reported by Nakamura et al.

(Nakamura et al., 2010) may have included effects due to non-specific SERT binding. Other notable differences between the study of Nakamura et al. (Nakamura et al., 2010) and ours are the samples sizes, diagnoses of autism versus Asperger's Disorder, and choice of radiotracer. One major difference between [^{11}C]DASB and [^{11}C] (+)McN-5652 is that [^{11}C]DASB provides higher BP_{ND} than [^{11}C] (+)McN-5652, which allows greater reliability in assessment of the SERT (Frankle et al., 2004; Szabo et al., 2002).

Makkonen et al. (Makkonen et al., 2008) used SPECT and the radiotracer [^{123}I] nor-beta-CIT in 15 children and adolescents with autism and 10 non-autistic comparison subjects and found decreased SERT capacity in medial prefrontal cortex in patients compared to control subjects. However, [^{123}I] nor-beta-CIT is limited as a measure of SERT to the midbrain given its nonspecificity and the relatively low concentration of SERT in other regions, such as the cortex (Laruelle et al., 1993; Neumeyer et al., 1991). Therefore, findings in regions other than midbrain should be interpreted with caution. Other notable differences between the study of Makkonen et al. and the current study are the sample sizes, the use of SPECT versus PET, the diagnoses of autism versus Asperger's Disorder, the ages of the participants, and that we used healthy controls for comparison while all of the control subjects in the study of Makkonen et al. had other neurological diagnoses (Makkonen et al., 2008).

To our knowledge, there are no studies specifically looking at the validity and reliability of scanning with [^{11}C]MDL 100907 and [^{11}C]DASB on the same day. However, it is unlikely that scanning with these two ligands on the same day obscured group differences in this protocol for several reasons: 1) DASB is highly selective for the SERT (K_i in rat cells of 1.1nM) compared to 5-HT_{2A} receptors (Wilson et al., 2000); 2) MDL 100907 is highly selective for 5-HT_{2A} receptors (K_i between 0.14nM and 1.86nM in human cells) compared to SERT (K_i > 10,000nM) as per the NIMH's Psychoactive Drug Screening Program (http://pdsp.med.unc.edu/); thus, direct interaction between the tracers was highly unlikely; 3) Tracer doses (i.e., doses that lead to less than 5% occupancy) of MDL 100907 and DASB were used in this study. As MDL 100907 is an antagonist and DASB is a reuptake inhibitor, tracer doses are likely to have no pharmacologic effects; 4) Both the Asperger's Disorder and healthy control groups participated in the same study design; and 5) The order of the injection was alternated, so that 50% of the subjects underwent the [^{11}C]DASB scan first, and 50% underwent the [^{11}C]MDL 100907 scan first.

In conclusion, this study found no significant differences in 5-HT_{2A} receptor and SERT availabilities in patients with Asperger's Disorder compared to controls and failed to replicate the results of previous imaging studies of serotonin biomarkers in this condition. Replication studies using [^{11}C]MDL 100907 and [^{11}C]DASB in individuals with Asperger's Disorder are needed to confirm the results of this study.

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Table 1

Demographic and scan data for [^{11}C]MDL 100907.*

Parameter	Asperger's	Controls
n	17	17
Age (years)	34.33 ± 11.05	32.99 ± 9.61
Gender	12M/5F	12M/5F
Ethnicity	0AA/2H/14C/1AS	2AA/3H/11C/1AS
Injected Activity (mCi)	13.31 ± 4.49	13.20 ± 3.79
Specific Activity (Ci/mmol)	1497.84 ± 985.15	1173.26 ± 643.56
Injected Mass (ug)	4.35 ± 2.28	5.07 ± 2.56
Clearance (liter/hour)	207.62 ± 45.21	224.51 ± 146.59
f_P (%)	0.28 ± 0.04	0.30 ± 0.05
Cerebellar V_T (ml/g)	21.54 ± 3.55	21.98 ± 2.87

* No significant differences between the two groups.

Table 2

Specific to non-specific binding coefficients (BP_{ND}) for [^{11}C]MDL 100907.*

Region	Asperger's	Controls
Amygdala	0.68 ± 0.26	0.65 ± 0.20
Anterior Cingulate	2.42 ± 0.66	2.26 ± 0.60
OFC	2.20 ± 0.63	2.01 ± 0.47
DLPFC	2.34 ± 0.59	2.02 ± 0.38
Temporal Cortex	2.43 ± 0.71	2.14 ± 0.47
Occipital Cortex	2.16 ± 0.47	1.95 ± 0.38
Parietal Cortex	2.06 ± 0.51	1.83 ± 0.42
Insula	2.08 ± 0.60	1.89 ± 0.44
Uncus	1.16 ± 0.57	1.10 ± 0.33
Entorhinal Cortex	1.04 ± 0.39	0.97 ± 0.41
Medial Temporal Lobe	0.61 ± 0.20	0.57 ± 0.16

* No significant differences between the two groups. OFC, orbitofrontal cortex.

DLPFC, dorsolateral prefrontal cortex.

Table 3

Demographic and scan data for [^{11}C]DASB.*

Parameter	Asperger's	Controls
n	8	8
Age (years)	29.74 ± 6.95	28.74 ± 6.96
Gender	7M/1F	7M/1F
Ethnicity	5C/0AA/2H/1AS	5C/1AA/1H/1AS
Injected Activity (mCi)	11.72 ± 3.14	13.36 ± 0.86
Specific Activity (Ci/mmol)	860.79 ± 495.60	1334.30 ± 912.78
Injected Mass (ug)	4.94 ± 2.40	4.25 ± 2.78
Clearance (liter/hour)	141.18 ± 29.30	173.36 ± 43.34
f_P (%)	0.10 ± 0.02	0.10 ± 0.02
Cerebellar V_T (ml/g)*	8.93 ± 1.01	11.24 ± 3.02

*No significant differences between the two groups.

Table 4

Specific to non-specific binding coefficients (BP_{ND}) for [^{11}C]DASB.*

	BPND	
Region	**Asperger's**	**Controls**
Amygdala	0.94 ± 0.25	1.13 ± 0.21
Insula	0.49 ± 0.08	0.56 ± 0.11
Thalamus	0.88 ± 0.24	1.03 ± 0.14
Uncus	0.62 ± 0.18	0.71 ± 0.21
Midbrain	1.70 ± 0.53	2.11 ± 0.22

* No significant differences between the two groups.