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Decreased $GABA_B$ Receptors in the Cingulate Cortex and Fusiform Gyrus in Autism

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Abstract

Autism is a behaviorally defined neurodevelopmental disorder and among its symptoms are disturbances in face and emotional processing. Emerging evidence demonstrates abnormalities in the GABAergic (gamma-aminobutyric acid) system in autism, which likely contributes to these deficits. $GABA_B$ receptors play an important role in modulating synapses and maintaining the balance of excitation-inhibition in the brain. The density of $GABA_B$ receptors in subjects with autism and matched controls was quantified in the anterior and posterior cingulate cortex, important for socio-emotional and cognitive processing, and the fusiform gyrus, important for identification of faces and facial expressions. Significant reductions in $GABA_B$ receptor density were demonstrated in all three regions examined suggesting that alterations in this key inhibitory receptor subtype may contribute to the functional deficits in individuals with autism. Interestingly, the presence of seizure in a subset of autism cases did not have a significant effect on the density of $GABA_B$ receptors in any of the three regions.

Keywords

GABA; Anterior Cingulate; Posterior Cingulate; autistic; seizure

Introduction

Autism is a pervasive developmental disorder (PDD) that shares many clinical characteristics with other PDDs such as Asperger syndrome and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS; Volkmar et al., 1996). The shared phenotypes of these disorders suggest some common neurobiological and genetic mechanisms. The core features of the disorder include restricted and repetitive behaviors, delayed language, and abnormal socio-emotional behaviors (APA, 1994). Although the

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etiology of autism is not known, there is growing consensus that the disorder, which ranges from mild to severe, results from a combination of genetic and environmental components (Fombonne, 1999). An important consideration when thinking about the neurobiology of the disorder is whether the multitude of symptoms is the result of a number of developmental "insults" to multiple regions of the brain, or if one "insult" results in a multitude of symptoms.

Neuropathology has been reported in the cerebellum, limbic system, and fusiform gyrus. Postmortem neuropathological studies have found reduced numbers of Purkinje cells (Bauman and Kemper, 1985; Ritvo et al., 1986; Bailey et al., 1998; Fatemi et al., 2002; Whitney et al., 2008), abnormal levels of glutamic acid decarboxylase (GAD) 65 and 67 (Fatemi et al., 2002) and GAD 65/67 mRNA levels (Yip et al., 2007, 2008, 2009), GABA receptors in the cerebellum (Fatemi et al., 2002), decreased neuron size and increased cell-packing density (Bauman and Kemper, 1985) in the hippocampus and anterior cingulate cortex (Simms et al., 2009), increased relative density of GABAergic interneurons in the hippocampus (Lawrence et al., 2010), and a reduced number of neurons in the lateral amygdala (Schumann and Amaral, 2006) and fusiform gyrus (Van Kooten et al., 2008). Bailey and colleagues (1998) and Simms et al. (2009) have also reported atypical laminar patterns in the frontal cortex and anterior cingulate gyrus, respectively. The abnormal cytoarchitecture observed in the autistic brain is indicative of an early developmental insult within these brain regions.

Functionally, the ACC has been associated with the pain system (Craig et al., 1996), regulation of attention (Botvinick et al., 1999), emotion (Davidson et al., 1999), vocalization (Jurgens and Ploog, 1970), cognition (MacDonald et al., 2000), and reward expectancy (Shidara and Richmond, 2002). The posterior cingulate cortex appears preferentially involved in visuospatial cognition (Olson et al., 1992; 1996), and is part of a network recruited when typically developing subjects see the faces or hear the voices of emotionally significant people in their lives (Maddock, 2001) and modulates emotion by responding to emotional scripts and faces (Mayberg et al., 1999). Individuals with autism are known to have difficulties in the perception of faces, direction of eye gaze, lack of eye contact and are impaired in face recognition abilities failing to use eye gaze and facial expression to regulate social interaction (Braverman et al., 1989; Davies et al., 1994; Joseph and Tanaka, 2003).

Functional brain imaging studies have described an extensive neural network implicated in face processing in humans. This network includes the fusiform gyrus, the superior temporal sulcus, anterior temporal pole, amygdala, orbitofrontal cortex, retrosplenial cortex, and the anterior and posterior cingulate cortices (Kanwisher et al., 1997; Shah et al., 2001). Several neuroimaging studies have found that individuals with autism display hypoactivation of the fusiform gyrus when compared to controls during a face recognition task (Schultz et al., 2000; Critchley et al., 2000; Pierce et al., 2001) but, there are also reports of normal activation of the fusiform gyrus during face processing tasks in autism (Pierce et al., 2004; Hadjikhani et al., 2004; Dalton et al., 2005).

Schultz et al. (2000) hypothesized that pathology in the fusiform gyrus may account for the hypoactivation during face processing. However, more recently Schultz's group and others have suggested the hypoactivation of the FFG is a consequence of abnormalities of regions within the face-processing circuit (Grelotti et al., 2002, 2005). Therefore it is important to determine if neuropathology exists in the FFG and/or if areas conveying information about emotional salience (ACC, PCC) may contribute to the deficits observed in face-processing in autism. Evidence is mounting that the GABAergic system is affected in multiple brain regions in adults with autism (Blatt et al., 2001; Fatemi et al., 2002, 2009a, b; Guptill et al., 2007; Yip et al., 2007, 2008, 2009; Oblak et al., 2009a,b; Lawrence et al., 2010).

GABA is the main inhibitory neurotransmitter in the brain and is important for proper cortical and synapse formation during development. $GABA_A$ and $GABA_C$ receptors are ligand gated ion channels and $GABA_B$ receptors are metabotropic. Activation of presynaptic $GABA_B$ receptors, inhibits the release of neurotransmitters and neuropeptides via inhibition of Ca^{2+} channels. Postsynaptic $GABA_B$ receptors activate inwardly rectifying potassium channels and induce the slow, long-lasting component of inhibitory postsynaptic potentials, the fast component of which is mediated through $GABA_A$ receptors.

GABA dysregulation has been suggested to play a key role in the increased rate of seizures in autism and others have suggested an imbalance of GABA and glutamate in autism, (Rubenstein and Merzenich, 1998; Hussman, 2001). All reports of decreased GABA receptors in autism have targeted $GABA_A$ receptors and benzodiazepine binding sites (Blatt et al., 2001; Guptill et al., 2007; Oblak et al., 2009a, b). Fatemi et al. (2009a, b) has provided further molecular evidence by showing decreased protein levels of both $GABA_A$ and $GABA_B$ subunits in the cerebellum and cortex of individuals with autism. These results raise the question as to whether there are consistent and common alterations in the GABA system throughout affected areas in autism. The current study utilized on-the-slide ligand binding autoradiographic techniques to examine and quantify the density of the $GABA_B$ receptors in three areas involved in socio-emotional and face-processing behaviors, the anterior and posterior cingulate cortex, and fusiform gyrus.

Methods and Materials

Brain Tissue

Fresh frozen brain tissue from the anterior and posterior cingulate cortices and fusiform gyrus was obtained from The Autism Research Foundation, the Autism Tissue Program, Harvard Brain Tissue Resource Center, and the NICHD Brain and Tissue Bank for Developmental Disorders at the University of Maryland, Baltimore, MD. A total of thirty-five blocks were obtained (15 autistic and 19 controls) and stored at −80°C. A summary of the case details is seen in Table 1. There was no significant difference in age or post-mortem interval between autism and control groups (student t-test).

Case Data

The following is a list of cases used in the study (Table 1). Note that seven of sixteen cases from the autism group had a history of at least one seizure (1078, 1484, 2825, 3845, 5173, 6337, 6677). As indicated in Table 1, based on availability of tissue blocks, there were seven autistic cases and nine control cases in the ACC study; six autistic and nine control cases for PCC study; and nine autistic and ten control cases from the FFG. The cases used in the study are designated in the far right column of Table 1 with an “X.” All cases used in the study had an autism diagnosis of moderate to severe. Detailed information about the regions of interest can be found in Supporting Information section.

Single-Concentration Binding Assay

Tissue blocks were sectioned coronally at 20 μm using a Hacker/Brights motorized cryostat at −20°C. Sections were thaw mounted on 2x3 inch gelatin coated glass slides. “Total binding” was measured using two sections per case and non-specific binding was determined using one section from each case. The tritiated antagonist ([^{3}H])CGP54626 (1.5 nM; specific activity 50.0 Ci/mmol; Perkin Elmer; Scheperjans et al., 2005) was used to label $GABA_B$ receptors. This antagonist selectively binds to the $GABA_B$ receptor subunits 1a and 1b (Kaupmann et al., 1998a,b). Non-specific binding was measured by adding a high concentration of a competitive displacer (CGP55845; 100μM; Scheperjans et al., 2005) to the tritiated ligand and buffer solution (50mM Tris-HCl, 2.5mM $CaCl_2$, pH 7.2). The

following steps were completed at 4°C: pre-incubation with buffer (15 minutes), incubation with ligand (plus blocker for non-specific binding; 1 hour), 3 washes in buffer (5 minutes each), and a dip in double deionized water. Variability in binding conditions was minimized by running all cases in parallel. Slides were dried overnight and loaded into X-ray cassettes with a set of ^{3}H polymer autoradiographic brain tissue standards (Autoradiographic ^{3}H Microscales, GE Healthcare) and apposed to tritium-sensitive film (^{3}H-Hyperfilm, Kodak) for 10 weeks. The exposed films were processed as follows at room temperature: developed with Kodak D19 (4 minutes), fixed with Kodak Rapidfix (3 minutes), rinsed in water (10 minutes) and air dried. Slides were stained with thionin to determine cytoarchitecture and laminar distribution of the ACC, PCC, and FFG. In the ACC, superficial layers corresponded to layers I–III, and deep layers to cortical layers V–VI (Vogt et al., 1995). In the PCC and FFG, superficial layers correspond to layers I–IV and deep layers correspond to layers V–VI.

Data Analysis

The film autoradiograms were digitized using an Inquiry densitometry system (Loats Associates) to gather quantitative measurements of optical density. Samples were obtained from the superficial and deep layers of the anterior cingulate cortex, posterior cingulate cortex, and fusiform gyrus. For interpolation of measured optical densities, a standard curve was constructed by fitting the optical densities for the ^{3}H tissue standards to the single-hit sensitometric equation (Zhu et al., 2003): optical density = $B1*(1 - 10^{k1(\text{specific activity})})+B3$, to generate a standard curve relating optical density to nCi per estimated tissue equivalent wet weight (Calon et al., 2001). Optimization of the adjustable parameters k1, B1, and B3 by nonlinear least squares regression using the Solver tool of Microsoft Excel (Microsoft Office 2007) yielded an excellent fit to the measured optical densities of the standards. The standard curve was then used to interpolate the measured optical densities for the tissue sections into nCi/mg. Binding in femtomoles per milligram (fmol/mg) was calculated based on the specific activity of the ligand.

Statistical Analyses

Student's t-tests with unequal variances were performed to determine if there were significant differences in the binding density between autistic and control cases in the superficial and deep layers of the ACC, PCC, and FFG. Mann-Whitney U non-parametric tests were also performed to determine if there were differences between the autism subgroup with a history of seizure and the autism subgroup with no seizure history. Although the number of cases with a history of seizure is small in each region (ranging from 3–4), this meets the minimal requirements for a non-parametric test of statistical significance. Mann-Whitney U tests were also performed on the autism subgroups receiving anticonvulsant therapy and those not receiving anticonvulsants in the ACC study because the number of cases (n=3) met the criteria to perform this statistical test; however, the PCC and FFG did not meet the requirements and therefore statistical tests were not performed.

Results

Overall, significant decreases were found in $GABA_B$ receptor binding density in autistic cases throughout the cingulate cortex and fusiform gyrus. Specific binding densities can be found in the supporting information (Tables I and II). Figure 1a and 1b are pseudocolored digitized images from hyperfilm to demonstrate the division of the anterior cingulate cortex into superficial and deep layers.

$GABA_B$ Receptor Binding in the Anterior Cingulate Cortex

In Figure 1a–c, in the anterior cingulate cortex, significant decreases in the binding density of $GABA_B$ receptors in the superficial layers of the autistic cases when compared to controls ($p=0.018$, ↓36.0%). In contrast there was no change in $GABA_B$ receptor density in the deep layers. Of the seven autistic cases, four had a history of seizure. There was also no difference between autistic seizure and autistic non-seizure subgroups or autistic antiepileptic therapy and autistic non-therapy, using a Mann-Whitney U non-parametric test ($p>0.05$).

$GABA_B$ Receptor Binding in the Posterior Cingulate Cortex

In Figure 2a–c, $GABA_B$ receptor binding studies in the posterior cingulate cortex showed a significant decrease in ^{3}H-CGP54626 binding in the superficial layers ($p=0.0076$; ↓36.3%), but unlike the ACC, there was also a significant difference in $GABA_B$ receptor binding density in the deep layers of the PCC ($p=0.050$; ↓22.8%). Three of the six autistic cases had a history of seizure and when these cases were compared to the autistic cases without seizure (Mann-Whitney U), there was no significant difference between the groups in either the superficial or deep layers of the PCC.

$GABA_B$ Receptor Binding in the Fusiform Gyrus

Similar to the PCC results, Figure 3a–c demonstrates that the binding of ^{3}H-CGP54626 to $GABA_B$ receptors was significantly decreased in the superficial layers ($p=0.019$; ↓24.0 %) and in the deep layers ($p=0.00095$; ↓29.8 %). Four of the nine autistic cases had a history of seizure, but the comorbid seizure disorder did not have a significant effect on receptor binding in any layer. Note that there appears to be one outlier case with low binding in the autism group (1664) and one in the control group (1026).

Discussion

The anterior and posterior cingulate cortex and fusiform gyrus are among many cortical structures implicated in autism due to their correlative functions with core behaviors including social-emotional and face recognition/expression deficits. Abnormal cortical circuitry is a common theory in autism (e.g. Kleinhans et al., 2008; Weng et al., 2009) and mounting evidence directly implicates cellular and molecular components of the GABAergic system (e.g. Fatemi et al., 2009a; Lawrence et al., 2010), including the $GABA_B$ receptor and its subunits (Fatemi et al., 2009b)

The $GABA_B$ receptor

The $GABA_B$ receptor is composed of $GABA_{B1}$ and $GABA_{B2}$ subunits that must both be present for functional $GABA_B$ receptors to be expressed on the cell surface. Cell culture studies have shown that the $GABA_{B1}$ subunit binds GABA; however, binding of GABA or any other endogenous ligand to the $GABA_{B2}$ subunit has not been demonstrated (Kniazeff et al., 2002). The $GABA_{B2}$ subunit, which exists as two isoforms, $GABA_{B1a}$ and $GABA_{B1b}$, is necessary for trafficking of $GABA_{B1}$ to the cell surface, and mediates G protein activation in response to binding of agonists to a binding site located on the $GABA_{B1}$ subunit (G_i/G_o; Kniazeff et al., 2002). Activation of $GABA_B$ receptors can influence long-term changes in synaptic strength and modulation of cortical circuits, and has been reported to restrict long-term potentiation (LTP) via hyperpolarization, whereas $GABA_B$ autoreceptors have been shown to promote the induction of LTP by disinhibiting the postsynaptic neuron in rat hippocampal slices (Davies et al., 1991; Olpe et al, 1993). Further evidence suggests that $GABA_B$ receptors have a critical role in developmental processes.

$GABA_B$ receptors during development

During pre- and postnatal brain development in the rat, $GABA_B$ receptors have a similar pre- and postsynaptic distribution as in adulthood in the neocortex, hippocampus, and dorsal cochlear nucleus (Lopez-Bendito et al., 2002 Lopez-Bendito et al., 2004; Lujan et al., 2004). Studies of the development of $GABA_B$ receptors in the cerebellum and olfactory cortex of rats suggest that $GABA_B$ receptors have a role in synapse and circuitry formation, and blockade of $GABA_B$ receptor signaling had a significant impact on the distribution of migratory neurons during corticogenesis (Lopez-Bendito et al., 2003; Panzanelli et al., 2004). Neuropathologic studies in the autistic brain have demonstrated abnormal neuronal migration and cytoarchitecture in the frontal cortex (Bailey et al., 1998) and anterior cingulate cortex (Simms et al., 2009). Casanova et al. (2002; 2003; 2006; 2009) reported an increase in the number of minicolumns and a decrease in neuropil in a number of cortical regions in autism. Furthermore, Van Kooten et al. (2008) found reduced volume and neuron number in the fusiform gyrus in autism cases; however, to our knowledge, neuropathology in the PCC has not yet been reported.

Insulin-like growth factor 1 (IGF-1) is important for normal development of the brain and promotes neuronal survival by rescuing neurons from apoptosis (Cheng et al., 2000; D'Mello et al., 1993). Reduced IGF-1 has been found in the cerebral spinal fluid (CSF) of children with autism (Vanhala et al., 2001; Riikonen et al., 2006). Tu and colleagues (2010) have recently found that $GABA_B$ receptors can protect neurons from apoptosis through a mechanism that involves transactivation of the IGF-1 receptor. IGF-1 triggers autophosphorylation of the IGF-1 receptor and activates the PI3 kinase/Akt signaling cascade which mediates the neuroprotective action of IGF-1 (Delcourt et al., 2007). Akt functions downstream of PI3 kinase and is critical for neuron survival (Bondy and Cheng, 2004). Therefore, reductions in $GABA_B$ receptors and/or IGF-1 in autism may result in the death of neurons, possibly contributing to reduced neuron numbers observed in the fusiform gyrus, amygdala, and anterior cingulate cortex (Schumann and Amaral, 2006; Van Kooten et al., 2008; Simms et al., 2009).

The current study demonstrates significant reductions in $GABA_B$ receptor density throughout the cingulate cortex and fusiform gyrus, and although the developmental origin of the $GABA_B$ receptor deficit is unknown, if this system is disturbed during the prenatal or early postnatal period, it could have profound implications towards the maturation of specific behaviors.

$GABA_B$ receptors and socio-emotional and face processing

Individuals with autism have severe deficits in processing faces (Klin et al., 1999; Grelotti et al., 2002; Joseph and Tanaka, 2003) that may be due to alterations in cortical network signaling because of deficits in the GABA system. The superficial layers of the cortex (layers I–IV) receive information from the thalamus and other cortical regions and project to inter- and intracortical areas while the deep layers also receive thalamic input and project to other cortical and subcortical regions. Based on the present findings, cortical information may be potentially disrupted because of reduced inhibitory receptors that could result in a failure to recruit cortical regions needed for processing emotional responses and facial recognition.

At the synaptic level, neuroligins are a family of postsynaptic cell adhesions molecules in the brain that interact with neurexins and are localized to the postsynaptic specializations of excitatory and inhibitory (including GABAergic) synapses (Ichtchenko et al., 1995, 1996). In vitro transfection studies have suggested a role for neuroligins in synapse formation (Dean et al., 2003); however, cell culture studies suggest that neuroligins are not required for

synapse formation but for synapse specification and modulation (Varoqueaux et al., 2006). In autism, mutations in both neuroligins and neurexins have been reported (Chih et al., 2004; Feng et al., 2006; Yan et al., 2008). Therefore, reductions in inhibitory receptors in the present study may result from an alteration in neuroligins and/or neurexins resulting in reduced GABAergic synaptic protein recruitment and stabilization within the cingulate cortex and fusiform gyrus.

Seizures and $GABA_B$ receptors

A subgroup of approximately 25–33% of individuals with autism have a relatively high frequency of seizures (Olsson et al., 1988; Volkmar and Nelson, 1990). Knock-out mice lacking the $GABA_{B1}$ or $GABA_{B2}$ subunit exhibit epileptiform activity, enhanced prepulse inhibition, altered locomotor activity, and impaired memory processing (Prosser et al., 2001; Schuler et al., 2001; Vacher et al., 2006). These knock-out mice suggest that differences in the number of $GABA_B$ receptor subunits may lead to the development of seizures due to changes in neurotransmitter release or inhibition of local circuits. Similar deficiencies in $GABA_B$ receptors in autism may result in seizures and decreased effectiveness in controlling cortical circuits.

In the current study, the density of $GABA_B$ receptors in ACC, PCC or FFG did not differ significantly between the autism subgroup with a history of seizure and the subgroup with no history of seizure. However this result is met with caution since the number of cases (n=3) was small for seizures. Although several of the cases used in this study were receiving or had received anticonvulsant therapy during their life, none of the drugs used are known to target $GABA_B$ receptors (Table 1). We were unable to determine if the anticonvulsants had an effect on $GABA_B$ binding density in all three regions because of the small sample size (n=2 in PCC, n = 1 in FFG). However, in the ACC, there was no effect of pharmacotherapy on binding density, but again the number of cases was small and the results should be met with caution.

We are unable to determine if the significant decrease in the density of binding is due to a loss of $GABA_B$ receptors on GABAergic or glutamatergic neurons of if there is a reduction in one of the $GABA_B$ receptor subunits. Fatemi et al. (2009b) found significant reductions in the protein level of $GABA_{B1}$ subunit in the parietal lobe, frontal lobe, and cerebellum of autistic individuals as well as reduced protein levels of the $GABA_{B2}$ subunit in the cerebellum. Based on these results it is possible that the reductions in the $GABA_B$ binding density in the present study are due to decreased availability of either of the subunits required for proper $GABA_B$ receptor surface expression and functioning. A detailed molecular analysis of the subunits across brain areas is thus needed to determine whether the autistic group has fewer $GABA_B$ receptor subunit(s) than controls.

Closing Comments

The cingulate cortex, an area that modulates emotion, attention, and gaze fixation and activated by socio-emotional events, may be responsible for the proper function of the fusiform gyrus through mechanisms that modulate activity in this region. The alterations in $GABA_B$ receptor densities in the three regions further support the theory that deficits in the GABA system are widespread in autism (Blatt et al., 2010) and that this alteration is not restricted to $GABA_A$ receptors as previously reported in these regions (Oblak et al., 2009a, b). The changes in $GABA_B$ receptors thus suggest possible pharmacotherapies since $GABA_B$ receptors are not responsive to antiepileptic drugs that typically target $GABA_A$ receptors. $GABA_B$ agonists such as baclofen might be considered as possible agents for clinical trials.

Finally, although the full syndrome as expressed in later childhood and adolescence appears to involve insults to multiple brain regions, it is not clear if these multiple systemic brain disturbances reflect deficits in multiple independent control processes, or whether the initial insult might have been more restricted. It is possible that deficits initially confined to one system might negatively impact the development of other neural systems, such that a more pervasive set of impairments evolves. This would suggest that multiple brain areas within specific networks become involved and more widespread behavioral effects emerge.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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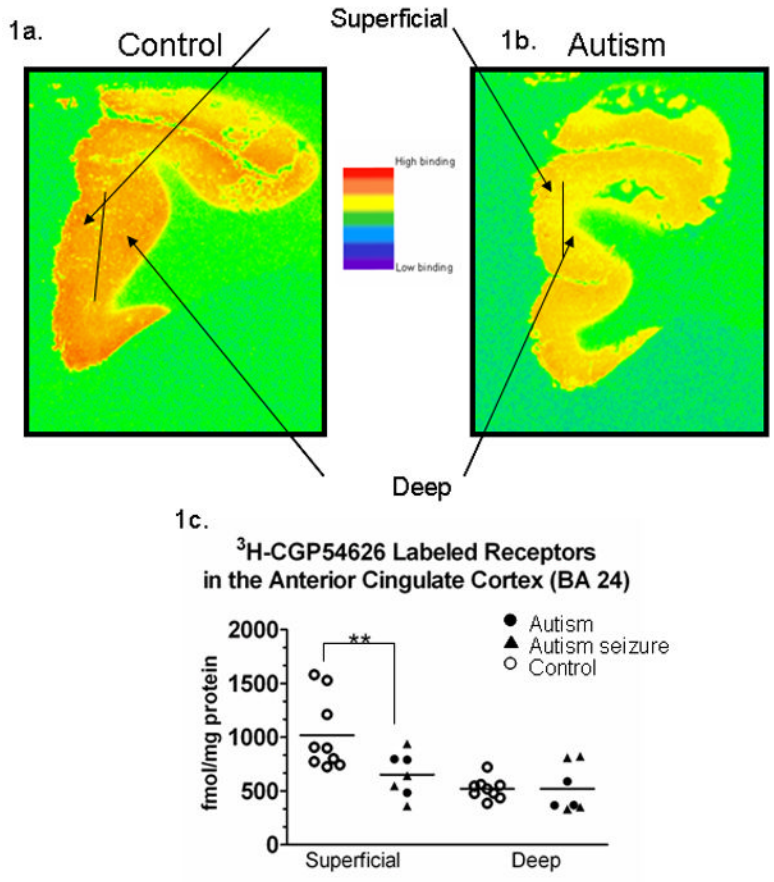

Figure 1.

Pseudocolored image of a control case (1a.) and an autism case (1b.) from the ACC off [^{3}H]-sensitive hyperfilm. The images demonstrate the superficial (I–III) and deep (V–VI) layers that were sampled (1a.) In 1c, a graph demonstrating [^{3}H] labeled $GABA_B$ receptor binding density in the anterior cingulate cortex. Each symbol represents the $GABA_B$ receptor density from an individual case (see key). There was a significant (**) reductions ($p=0.018$) in the density of receptors in the autism cases in the superficial layers. Note these are sample sections from individual cases, and although it appears that there is a difference in the deep layers in these cases, statistically there was no significant difference in binding density between autism and control cases.

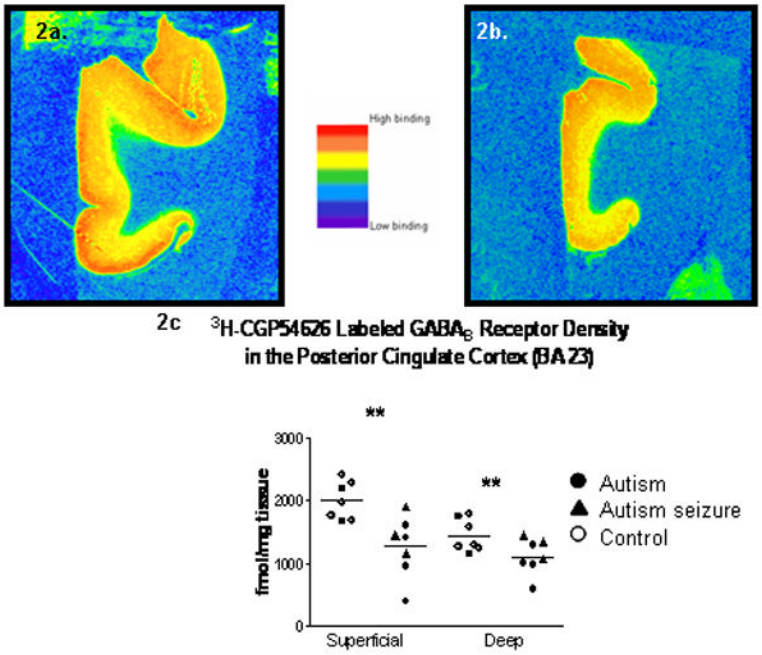

Figure 2.

Pseudocolored images from a control (2a.) and autistic (2b.) case from the PCC. Graphs of the [^{3}H]-CGP54626 labeled GABA$_B$ receptor binding density in the posterior cingulate cortex. Significant (**) decreases were found in the superficial (p=0.0076) and deep (p=0.050) layers of the autistic cases when compared to controls.

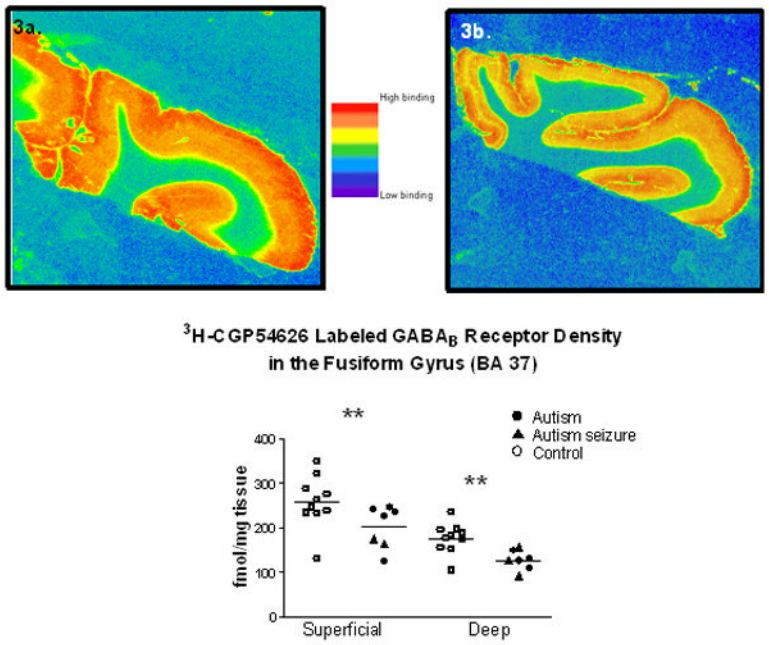

Figure 3.

Graph demonstrating [^{3}H]-CGP54626 labeled GABA$_B$ receptor binding density in the fusiform gyrus from a control (3a.) and an autistic case (3b.). Figure 3c is a scatter plot of all cases included in the study. Significant reductions (**) in the superficial (p=0.019) and deep (p=0.00095) layers were found in the autism cases.

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Table 1

Anterior Cingulate, Posterior Cingulate, and Fusiform Gyrus case information.

CASE	DIAGNOSIS	AGE	PMI (HOURS)	CAUSE OF DEATH	GENDER	AREA		
						ACC	PCC	FFG
1078*†	Autism	22	14.3	Drowning	Male	X		
1401	Autism	21	20.6	Sepsis	Female	X	X	
1484*	Autism	19	15	Burns	Male	X	X	
1664	Autism	20	15	Unknown	Male			X
2825* ▲	Autism	19	9.5	Heart attack	Male	X	X	
3845*‡	Autism	30	28.4	Cancer	Male	X	X	
4099	Autism	19	3	Congestive Heart Failure	Male	X	X	
4899	Autism	14	9	Drowning	Male			X
5000	Autism	27	8.3	Drowning	Male			X
5027	Autism	37	26	Bowel Obstruction	Male			X
5144	Autism	20	23.7	Auto Trauma	Male			X
5173* ◇	Autism	30	20.3	GI bleeding	Male			X
5754	Autism	20	29.98	Unknown	Male	X	X	
6337*	Autism	22	25	Choked	Male			X
6677*	Autism	30	16	Congestive heart failure	Male			X
602	Control	27	15	Accident	Male			X
1026	Control	28	6	Congenital Heart Disease	Male			X
1365	Control	28	17	Multiple Injuries	Male			X

CASE	DIAGNOSIS	AGE	PMI (HOURS)	CAUSE OF DEATH	GENDER	AREA		
						ACC	PCC	FFG
4103	Control	43	23	Heart attack/disease	Male	X	X	
4104	Control	24	5	Gun shot	Male	X	X	
4188	Control	16	13	Gun Shot	Male	X		
4267	Control	26	20	Accidental	Male	X	X	
4268	Control	30	22	Heart attack/disease	Male	X	X	
4269	Control	28	24	Heart disease	Male	X	X	
4271	Control	19	21	Epiglotitus	Male	X	X	
4275	Control	20	16	Accidental	Male	X	X	
4364	Control	27	27	Motor Vehicle Accident	Male	X		
4605	Control	29	18.3	Renal Failure	Male			X
4642	Control	28	13	Cardiac Arrythmia	Male			X
4916	Control	19	5	Drowning	Male			X
5873	Control	28	23.3	Unknown	Male	X		
6004	Control	36	18	Unknown	Female	X		
6207	Control	16	26.2	Heart Attack	Male	X		
6221	Control	22	24.2	Unknown	Male	X		

Note: Cases with an asterisk (*) had a history of at least one seizure.

The following symbols indicate medication history:

†Dilantin, Tegretol, Theodur, Phenobarbital

▲Klonopin, Mysoline, Phenobarbitol, Thorazine

‡Dilantin, Mellaril, Phenobarbital

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◇Cisapride, Clorazepate, Depakote, Dilantin, Mysoline, Phenobarbital