Report

Current Biology

Reduced GABAergic Action in the Autistic Brain

Highlights

- Behavioral marker of inhibitory/excitatory neurotransmission is perturbed in autism
- Marker predicts higher-order autistic symptom severity
- Inhibitory and excitatory neurotransmitters measured in the brain predict behavior
- Action of the inhibitory neurotransmitter, GABA, is reduced the autistic brain

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In Brief

An imbalance in inhibitory/excitatory neurotransmission is proposed to affect the autistic brain, but empirical evidence in humans is lacking. Robertson et al. report a link between a robust autistic perceptual symptom and reduced action of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), in the brains of autistic individuals.

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Current Biology
Report

Reduced GABAergic Action in the Autistic Brain

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SUMMARY

An imbalance between excitatory/inhibitory neurotransmission has been posited as a central characteristic of the neurobiology of autism [1], inspired in part by the striking prevalence of seizures among individuals with the disorder [2]. Evidence supporting this hypothesis has specifically implicated the signaling pathway of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), in this putative imbalance: GABA receptor genes have been associated with autism in linkage and copy number variation studies [3–7], fewer GABA receptor subunits have been observed in the post-mortem tissue of autistic individuals [8, 9], and GABAergic signaling is disrupted across heterogeneous mouse models of autism [10]. Yet, empirical evidence supporting this hypothesis in humans is lacking, leaving a gulf between animal and human studies of the condition. Here, we present a direct link between GABA signaling and autistic perceptual symptomatology. We first demonstrate a robust, replicated autistic deficit in binocular rivalry [11], a basic visual function that is thought to rely on the balance of excitation/inhibition in visual cortex [12–15]. Then, using magnetic resonance spectroscopy, we demonstrate a tight linkage between binocular rivalry dynamics in typical participants and both GABA and glutamate levels in the visual cortex. Finally, we show that the link between GABA and binocular rivalry dynamics is completely and specifically absent in autism. These results suggest a disruption in inhibitory signaling in the autistic brain and forge a translational path between animal and human models of the condition.

RESULTS AND DISCUSSION

During binocular rivalry, two images, one presented to each eye, vie for perceptual dominance as neuronal populations that are selective for each eye's input suppress each other in alternation [16, 17]. The strength of perceptual suppression during rivalry is thought to depend on the balance of inhibitory and excitatory cortical dynamics [12–15] and may serve as a non-invasive perceptual marker of the putative perturbation in inhibitory signaling thought to characterize the autistic brain.

We therefore measured the dynamics of binocular rivalry in individuals with and without a diagnosis of autism (41 individuals, 20 with autism). As predicted, individuals with autism demonstrated a slower rate of binocular rivalry (switches per trial: controls = 8.68, autism = 4.19; $F(1,37) = 16.52$, $\eta_p^2 = 0.311$, $p = 0.001$; Figure 1A), which was marked by reduced periods of perceptual suppression (proportion of each trial spent viewing a dominant percept, (dominant percept durations)/(dominant + mixed percept durations): controls = 0.69; autism = 0.55; $F(1,36) = 7.27$, $\eta_p^2 = 0.172$, $p = 0.011$; Figure 1B). The strength of perceptual suppression inversely predicted clinical measures of autistic symptomatology (Autism Diagnostic Observation Schedule [ADOS]: $R_s = -0.39$, $p = 0.027$; Figure 1) and showed high test-retest reliability in a control experiment ($R = 0.94$, $p < 0.001$; see Supplemental Experimental Procedures and also [18]). These results replicate our previous findings in an independent sample of autistic individuals [11] and confirm rivalry disruptions as a robust behavioral marker of autism.

To test whether altered binocular rivalry dynamics in autism are linked to the reduced action of inhibitory (γ-aminobutyric acid [GABA]) or excitatory (glutamate [Glx]) neurotransmitters in the brain, we measured the concentration of these neurotransmitters in visual cortex using magnetic resonance spectroscopy (MRS). Spectra were acquired from an occipital voxel (2.5 × 2.5 × 3 cm), centered bilaterally on the calcarine sulcus (Figure 2A).

GABA and glutamate are predicted to contribute to different aspects of binocular rivalry dynamics: mutual inhibition between (GABA) and recurrent excitation within (glutamate) populations of neurons coding for the two oscillating percepts [14]. Specifically, in classic models of binocular rivalry, a period of perceptual suppression is maintained through excitation within the neuronal population selective for the dominant image, as well as cross-inhibition of the neuronal population selective for the non-dominant image [12, 19, 20]. Critically, reducing either mutual inhibition or recurrent excitation is predicted to reduce the strength of perceptual suppression during rivalry in one implementation of this model [14], mirroring the dynamics we observed in autism. We therefore considered each neurotransmitter separately to test whether inhibitory or excitatory signaling was selectively disrupted in the autistic brain.

Given prior evidence from genetic, animal, and post-mortem studies, we hypothesized that inhibitory signaling may be affected in the autistic brain. This disruption could take the form of reduced levels of GABA or glutamate. However, reports

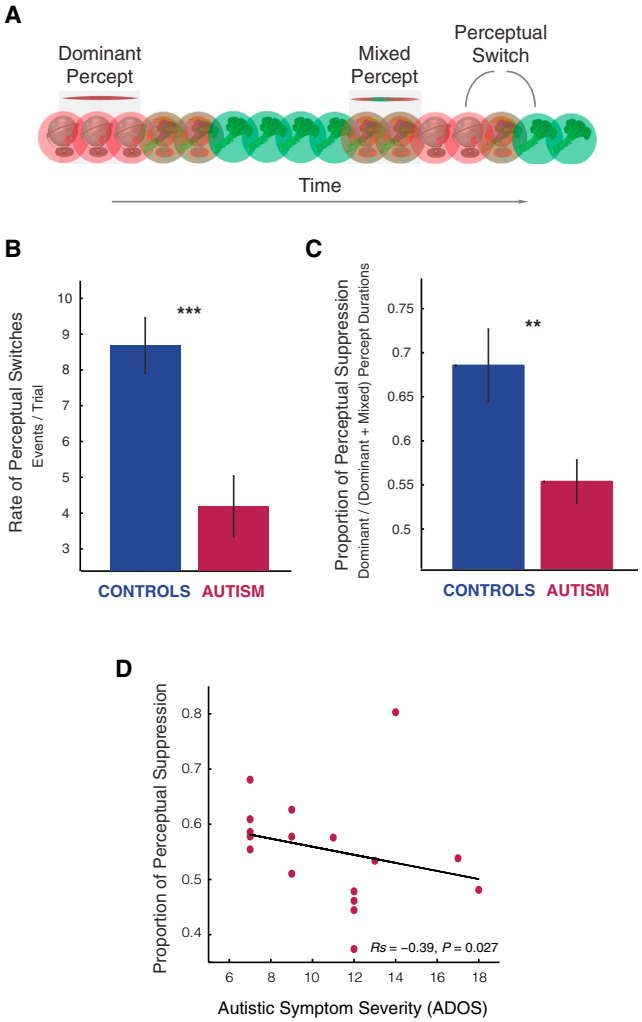

Figure 1. Atypical Dynamics of Binocular Rivalry in Autism

(A) Schematic of perceptual experience during binocular rivalry. Two images, one presented to each of an individual's eyes, oscillate back and forth in perceptual awareness as each is suppressed in turn. Throughout a run, participants were instructed to continuously report their perceived image (red, green, mixed) through button press (right, left, up).

(B) Slower rate of binocular rivalry alternations in autism. Individuals with autism demonstrated fewer perceptual switches between the inputs to their left and right eyes, compared with control participants ($\eta_p^2 = 0.311$, p = 0.001).

(C) Reduced proportion of perceptual suppression in autism. Individuals with autism demonstrated a reduced strength of perceptual suppression, periods of time during which one image is fully suppressed from visual awareness ($\eta_p^2 = 0.172$, p = 0.01).

(D) The strength perceptual suppression during binocular rivalry inversely predicted autistic symptom severity, measured using the ADOS, a clinical measure of autistic symptomatology.

In all plots, error bars represent 1 SEM. **p ≤ 0.01, ***p ≤ 0.001 difference between the two groups. See also Table S1.

of perturbations of key components of the GABA signaling pathway, such as receptors [3–9] and inhibitory neuronal density [10], suggest that GABA levels themselves may not be altered in autism but instead may be less predictive of rivalry dynamics.

As predicted by models of binocular rivalry, GABA concentrations in visual cortex strongly predicted rivalry dynamics in controls, where more GABA corresponded to longer periods of perceptual suppression ($R_s = 0.62$, p = 0.002; Figure 2B). However, this relationship was strikingly absent in individuals with autism ($R_s = 0.02$, p = 0.473; Figure 2B). The difference between the two correlations was significant ($\eta_p^2 = 0.167$, p = 0.013; Figure 2C), indicating a reduced impact of GABA on perceptual suppression in the autistic brain.

Importantly, this finding was specific to GABA: glutamate strongly predicted the dynamics of binocular rivalry in autism ($R_s = 0.60$, p = 0.004; Figure 2B), to the same degree as that found in controls ($R_s = 0.40$, p = 0.031 in controls; p = 0.71 for the difference of this effect between autism and controls; Figure 2C). The absence of a group difference in the concentrations of GABA and Glx (both p > 0.32; Figure S1; Table S2) indicate that GABA levels themselves are not altered in the autistic visual cortex [21], despite a specific reduction in the effect of GABA on autistic visual behavior. These findings suggest that alterations in the GABAergic signaling pathway may characterize autistic neurobiology. Consistent with prior evidence from animal and post-mortem studies, such dysfunction may arise from perturbations in key components of the GABAergic pathway beyond GABA levels, such as receptors [3–9] and inhibitory neuronal density [10].

These results demonstrate reduced GABAergic, but conserved glutamatergic, action in the autistic visual system. No other metabolite measured predicted rivalry dynamics in either group (all p > 0.11 for TNAA, TCho, TCr, and Ins), and GABA was the only metabolite to show a markedly reduced impact on the dynamics of binocular rivalry in autism (all other effects between autism and controls: p > 0.29; Figure 2C). Furthermore, this relationship was specific to GABA measured in the visual cortex: binocular rivalry dynamics were not related to any metabolites measured in a control region of interest, the motor cortex, in either group (all $R_s < 0.17$, all p > 0.25).

The specificity of this effect to GABA and not glutamate argues against the possibility that these findings are driven by differences in the spectral quality between the two groups. Further, spectral fit errors (an indication of data quality) and frequency drift (an indication of subject motion) were within the expected ranges and matched between groups (all p > 0.46; Figure S1; Table S2). Repeatability control experiments indicated that our metabolite measurements were highly reliable (coefficient of variation [CVs] < 8%) with a high reproducibility relative to the effect range of our study (SDs < 13% of the group range for each metabolite) (see Supplemental Experimental Procedures). These results confirm previous reports of high test-retest reliability of in vivo MRS measurements [22] and add to a growing literature of replicated relationships between GABA concentration and psychophysical performance, including sensory sensitivity thresholds [23, 24], motor response inhibition [25], and binocular rivalry dynamics [15, 26].

Atypical sensory perception has been noted since the earliest reports of autism [27], although little is known about the neural underpinnings of these symptoms. Interestingly, recent reports of reduced spatial suppression [28], decreased global motion perception [29, 30], larger population receptive fields [31], and more variable evoked responses [32, 33] in autism mirror the perceptual consequences of reduced GABAergic inhibition in animal studies [34, 35]. Computational accounts suggest that

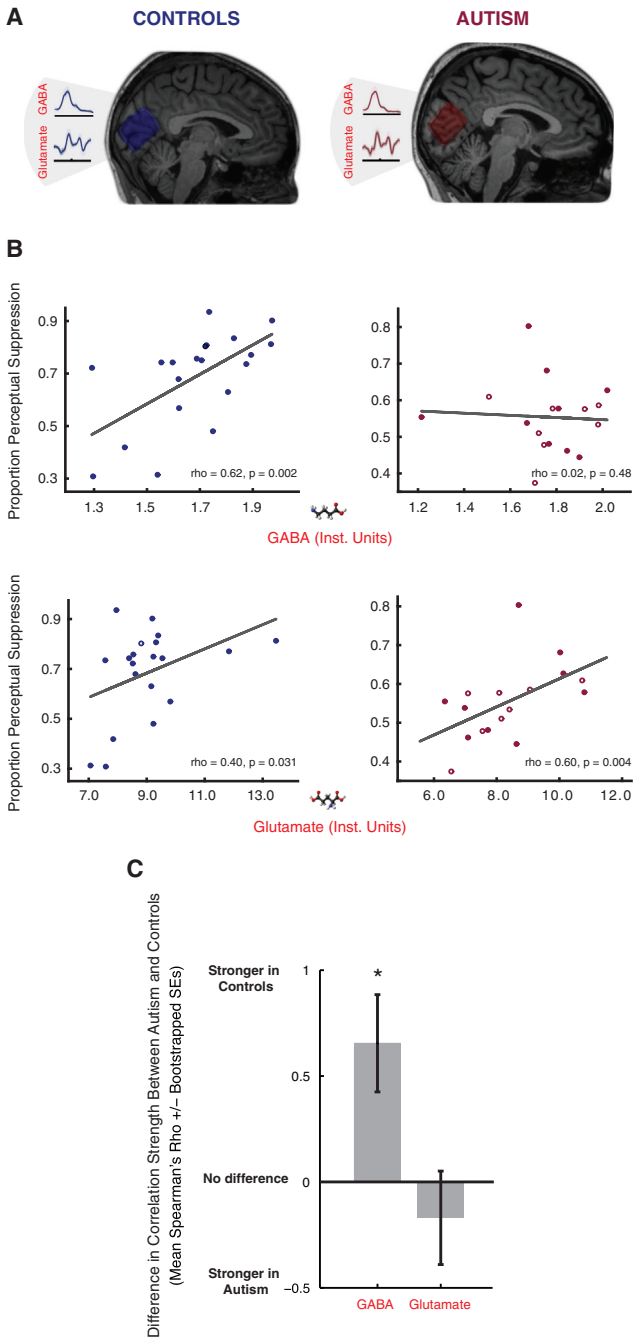

Figure 2. Reduced GABAergic, but Conserved Glutamatergic, Action in the Autistic Visual Cortex

(A) Magnetic resonance spectra were acquired from individuals with and without autism: one example control (left) and autistic (right) participant shown here, with the acquisition region (visual cortex) shown in color (80% probability of VOI placement). Spectra included the neurotransmitters predicted to govern binocular rivalry dynamics from computational models, GABA and glutamate, as well as control metabolites TNAA, TCho, TCr, and Ins.

(B) GABA strongly predicted the strength of perceptual suppression during rivalry in control individuals (R_s = 0.062, p = 0.002, top left), but this relationship was absent in autism (R_s = 0.02, p = 0.473, top right). However, glutamate strongly predicted binocular rivalry dynamics in both controls (rho = 0.40, p = 0.031, bottom left) and autism (R_s = 0.60, p = 0.004, bottom right).

(C) GABA was the only molecule to show a significantly stronger effect on rivalry dynamics in controls, as compared to autism, demonstrating a selective disruption in GABAergic action in the autistic brain (η_p^2 = 0.167, p = 0.013). In all plots, medicated individuals are labeled with unfilled circles.

Error bars represent 1 SEM. See also Figures S1 and S2 and Table S2.

reducing inhibition may account for a wide range of autistic perceptual symptoms [36]. One such account predicted reduced perceptual suppression during rivalry in autism but found only a trend toward the finding ([37], but see [38]). Further work is needed to test whether this litany of visual disruptions indeed results from reduced GABAergic signaling in the autistic brain, as we demonstrate here for one robust autistic visual symptom.

Our findings provide evidence for an empirical link between a specific neurotransmitter measured in the brains of individuals with autism and an autistic behavioral symptom. Although perceptual in nature, this symptom strongly predicts higher-order clinical measures of autistic symptomatology and may be well poised to serve as a behavioral marker of a perturbation in GABAergic signaling in the autistic brain. Together with the pivotal roles of GABA in canonical cortical computations [39] and neurodevelopment [40], these findings point to the GABAergic signaling pathway as a prime suspect in the neurobiology of this pervasive developmental disorder [41]. Future work should replicate these findings and investigate GABAergic signaling in autism at multiple developmental time points to establish whether GABAergic perturbations predict, or arise in response to, the developmental onset of autistic symptomatology.

EXPERIMENTAL PROCEDURES

Participants

We tested 41 adolescents and adults: 21 controls and 20 autism, matched for age and IQ (Table S1). All individuals with autism met DSM-IV diagnostic criteria (15 Asperger's, 1 high-functioning autism, 4 pervasive developmental disorder not otherwise specified [PDD-NOS]), as assessed by an experienced clinician, and met cutoff for the category "Autism Spectrum Disorder" after a research-reliable administration of the ADOS-2 [42]. Twelve participants (1 control, 11 autism) were being treated with psychiatric medications: antidepressants (n = 8), antipsychotics (n = 2), antiepileptics (n = 4), and anxiolytics (n = 2). Excluding participants taking medications known to interact with the GABAergic system (n = 8) did not qualitatively alter the results. All participants had normal or corrected-to-normal vision and IQ > 70. Written consent was obtained in accordance with a protocol approved by the Massachusetts Institute of Technology Institutional Review Board.

Binocular Rivalry Paradigm and Analysis

Binocular rivalry stimuli and analysis were identical to those used in [11], except that the stimuli were slightly smaller. On each run, two grayscale objects (e.g., a baseball and a piece of broccoli) appeared on the left and right of the screen. Each object was displayed within a tinted square (green or red; width: 2.2°), surrounded by a black circle to support binocular fusion (radius: 3.1°). Stimuli were viewed through a mirror stereoscope, which reflected the left and right sides of the screen into the participants' left and right eyes so that each eye was presented with only one of the two images (red or green).

Testing sessions were composed of two 30-s practice runs and six 45-s experimental runs. Participants were asked to continuously report whether they perceived a fully dominant percept—the red image (right key) or the green image (left key)—or a mixture of the two images (up key).

Since the key press was continuous (sampling rate: 4 ms), a sequence of perceptual transitions was computed as events in which one continuous key press was terminated and another began. For each participant and trial, the frequency of perceptual switches as well as the duration of any percept (red,

green, or mixed) were calculated. The primary measure of interest, the proportion of perceptual suppression, was calculated as the proportion of each trial spent viewing a fully dominant percept: (dominant percept durations)/(dominant + mixed percept durations).

See Supplemental Experimental Procedures for information regarding test-retest reliability of rivalry dynamics.

MRI and MRS Acquisition

Magnetic resonance (MR) data were collected using a Siemens Trio 3T MRI scanner at MIT, equipped with a 32-channel head coil. At the beginning of each scan session, we acquired a high-resolution, whole-brain anatomical volume using a T1-weighted MPRAGE sequence (124 slices; voxels = 1 × 1 × 1 mm; repetition time = 2,530 ms; echo time = 2.94 ms; matrix = 256 × 256 × 176 mm; field of view = 256 × 256 × 176 mm).

Subsequently, single voxel ^{1}H MR spectra (MRS) were acquired from early visual and motor volumes of interest (VOIs). Prior to MRS acquisition, whole-volume first and second-order shims were adjusted using the automatic GRE shim sequence, and manual shimming was additionally performed within each VOI to optimize magnetic field homogeneity (mean full width at half maximum of water signal: 15.9 Hz [controls], 15.2 Hz [autism]; mean T2*: 39.7 ms [controls], 40.7 ms [autism]).

A Mescher-Garwood Point Resolved Spectroscopy (MEGA-PRESS) scan [43] (320 spectral averages; repetition time = 1,500 ms; echo time = 68 ms; eight-step phase cycle) and a localized unsuppressed water scan (four averages; repetition time = 10,000 ms; echo time = 30 ms) were acquired in each VOI. A frequency-selective inversion pulse was applied at 1.9 and 7.5 ppm in alternating spectral lines, and the edit-ON and edit-OFF spectra were subtracted to generate a difference spectrum containing total GABA.

The visual cortex VOI (2.5 × 2.5 × 3.0 cm) was placed using standard anatomical landmarks [44], angled along the calcarine sulcus and set dorsal to the cerebellum and anterior from the anterior sinus. The motor cortex VOI (2.5 × 2.5 × 3.0 cm) was centered on the hand knob of the left hemisphere and angled along the primary motor strip [45].

During the MEGA-PRESS scan of visual cortex, participants performed a simple visual task at fixation. During the MEGA-PRESS scan of motor cortex, participants performed a simple finger-tapping task.

MRI Analysis

Individuals' anatomical scans were reconstructed and segmented into gray matter, white matter, and cerebrospinal fluid (CSF) maps using statistical parametric mapping (SPM8, Wellcome Trust Center for Neuroimaging). The tissue composition within each VOI was computed by creating a mask of the portion of the anatomical volume covered by the VOI.

MRS Analysis

GABA concentration was quantified from the MEGA-PRESS difference subspectra using the Gannet GABA analysis toolkit [46]. Gannet models the GABA peak using a simple, five-parameter Gaussian model, fit between 2.19 and 3.55 ppm and the water peak using a Gaussian-Lorentzian function. Gannet applies a correction factor for co-edited macromolecule signal and editing efficiency during water scaling (see below). All other metabolic signals were quantified from the edit-OFF subspectra using TARQUIN [47], which uses a linear combination of simulated basis sets based on quantum calculations to fit spectra in the time domain. Macromolecules are modeled as components of the TARQUIN fit.

In all analyses, metabolite values were scaled to water and expressed in institutional units (IU). Nuclear magnetic resonance (NMR) visible water was estimated at 78%, as each VOI primarily contained gray matter [48], and the following formula was used to calculate the water relaxation factor: $\exp(-TE_{water}/T2_{water})/\exp(-TE_{metabs}/T2_{metabs})$. The resulting metabolite concentrations were corrected for the proportion of gray matter in each VOI. Cramér-Rao lower bound values were reliably < 20% for each metabolite and group (GABA: 6.53 [autism], 5.41 [control]; Glx: 8.88 [autism], 9.12 [control]). Therefore, all fitted spectra were accepted for analysis (Figure S2).

In total, we were able to resolve the metabolic signals of the following molecules: GABA, Glx, TNAA, TCho, TCr, and myo-inositol (Ins). Glutamate and its metabolic precursor glutamine were fitted together (Glx) due to their overlapping resonances at 3T, as were N-Acetylaspartate and N-acetylaspartylglutamate (TNAA), creatine and phosphocreatine (TCr), and glycerophosphocholine and phosphocholine (TCho).

It should be noted that MEGA-PRESS measurements of GABA typically include macromolecule signals with similar resonant frequencies. As a result, they are often referred to as GABA+. All results were qualitatively similar to those reported here when metabolites were quantified using the MRS analysis software LCModel.

See Supplemental Experimental Procedures for information regarding test-retest reliability of MRS measurements.

Statistical Analyses

Spearman's rank correlations coefficients (R_s) were used to compare the relationship between neurotransmitter concentrations and rivalry dynamics. Two-tailed, uncorrected p values were calculated from permutation tests, and correlation coefficients were calculated from bootstrapped confidence intervals of these correlations, sampled 10,000 times with replacement. The strength of two relationships was computed by performing an F test on the linear regression coefficients of each relationship. All results remained significant using Pearson's coefficients (all $p < 0.02$) and when results were corrected for multiple comparisons between GABA and Glx (all $p < 0.026$).

Participants whose rivalry percept durations were determined to fall outside of 2 SDs of the group mean were excluded from analyses (one control, two autism). One autism participant was unable to complete the MRS scan.

Participants' psychometric data (age and IQ, on which the two groups were matched) did not correlate with any of our experimental variables of interest (all $p > 0.212$). Therefore, statistical analyses were performed without psychometric data included as covariates.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, two figures, and two tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2015.11.019.

AUTHOR CONTRIBUTIONS

Conceptualization, C.E.R. and N.K.; Methodology, C.E.R., N.K., and E.-M.R.; Investigation, C.E.R. and E.-M.R.; Formal Analysis, C.E.R.; Visualization, C.E.R.; Writing – Original Draft, C.E.R.; Writing – Reviewing & Editing, C.E.R, N.K., and E.-M.R.

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