PNAS papers on Autism

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Children with autism spectrum disorder show reduced adaptation to number


June 2015 issue
Introduction

- Autism is a heritable, lifelong neurodevelopmental condition with striking effects on social communication.
- It is also associated with a range of nonsocial symptoms, including both hypersensitivity and hyposensitivity to perceptual stimuli, and sensory-seeking behaviors such as attraction to light, intense looking at objects, and fascination with brightly colored objects. These sensory atypicalities form part of the diagnostic criteria for autism.
- Proposed a **Bayesian account of autism**, suggesting that it is not sensory processing itself that is disrupted in individuals with autism, but the interpretation of the sensory input.
Method

- In this paper, the authors examine the extent and nature of diminished adaptation in children with autism by measuring adaptation to numerosity.
- Why?
  - High level perceptual attribute
  - Numerosity is functionally and neutrally distinct from face stimuli: Parietal function
  - Unlike face recognition skills, number skills are often reported anecdotally as a relative strength for individuals with autism
Experiment

• Measured adaptation with a child-friendly computer game in which the children were asked to help an animated fish (“Freddy”) shown in center screen to find food.

• Participants were asked to indicate which of the two patches of dots were more numerous (“contained more food”)

• In the baseline condition, “adaptation” was to a neutral numerosity (40 dots each side, the average number in the test. In the adaptation condition the adaptation stimuli comprised 80 dots on the left and 20 dots on the right.
we plotted psychometric functions plotting the proportion of responses where the patch at left appeared more numerous than the patch at right, against the number of dots in the left test patch.

The data were fitted with cumulative Gaussian functions, whose median (50% point) estimates the point of subjective equality (PSE), the point where the two patches are judged equally numerous.

Fig. 2A shows representative psychometric functions for a typical child and Fig. 2B shows those for a child with autism.

After adaptation, however, the curve of the typical child moved to the right, yielding a PSE of 53. This means that for the dot clouds to appear perceptually equal, the side adapted to high numbers needed to contain 54 dots and the other side 27 dots. Adaptation also occurred with the child with autism spectrum disorder (ASD), but to a much lesser extent, with a PSE of 47.
Result 2

- Consider the adaptation effect of the individual participants.
- Define adaptation magnitude as the percentage of increase or decrease in PSE and plotted this on the ordinate of Fig. 3A, separately for children with ASD (red symbols) and typical children (blue symbols).
- Adaptation effects for the autistic children are on average three times less than those for the typical children, and not one single autistic child has adaptation levels that encroach on the 95% confidence intervals for the typical group.
- Difference is significant. $P < 0.0001$
Conclusion

- The results clearly show that children with autism adapt to numerosity much less than typical children, by only one-third as much. Discrimination precision, however, was similar in both groups of children, showing that the difference in adaptation does not reflect inattention or some other more generic difficulty with judging number in these children.

- The underlying (altered) computational mechanisms in reduced adaptation may be more readily explained by the recent Bayesian models of autism which clearly predict that individuals with autism should give less weighting to prior or predictive information, such as the consequences of previous stimulation.
Low load for disruptive mutations in autism genes and their biased transmission


October 2015 issue
Introduction

• 2007: “unified” genetic theory of autism
  • This theory proposes that much of ASD is caused by new mutation, sometimes directly contributing to the disorder through germ-line mutation, or transmitted by parents, especially females, who carry a variant of recent vintage without experiencing severe consequences.
  
• Since then, evidence for causal DN(De novo) mutation has accumulated
• Calculate “vulnerability” in genes: the likelihood that a disruptive mutation in the gene results in ASD.
• ~500 causative ASD target genes
Method

• Obtain measure of tolerance based on ratios of rare disruptive mutations to length in a given gene
• Obtain strong statistical evidence for low disruptive loads in autism genes, especially in the autism genes affecting children of lower IQ, and for preferential transmission of disruptive mutations in rarely disrupted genes from mothers to children with severe ASD.
• Use the tolerance score to reorder the likelihood of candidate autism genes among the known targets.
• Compare gene rankings based on tolerance for LGD(likely gene disruptions) mutations with the RVIS(residual variation intolerance score), a tolerance score derived largely from missense mutations.
Target classes of DN LGD mutations occurring in “sib” (unaffected sibling), “autL” (affected, lower nonverbal IQ half), “autH” (affected, higher nonverbal IQ half), “aut” (all affected), and “rec in aut” (targets hit in >1 affected) are shown. For each class, we report the gene count, and the proportion expected to be causal, as determined by the ascertainment differential (Methods). In successive columns, the numbers of observed UR synonymous and LGD variants are reported, as well as the ratio of the latter to former for each class. Based on permutations of labels, we compute the $P$ value of the observed ratios on the assumption that they arise from a gene class similar to the sibling targets. Target classes from affected children show a markedly lower load for UR LGD variants than the class from siblings, although this difference is not significant for the affected children of higher IQ. We also derived the expected loads in the gene classes by multiplying the fourth column (number of UR syn) by 0.12, the ratio of LGD mutations to synonymous mutations in the unaffected sibling class. The expected loads allow us to compute class vulnerability as the ratio of observed to expected and, more importantly, to use a linear model to compute vulnerability of causal genes within classes (Methods). The estimates of the causal class vulnerability for the true autism genes based on the rec in aut, autL, and aut values are close (0.17, 0.19 and 0.15, respectively) and quite low.

<table>
<thead>
<tr>
<th>DN LGD targets</th>
<th>Gene count</th>
<th>Proportion expected to be causal</th>
<th>No. of UR syn mutations</th>
<th>No. of UR LGD mutations</th>
<th>LGD/syn mutations</th>
<th>$P$ value</th>
<th>Expected no. of UR LGD mutations</th>
<th>Class vulnerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>sib</td>
<td>173</td>
<td>0.02</td>
<td>7,372</td>
<td>881</td>
<td>0.12</td>
<td>0.9842</td>
<td>881</td>
<td>1.00</td>
</tr>
<tr>
<td>rec in aut</td>
<td>39</td>
<td>0.90</td>
<td>2,568</td>
<td>79</td>
<td>0.03</td>
<td>&lt;0.0001</td>
<td>307</td>
<td>0.26</td>
</tr>
<tr>
<td>autL</td>
<td>204</td>
<td>0.44</td>
<td>10,244</td>
<td>790</td>
<td>0.08</td>
<td>0.0011</td>
<td>1,224</td>
<td>0.65</td>
</tr>
<tr>
<td>autH</td>
<td>151</td>
<td>0.30</td>
<td>7,039</td>
<td>678</td>
<td>0.10</td>
<td>0.1066</td>
<td>841</td>
<td>0.81</td>
</tr>
<tr>
<td>aut</td>
<td>509</td>
<td>0.36</td>
<td>24,758</td>
<td>2,062</td>
<td>0.08</td>
<td>0.0009</td>
<td>2,959</td>
<td>0.70</td>
</tr>
</tbody>
</table>
Likelihood of Being an Autism Gene, Given Its Vulnerability.

- Rerank ASD target genes as causal targets using tolerance scores.
- Compute posterior probabilities using the ascertainment differential for that class as a prior to compute LGD ratios between genes in different classes.
- Locally weighted scatterplot smoothing (LOWESS) function.

Numbers of UR variants per gene. (Left) Numbers of UR synonymous variants (x axis) and UR LGD variants (y axis) found in the parents of the SSC and the EVS database for each of ~18,000 protein-coding genes that were successfully captured by whole-exome sequencing. (Right) Similar, with the exception that the y axis represents the number of UR missense variants. Random noise is added to the integer counts for better visibility. In addition to the observed counts, the panels show fits to the number of UR synonymous variants: a linear function fit (red line), $L = a \times S$; a square root fit (yellow line), $L = b \times \sqrt{S}$; and a nonparametric LOWESS fit (blue line). The LOWESS fit agrees closely with the square root model for the number of UR LGD mutations as a function of the number of UR synonymous variants, but it aligns better with the linear fit for the number of UR missense as a function of UR synonymous variants.
Prioritizing using discriminant for whether a gene is a vulnerable autism target or a typical gene

- A gene is typical or vulnerable based on the expectation that a DN target gene in a class is causal (i.e., based on the ascertainment differential of the class).
- Compare the observed mutational load for each gene in our database against the prediction based on the LOWESS fit to the load of UR synonymous mutations, obtaining an expected load for a typical gene.
- Use a Poisson distribution based on that expectation to derive the likelihood for the observed LGD load.
- Assign the expectation for highly vulnerable genes somewhat arbitrarily as 10% of the LGD expectation for a typical gene, given its synonymous load.
Posterior Probabilities calculated for vulnerable autism gene

- Combining the prior with the likelihood of the observed load of UR LGD mutations under the two models provides a global ranking of DN target genes for the classes of recurrent LGD targets, recurrent missense targets, and LGD targets in lower and higher IQ affected individuals.
Conclusion

• Gene targets of de novo mutation in autistic children have a lighter load of rare disruptive variation than typical human genes. This finding suggests such mutations are under negative selection and autism genes are highly vulnerable to mutation.

• Disruptive variants in these genes have biased transmission: They are more frequently transmitted to affected children, and more often from mothers than from fathers.

• Targets of mutation in lower intelligence quotient (IQ) affected children have a lower load of disruptive mutations than targets of mutation in higher IQ affected children.

• Biased transmission is seen more frequently to affected children of lower IQ.

• These observations are consistent with a correlation between severity of mutations and phenotype, and based on them, we list candidate autism genes ordered by likelihood.
Self-motion perception in autism is compromised by visual noise but integrated optimally across multiple senses


May 2015 issue
Introduction

• Descriptions of impaired coherent motion perception in autism spectrum disorder (ASD) underlie theories that individuals with ASD have difficulty integrating local “parts” into a global percept. This notion maintains widespread influence and motivates recent theories of defective multisensory integration in ASD. However, heightened sensitivity to sensory noise, used to manipulate task difficulty in predominant visual motion stimuli, may provide an alternative explanation for impaired performance.

• By manipulating task difficulty independently of visual stimulus noise, here the authors test the hypothesis that heightened sensitivity to noise, rather than integration deficits, may characterize ASD.
ASD example

Behavioral responses of an example participant with ASD are presented for three separate blocks, tested with 100% (A), 90% (B), and 50% (C) visual motion coherence. For each block, psychometric curves represent the ratio of rightward choices as a function of heading direction, based on visual-only (red), vestibular-only (blue), or combined visual–vestibular (green) cues. Data (circles) were fitted with cumulative Gaussian functions (solid lines).

These results are similar to those expected from typical adolescents or adults.

The introduction of visual noise affects visual reliability. Reduced reliability is demonstrated by the deterioration (flattening) of the psychometric curve—seen already with slight noise (90% coherence; Fig. 1B, red curve) and more strongly for higher noise (50% coherence; Fig. 1C, red curve). Despite this steep deterioration in visual reliability, multisensory integration is still evident in the combined condition: In Fig. 1C, the participant relies primarily on the now-more-reliable vestibular cue (the green curve is now more similar to the blue curve). Also, when the cues are of more similar reliability (Fig. 1B), the combined cue is more reliable than each of the individual cues alone.
ASD Sensitivity to Visual Noise

(A) Filled and textured red bars represent the log-scale mean ± SEM visual psychometric thresholds for 100% and 90% motion coherence, respectively. These were similar for controls (left) but significantly different for participants with ASD (right). *$P < 0.05$.

(B) Left - Red solid and dashed lines represent the log-scale mean visual thresholds, as a function of visual motion coherence for participants with ASD and controls, respectively. Error bars mark 1 SEM. Right - Similarly, black solid and dashed lines represent the mean visual-to-vestibular threshold ratios for participants with ASD and controls, respectively.

(C) Filled blue bars represent the log-scale mean ± SEM vestibular psychometric thresholds, which were similar for control and ASD participants.

The little noise added during 90% coherence is largely undisruptive in normal participants, but it largely affects participants with ASD, who demonstrated a significant increase in threshold.

Participants with ASD are more strongly affected by visual sensory noise. ($P = 0.004$)
Conclusion

• Results found that although perception of visual motion through a cloud of dots was unimpaired without noise, the addition of stimulus noise significantly affected adolescents with ASD, more than controls.

• Strikingly, individuals with ASD demonstrated intact multisensory (visual–vestibular) integration, even in the presence of noise.

• Additionally, when vestibular motion was paired with pure visual noise, individuals with ASD demonstrated a different strategy than controls, marked by reduced flexibility. This result could be simulated by using attenuated (less reliable) and inflexible (not experience-dependent) Bayesian priors in ASD.
Conclusion

• Here the authors indeed found increased sensitivity in ASD to sensory noise. Noiseless motion perception and multisensory integration (even with noise) were unimpaired. These findings question prevalent theories of global and multisensory integration deficits in ASD. Rather, they suggest increased reliance on—and sensitivity to—incoming sensory information and less use of prior knowledge in ASD.
A computational perspective on autism


July 2015 issue
Introduction

• The authors propose that alterations in nonlinear, canonical computations occurring throughout the brain may underlie the behavioral characteristics of autism.

• One such computation, called divisive normalization, balances a neuron’s net excitation with inhibition reflecting the overall activity of the neuronal population.

• Through neural network simulations, we investigate how alterations in divisive normalization may give rise to autism symptomatology.
Evidence for an E/I Imbalance in Autism

- E/I imbalance can alter neurodevelopment
- Autism symptomatology arises from an increased E/I ratio
- An increased E/I ratio is also supported by biochemical analyses
- Divisive normalization = dividing the net excitatory drive to a neuron by a measure of the population activity
  - Affects neural activity
  - Autism may affect multiple parameters involved in calculation of the model neuron response equation
  - supressive field gain term (c) : which determines the context sensitivity of the neurons, controlling how much each neuron's responses are influenced by the stimulus-dependent population activity.
  - Defined “autism model” of primary visual cortex in which there is a 25% reduction in c relative to the “typically developing control” model.
Simulation 1: Visual Spatial Suppression

(A) Psychophysical data showing that the ability to judge direction of motion decreases as stimulus size increases for high contrast stimuli. This is true for both typically developing controls (TD; red) and subjects with autism (ASD; blue), but ASD subjects consistently outperform TD subjects. Larger inverse thresholds indicate better performance.

(B) Psychophysical data showing that for a small stimulus, ASD and TD subjects perform equivalently in judging direction of motion for a low-contrast stimulus, but ASD subjects perform better when the stimulus has a high contrast.

(C) Simulation results showing population gains for the control (red) and autism (blue) models as a function of stimulus size for high contrast stimuli. The models’ responses follow the same pattern as the psychophysical data in A.

(D) Simulation results for the control and autism models as a function of stimulus contrast for small stimuli. The models’ responses follow the same pattern as the psychophysical data in B.
**Simulation 2: Tunnel Vision**

(A) Psychophysical data showing that performance worsens as the target distance from the cue increases for both typically developing controls (TD; red) and subjects with autism (ASD; blue). Larger relative performance scores indicate faster, more accurate detection. Note that the rate at which performance decays is greater for ASD than TD subjects (there is greater overall change).

(B) Psychophysical data showing that the performance gradient increases with the degree of autism symptomatology assessed using the autism spectrum quotient (AQ). ASD subjects (blue points) were identified based on Autism Diagnostic Observation Schedule scores.

(C) Simulation results showing population gains for the control (red) and autism (blue) models as a function of target distance from the cue. The models' responses follow the same pattern as the psychophysical data in A and further reproduce the nonmonotonic shape of the attentional field. To highlight the gradient difference between the control and autism models, the y axes are shifted to align the troughs of the curves.

(D) Simulation results showing that, as the suppressive field gain term decreases (simulating an increasing degree of autism symptomatology), the gradient of the population gain increases, consistent with the psychophysical data in B. The colored dots correspond to the control and autism models in C.

As the distance between the attentional cue and target increases, the rate at which performance falls off is greater for subjects with autism than typically developing controls, suggesting there is a sharper gradient of attention in autism, or “tunnel vision.”
Simulation 3: Neural Implementation of Bayesian Priors

• How Bayesian priors can be implemented through divisive normalization, establishing a link between alterations in neural computation and high-level hypotheses about how autism affects the ability to perform statistical inference.

• An attenuation of Bayesian priors correctly predicts reduced differences in sensitivity to cardinal and oblique orientations in autism.

• Divisive normalization can account for the proposed attenuation of Bayesian priors by reduction in the suppressive field gain term (c) to reduce effect of priors.

• Consistent with the observation that many autism susceptibility genes code for synaptic proteins or control synaptic development and function, suggesting that the effect of experience on synapses is altered in autism.
Conclusion

• In this paper, the authors propose that autism symptomatology reflects alterations in neural computation.

• Using neural network simulations, they show that a reduction in the amount of inhibition occurring through a computation called divisive normalization can account for perceptual consequences reported in autism, as well as proposed changes in the extent to which past experience influences the interpretation of current sensory information in individuals with the disorder.

• The findings show that a reduction in the amount of inhibition that occurs through divisive normalization can account for perceptual consequences of autism, consistent with the hypothesis of an increased ratio of neural excitation to inhibition (E/I) in the disorder.
Thank you for your patience