Review

Biological Psychiatry

Vision as a Beachhead

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ABSTRACT

When neural circuits develop abnormally due to different genetic deficits and/or environmental insults, neural computations and the behaviors that rely on them are altered. Computational theories that relate neural circuits with specific quantifiable behavioral and physiological phenomena, therefore, serve as extremely useful tools for elucidating the neuropathological mechanisms that underlie different disorders. The visual system is particularly well suited for characterizing differences in neural computations; computational theories of vision are well established, and empirical protocols for measuring the parameters of those theories are well developed. In this article, we examine how psychophysical and neuroimaging measurements from human subjects are being used to test hypotheses about abnormal neural computations in autism, with an emphasis on hypotheses regarding potential excitation/inhibition imbalances. We discuss the complexity of relating specific computational abnormalities to particular underlying mechanisms given the diversity of neural circuits that can generate the same computation, and we discuss areas of research in which computational theories need to be further developed to provide useful frameworks for interpreting existing results. A final emphasis is placed on the need to extend existing ideas into developmental frameworks that take into account the dramatic developmental changes in neurophysiology (e.g., changes in excitation/inhibition balance) that take place during the first years of life, when autism initially emerges.

Keywords: Autism, Computational theory, E/I balance, Neuroimaging, Psychophysics, Sensory, Vision, Visual cortex

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The excitation/inhibition (E/I) imbalance hypothesis posits that autism is caused by abnormally high E/I ratios throughout the brain, due to excessive excitation, weak inhibition, or both (1–4). Evidence in favor of this hypothesis comes mostly from genetic association (5–7), postmortem (8,9), and animal model (10–13) studies. Furthermore, increased excitation and/or reduced inhibition are basic characteristics of epilepsy (14), which is a common comorbidity of autism (15,16). Indeed, many syndromic forms of autism including Rett, Dravet, Angelman, and fragile X syndromes and tuberous sclerosis are associated with high rates of epilepsy (17,18) and/or subclinical epileptiform activity (19).

When considering the potential cognitive and behavioral impact of E/I imbalances, it is important to consider the timing of their appearance. For example, individuals who develop epilepsy during adulthood exhibit some cognitive impairments but generally tend to live out full and productive lives (20). However, when epilepsy is evident during infancy or childhood, cognitive impairments tend to be much more severe (21), as is the case, for example, in infantile spasms (22) and Landau-Kleffner syndrome (23). This vulnerability to damage by early E/I imbalances may be associated with the closure of critical periods that solidify the function of neural circuits according to early neural activity (24).

The E/I balance changes dramatically during fetal development and in the first year of life. Most prominently, the existence of high intracellular chloride concentrations during fetal development means that gamma-aminobutyric acid (GABA) is an excitatory neurotransmitter during this period (25). The lack of inhibition during these early developmental periods is associated with giant depolarization potentials that are highly synchronized across vast neural populations of the developing brain (26). Establishing adult-like E/I balance involves a long sequence of developmental alterations as neurons migrate, differentiate, form synapses, and alter their intracellular ionic concentrations and membrane conductance properties (27,28). A critical stage of this maturation happens at birth, when neural systems are exposed to external input and activity-dependent plasticity takes on a leading role in shaping neural activity and architecture (29). Ensuing development of the different sensory, motor, and cognitive systems is associated with considerable changes in neural selectivity and reliability, which are thought to depend largely on the maturation of inhibitory GABAergic interneurons during experience-dependent critical periods (30). Many physiological mechanisms are involved in developing and maintaining E/I balances throughout the brain (31), and different pathologies are therefore likely to be associated with distinct forms of spatiotemporal E/I imbalances. Consequently, neural computation in the adult brain relies on the proper early development and maintenance of the E/I balance.

In this article, we examine how computational theories, specifically those stemming from human visual psychophysics and related neuroimaging studies, may be used to inform us about the neuropathology of autism and the potential links to underlying E/I imbalances. Although neither psychophysics

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nor neuroimaging is capable of directly measuring synaptic excitation and inhibition, these two methodologies have the potential for offering valuable information when three conditions are met. First, the empirical phenomena must be detailed, robust, and replicable. Second, there must be a computational theory that accounts for the empirical findings and is able predict individual differences in perception and brain activity when tested in different situations and using different stimuli. Third, there needs to be sufficient physiological evidence elucidating the underlying circuit and cellular mechanisms that perform the computation. If all of these criteria are met, positive findings would not only provide support for the E/I imbalance hypothesis, but would also provide practical noninvasive measures (i.e., biomarkers) that could be used for diagnosis, tracking the efficacy of existing interventions, and testing new interventions. The visual system is particularly well suited for this particular program of research; computational theories of vision are well established, and empirical protocols for measuring the parameters of those theories are well developed.

COMPUTATIONAL THEORY

The neocortex has a modular design with modular circuits and with modular computations. Anatomical evidence suggests the existence of canonical microcircuits that are replicated across cortical areas (32,33). Consequently, it has been hypothesized that the brain relies on a set of canonical neural computations, repeating them across brain regions and sensory modalities and thereby applying similar operations of the same form, hierarchically, to achieve different behavioral goals (34–38). Examples of proposed canonical computations include feedforward selectivity (39), habituation/adaptation (40), oscillatory synchronization (41), divisive normalization (38), and predictive coding (42). The great power of these mathematical models is that they can accurately explain a variety of robust perceptual and behavioral phenomena, regardless of how they may be implemented in neural circuits of different brain areas and species (e.g., see Normalization, below). Identifying abnormalities in specific computations in individuals with particular psychiatric and neurodevelopmental disorders would, therefore, be extremely useful for characterizing the neuropathology or neuropathologies apparent in each disorder.

Although this logic is very appealing, empirical studies that have used computational theories to try to explain perceptual and behavioral differences in autism have reported inconsistent results. We discuss some of these efforts and consider how they may be improved in the future while keeping in mind that 1) autism is a family of distinct biological disorders (43,44) in which different individuals likely exhibit abnormalities in different computations and 2) autism is a developmental disorder, and it is essential to acquire empirical evidence at early ages to determine the validity of potential findings (i.e., existence of altered computations) during autism onset (45).

BINOCULAR RIVALRY

A perceptual phenomenon called binocular rivalry occurs when incompatible monocular images are presented to the two eyes (46,47). For example, when one eye is presented with an oriented grating and the other eye is presented with an orthogonally oriented grating, separate neural populations in early visual cortex represent each of the stimuli and actively compete, such that observers experience alternating periods of dominance in which one grating is visible and the other is invisible or nearly invisible. Several computational models have been proposed to characterize the alternating periods of perceptual dominance experienced during rivalry [e.g., (48–50)]. These models rely on a balance of excitation and inhibition between neurons representing the two competing percepts, so that when one percept is dominant the other percept is suppressed. The models typically include subtractive inhibition (possibly GABA mediated) to account for the ability of the currently dominant neural ensemble to suppress the competing neural ensemble, and adaptation or noise/variability to account for alternations between percepts and the neural ensembles that represent them. An E/I imbalance in autism would, therefore, be expected to generate several perceptual changes that can be measured with simple behavioral/psychophysical methods. Such psychophysical measures could then be applied in a computational model to estimate the underlying levels of neural excitation and inhibition.

To test this hypothesis, we conducted two experiments with high-functioning adults with autism and with IQ- and age-matched control subjects (51). In the first experiment, we examined mixed perception during presentation of traditional rival stimuli. Typically, when the two eyes are presented with incompatible images, perception alternates between the two eyes. However, a mixture of the two images may be perceived for a portion of the time. Using model simulations, we determined that low levels of either cortical inhibition or cortical excitation would cause an increase in mixed perception. In the second experiment, we measured the speed of alternation from one percept to the other by presenting large rival stimuli that create traveling waves in which the dominance of one percept emerges locally and then expands to overtake the other. Using model simulations, we determined that low levels of inhibition or high levels of excitation would cause an increase in the speed of traveling waves. The two experiments were, therefore, complementary tests of the E/I imbalance hypothesis, to distinguish atypical levels of excitation from atypical levels of inhibition. A high E/I ratio would be evident in high traveling wave speeds. A high level of both excitation and inhibition would be evident in a low proportion of mixed perception and slow traveling wave speeds. Normal excitation and inhibition levels would be evident in a normal proportion of mixed perception and normal travelling wave speeds. Surprisingly, the empirical data revealed no significant differences in any of these measures across autism and control groups, and no evidence for a relationship between the binocular rivalry measures and the severity of autism.

In contrast with our findings, two subsequent studies using either gratings or objects as stimuli reported that the dynamics of binocular rivalry are different in autism (52,53). Specifically, individuals with autism demonstrated a slower rate of binocular rivalry alternations and longer durations of mixed percepts than matched control subjects. Applying these psychophysical findings to the computational models described above (51)

suggests that individuals with autism have weaker inhibition than control subjects. A follow up study using magnetic resonance spectroscopy reported that GABA levels in visual cortex were similar across the autism and control groups, but revealed that the typical correlation between binocular rivalry dynamics and GABA levels that appears across control individuals was absent in the individuals with autism (54).

Assuming that the computational models of binocular rivalry are correct, these findings suggest that there may be differences in inhibition levels in at least some individuals with autism, which are not associated with a general decrease in GABA concentrations. Possible explanations may include differences in the amount or function of GABA receptors (5–7). Although these results are inspiring, it will be important to determine why they were not apparent in our earlier experiments. A possible explanation may be that differences in binocular rivalry dynamics may be apparent only in some, but not in all, individuals with autism, an idea consistent with the growing recognition that there may be multiple autisms. Furthermore, developing protocols for examining binocular rivalry in young children will be necessary to determine whether similar findings are apparent during early stages of autism development.

NORMALIZATION

Divisive normalization is a canonical computation that explains stimulus-evoked neural responses apparent in many brain systems across multiple species (38,55). The defining characteristic of normalization is that the response of each neuron is divided by a factor that includes the summed activity of a pool of neurons. For example, in V1, the normalization pool (the neurons that contribute to the denominator) may include neurons selective for a range of orientations and spatial positions (i.e., receptive field locations). Normalization thereby predicts and explains well-documented neuronal effects, such as cross-orientation suppression in which the response of a V1 neuron to its preferred orientation is suppressed when the stimulus is superimposed with an orthogonal orientation. The extent to which the response is suppressed (i.e., normalized) depends on the relative contrasts of the two orthogonal orientations (38). Analogous psychophysical effects are evident in orientation-discrimination thresholds, which are higher when a cross-orientation mask is added to the stimuli (56). Normalization can be implemented in a recurrent neural circuit using a variety of distinct mechanisms. For example, normalization is implemented by GABA-mediated presynaptic inhibition in the olfactory system of the fruit fly (57,58), but it seems to be implemented by a decrease in excitation (59), rather than by GABA inhibition, in at least some parts of mammalian cortex (60). Regardless of the underlying mechanism, examining psychophysical phenomena associated with normalization (e.g., cross-orientation suppression) in individuals with autism would offer a powerful tool for characterizing potential E/I imbalances in autism.

With this in mind, it has recently been proposed that autism may be characterized by abnormal divisive normalization due to weak inhibition (61). Part of the support for this conjecture is a study that reported differences in spatial suppression in children with autism (62). Spatial suppression is a perceptual phenomenon that describes a counterintuitive reversal of motion perception (63). The observer's task is to report the direction of motion (right or left) of a vertically oriented grating pattern (alternating dark–bright stripes). The phenomenon is quantified by measuring duration thresholds: the minimal duration for which performance is reliably better than chance. Both the size and contrast of the grating are varied across trials. When typical observers view low-contrast stimuli, the duration thresholds are shorter (performance is better) as stimulus size increases. However, for high-contrast stimuli, the duration thresholds are longer (worse performance) for larger stimulus sizes. That is, the direction of motion is harder to perceive correctly even though the grating pattern is more readily visible (large and high contrast). It has been hypothesized that this phenomenon can be explained by normalization, which predicts stronger inhibition in responses to higher contrasts. Because children with autism exhibited more accurate motion perception than the control group at higher contrasts (62), it was suggested that children with autism have abnormal normalization due to weak inhibition (61).

Spatial suppression experiments with typical participants, however, have revealed several findings that are not compatible with normalization. First, motion perception is adversely affected only for opposite (e.g., right/left) and not for orthogonal (e.g., rightward/upward) motion directions (unpublished observations). Second, the effect is specific to duration thresholds, and not to other measures of motion perception such as direction-discrimination thresholds (DJ Heeger, Ph.D., unpublished observations, 2014). Third, typical observers consistently perceive the motion direction of large, high-contrast gratings as moving in the opposite direction of their physical motion (e.g., leftward motion is reliably perceived as rightward, and vice versa) (64,65). Normalization, however, predicts that motion direction would become indistinguishable (i.e., performance should be at chance level) rather than reliably perceived as the opposite of the stimulus motion. So it is unlikely that spatial suppression can be explained by the normalization model. It may therefore be misleading to apply the normalization model to interpret psychophysical findings from spatial suppression experiments in terms of excitation and inhibition levels. Although there may be differences in spatial suppression between children with autism and control subjects, they do not necessarily indicate a problem with normalization or inhibition. Therefore, further studies about E/I imbalances in autism would benefit from using standard psychophysical and neuroimaging protocols that have been developed to measure normalization, such as cross-orientation suppression and surround suppression (38,56,66,67).

RELIABILITY OF SENSORY-EVOKED RESPONSES

The original E/I imbalance hypothesis of autism proposed that E/I imbalances would generate abnormally noisy/variable neural activity (1). Several psychophysics studies have indeed reported greater trial-to-trial variability in ratings of tactile pleasantness (68) or roughness (69). Individuals with autism also exhibit more variable movement kinematics, as documented by several motor control studies (70). Furthermore, high-functioning adults with autism exhibit excessive trial-to-trial variability in functional magnetic resonance imaging

responses of visual, auditory, and somatosensory cortices (71,72). Similarly, adolescents with autism exhibit excessive variability in visually evoked potentials measured with electroencephalography (73). Note that in both functional magnetic resonance imaging and electroencephalogram studies, the mean response amplitudes were statistically indistinguishable across groups, but trial-to-trial variability in evoked responses was significantly greater in autism.

Although the behavioral and clinical significance of behavioral and neural variability are topics of active research (74), there is, as yet, no computational theory that predicts the magnitude of neural response variability in typical individuals or relates variability to specific (or altered) levels of excitation or inhibition. This issue is further complicated by the fact that neural and behavioral variability changes dramatically throughout development, with children exhibiting far larger variability than adults (75,76). Hence, the ability to use behavioral or neural variability measures as quantitative indicators of E/I balance will require the development of a corresponding computational theory.

MINIMIZING ENERGY, MAXIMIZING INFORMATION TRANSFER

Maintaining a gross E/I balance in the brain is a fundamental necessity due to the limited availability of energy. The human brain consumes about 20% of the body's energy during rest in adulthood and about 50% in childhood (77). Most of this energy is used for neural signaling/spiking (78), which requires maintaining and restoring ionic balances (Na^+/K^+ and Ca^{2+}) and recycling the glutamate that is released by excitatory neurons that comprise 80–90% of the neurons in the cortex (79). The energy cost of neural spiking is so high that only a small fraction of the neurons in the brain can be active concurrently (80) and then require fast irrigation with oxygenated blood at a level that is proportional to the amplitude of neural activity (81,82). When neural energy requirements are not met due to a shortage of oxygen, neurons are notoriously susceptible to damage and cell death, as in, for example, cases of ischemia (83).

Neural systems in the adult brain, therefore, maximize information transfer while minimizing firing rates (84,85). This is achieved by different types of inhibitory interneurons that quickly respond to excitatory neural activity and counter excitatory synaptic currents with equally strong inhibitory currents (86). When functioning correctly, this tightly orchestrated balancing act not only dampens excitation (i.e., limits overall spike rates), but also synchronizes neural activity by forming oscillations at specific frequencies (87) and sharpens the tuning of sensory neurons to specific sensory features (88) and temporal events (89). Although the E/I balance can change dynamically across different brain states (90) and task demands (91), numerous homeostatic mechanisms ensure that it remains within a limited range (31,92).

Neural circuits adapt through development, presumably to optimize particular homeostatic criteria. These homeostatic criteria are not (yet) known, but it is reasonable to hypothesize, for example, that a circuit aims to maintain a particular level (averaged over a period of time) of mean response amplitudes. Neural circuits with deficits in synaptic function also adapt through development toward the same (or similar) homeostatic criteria as intact circuits. If there is a deficit in a particular GABA receptor subunit, for example, then the circuit will upregulate other inhibitory mechanisms and/or downregulate excitatory mechanisms. In doing so, however, some other aspect of circuit function might be lost. Continuing with the same example, attempting to optimize mean responses might require sacrificing response reliability. Any number of physiological deficits might affect the mean responses, thereby invoking similar compensatory processes. Consequently, different deficits (caused by different genetic predispositions or environmental insults) might lead through development to a similar outcome. The compensatory processes will rely, however, on the availability of functioning mechanisms, so two individuals with the same initial deficit might rely on different compensatory mechanisms because of different genetic backgrounds or developmental histories. Consequently, it should not be surprising that the same initial deficit (either genetic or environmental) can lead, through development, to different outcomes. So, even in the best-case scenario, a common developmental outcome would be applicable to only a subpopulation of individuals with autism, and heterogeneity would be evident across the population.

Developing and testing computational theories that specify the homeostatic criteria that are being optimized during development could go a long way toward understanding when different initial deficits lead to common outcomes or when common initial deficits lead to different outcomes (e.g., different subtypes of autism, or different types of developmental disorders). We are neither advocating more research into the sequence of steps that occurs during development nor advocating more research into the mechanisms of development, but rather suggesting a complementary line of research to characterize optimization criteria at a computational or normative level of abstraction. For example, perhaps neural circuits develop under the constraints of minimizing energy utilization while maximizing information transfer, analogous to minimizing energy and maximizing entropy in a physical system. Characterizing the optimized performance parameters and their development across the lifespan will provide new ways of determining how different individuals with neurodevelopmental disorders deviate from the norm. We suggest that this will yield important information for understanding their underlying neuropathologies.

CONCLUSIONS

Although there is indeed evidence that larger E/I ratios may contribute to the abnormal development of autism, it is important to remember that other studies have reported decreased E/I ratios in autism. These include reports of several autism animal models that exhibit abnormally low excitation (93), abnormally high inhibition (94), or a mixture of different imbalances in different brain areas (95). These findings demonstrate the heterogeneity of underlying etiologies in different subgroups of individuals with autism, which have also been acknowledged repeatedly in genetic studies (43,44). With this in mind, we suggest that using psychophysics and neuroimaging techniques along with computational theories, as described throughout this article, may offer a fruitful way of

identifying and characterizing specific subgroups of individuals with autism who share more homogeneous etiologies. Furthermore, computational theories that can explain developmental changes and potential neurodevelopmental abnormalities are currently missing, and their development is highly warranted.

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ARTICLE INFORMATION

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REFERENCES

1. Rubenstein JLR, Merzenich MM (2003): Model of autism: Increased ratio of excitation/inhibition in key neural systems. Genes, Brain Behav 2:255–267.
2. Markram H, Rinaldi T, Markram K (2007): The Intense World Syndrome – An alternative hypothesis for autism. Front Neurosci 1:77–96.
3. Jamain S, Radyushkin K, Hammerschmidt K, Granon S, Boretius S, Varoqueaux F, *et al*. (2008): Reduced social interaction and ultrasonic communication in a mouse model of monogenic heritable autism. Proc Natl Acad Sci U S A105:1710–1715.
4. Vattikuti S, Chow CC (2010): A computational model for cerebral cortical dysfunction in autism spectrum disorders. Biol Psychiatry 67: 672–678.
5. Collins AL, Ma D, Whitehead PL, Martin ER, Wright HH, Abramson RK, *et al*. (2006): Investigation of autism and GABA receptor subunit genes in multiple ethnic groups. Neurogenetics 7:167–174.
6. Sanders SJ, Ercan-Sencicek AG, Hus V, Luo R, Murtha MT, Moreno-De-Luca D, *et al*. (2011): Multiple recurrent de novo CNVs, including duplications of the 7q11.23 Williams syndrome region, are strongly associated with autism. Neuron 70:863–885.
7. Chen C-H, Huang C-C, Cheng M-C, Chiu Y-N, Tsai W-C, Wu Y-Y, *et al*. (2014): Genetic analysis of GABRB3 as a candidate gene of autism spectrum disorders. Mol Autism 5:36.
8. Fatemi SH, Reutiman TJ, Folsom TD, Thuras PD (2009): GABA(A) receptor downregulation in brains of subjects with autism. J Autism Dev Disord 39:223–230.
9. Fatemi SH, Reutiman TJ, Folsom TD, Rustan OG, Rooney RJ, Thuras PD (2014): Downregulation of GABAA receptor protein subunits α6, β2, δ, ε, γ2, θ, and ρ2 in superior frontal cortex of subjects with autism. J Autism Dev Disord 44:1833–1845.
10. Chao H-T, Chen H, Samaco RC, Xue M, Chahrour M, Yoo J, *et al*. (2010): Dysfunction in GABA signalling mediates autism-like stereotypies and Rett syndrome phenotypes. Nature 468:263–269.
11. Gogolla N, Leblanc JJ, Quast KB, Südhof TC, Fagiolini M, Hensch TK (2009): Common circuit defect of excitatory-inhibitory balance in mouse models of autism. J Neurodev Disord 1:172–181.
12. Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, *et al*. (2011): Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature 477:171–178.
13. Rinaldi T, Silberberg G, Markram H (2007): Hyperconnectivity of local neocortical microcircuitry induced by prenatal exposure to valproic acid. Cereb Cortex 18:763–770.
14. Scharfman HE (2007): The neurobiology of epilepsy. Curr Neurol Neurosci Rep 7:348–354.
15. Tuchman R, Rapin I (2002): Review Epilepsy in autism 1:352–358.
16. Jeste SS, Tuchman R (2015): Autism spectrum disorder and epilepsy: Two sides of the same coin? J Child Neurol 30:1963–1971.
17. Nelson SB, Valakh V (2015): Excitatory/inhibitory balance and circuit homeostasis in autism spectrum disorders. Neuron 87:684–698.
18. Tai C, Abe Y, Westenbroek RE, Scheuer T, Catterall WA (2014): Impaired excitability of somatostatin- and parvalbumin-expressing cortical interneurons in a mouse model of Dravet syndrome. Proc Natl Acad Sci U S A 111:E3139–E3148.
19. Ghacibeh GA, Fields C (2015): Interictal epileptiform activity and autism. Epilepsy Behav 47:158–162.
20. Elger CE, Helmstaedter C, Kurthen M (2004): Chronic epilepsy and cognition. Lancet Neurol 3:663–672.
21. Lespinet V, Bresson C, N'Kaoua B, Rougier A, Claverie B (2002): Effect of age of onset of temporal lobe epilepsy on the severity and the nature of preoperative memory deficits. Neuropsychologia 40: 1591–1600.
22. Widjaja E, Go C, McCoy B, Snead OC (2015): Neurodevelopmental outcome of infantile spasms: A systematic review and meta-analysis. Epilepsy Res 109:155–162.
23. Pearl PL, Carrazana EJ, Holmes GL (2001): The Landau-Kleffner Syndrome. Epilepsy Curr 1:39–45.
24. Hensch TK (2005): Critical period plasticity in local cortical circuits. Nat Rev Neurosci 6:877–888.
25. Rivera C, Voipio J, Payne JA, Ruusuvuori E, Lahtinen H, Lamsa K, *et al*. (1999): The K+/Cl- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. Nature 397:251–255.
26. Cellot G, Cherubini E (2013): Functional role of ambient GABA in refining neuronal circuits early in postnatal development. Front Neural Circuits 7:136.
27. Bystron I, Blakemore C, Rakic P (2008): Development of the human cerebral cortex: Boulder Committee revisited. Nat Rev Neurosci 9: 110–122.
28. Dorrn AL, Yuan K, Barker AJ, Schreiner CE, Froemke RC (2010): Developmental sensory experience balances cortical excitation and inhibition. Nature 465:932–936.
29. Ben-Ari Y (2015): Is birth a critical period in the pathogenesis of autism spectrum disorders? Nat Rev Neurosci 16:498–505.
30. Takesian AE, Hensch TK (2013): Changing Brains: Applying Brain Plasticity to Advance and Recover Human Ability. Progress in Brain Research, vol. 207. New York: Elsevier.
31. Turrigiano G (2011): Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. Annu Rev Neurosci 34:89–103.
32. Douglas RJ, Martin KA (1991): A functional microcircuit for cat visual cortex. J Physiol 440:735–769.
33. Douglas RJ, Koch C, Mahowald M, Martin KA, Suarez HH (1995): Recurrent excitation in neocortical circuits. Science 269:981–985.
34. Heeger DJ, Simoncelli EP, Movshon JA (1996): Computational models of cortical visual processing. Proc Natl Acad Sci U S A 93:623–627.
35. Riesenhuber M, Poggio T (2002): Neural mechanisms of object recognition. Curr Opin Neurobiol 12:162–168.
36. Riesenhuber M, Poggio T (1999): Hierarchical models of object recognition in cortex. Nat Neurosci 2:1019–1025.
37. Simoncelli EP, Heeger DJ (1998): A model of neuronal responses in visual area MT. Vision Res 38:743–761.
38. Carandini M, Heeger DJ (2012): Normalization as a canonical neural computation. Nat Rev Neurosci 13:51–62.
39. Miller KD (2016): Canonical computations of cerebral cortex. Curr Opin Neurobiol 37:75–84.
40. Brenner N, Bialek W, de Ruyter van Steveninck R (2000): Adaptive rescaling maximizes information transmission. Neuron 26:695–702.
41. Siegel M, Donner TH, Engel AK (2012): Spectral fingerprints of large-scale neuronal interactions. Nat Rev Neurosci 13:121–134.

42. Bastos AM, Usrey WM, Adams RA, Mangun GR, Fries P, Friston KJ (2012): Canonical microcircuits for predictive coding. Neuron 76: 695–711.
43. State MW, Šestan N, Jamain S, Sebat J, Szatmari P, State MW, *et al*. (2012): Neuroscience. The emerging biology of autism spectrum disorders. Science 337:1301–1303.
44. Abrahams BS, Geschwind DH (2008): Advances in autism genetics: On the threshold of a new neurobiology. Nat Rev Genet 9:341–355.
45. Courchesne E, Pierce K, Schumann CM, Redcay E, Buckwalter JA, Kennedy DP, Morgan J (2007): Mapping early brain development in autism. Neuron 56:399–413.
46. Blake R, Logothetis NK (2002): Visual competition. Nat Rev Neurosci 3:13–21.
47. Wheatstone C (1962): On some remarkable and hitherto unobserved phenomena of binocular vision. Optom Wkly 53:2311–2315.
48. Laing CR, Chow CC (n.d.): A spiking neuron model for binocular rivalry. J Comput Neurosci 12:39–53.
49. Said CP, Heeger DJ (2013): A model of binocular rivalry and cross-orientation suppression. PLoS Comput Biol 9:e1002991.
50. Wilson HR (2003): Computational evidence for a rivalry hierarchy in vision. Proc Natl Acad Sci U S A 100:14499–14503.
51. Said CP, Egan RD, Minshew NJ, Behrmann M, Heeger DJ (2013): Normal binocular rivalry in autism: Implications for the excitation/inhibition imbalance hypothesis. Vision Res 77:59–66.
52. Freyberg J, Robertson CE, Baron-Cohen S (2015): Reduced perceptual exclusivity during object and grating rivalry in autism. J Vis 15:11.
53. Robertson CE, Kravitz DJ, Freyberg J, Baron-Cohen S, Baker CI (2013): Slower rate of binocular rivalry in autism. J Neurosci 33:16983–16991.
54. Robertson CE, Ratai E-M, Kanwisher N (2016): Reduced GABAergic action in the autistic brain. Curr Biol 26:80–85.
55. Heeger DJ (1992): Normalization of cell responses in cat striate cortex. Vis Neurosci 9:181–197.
56. Brouwer GJ, Heeger DJ (2011): Cross-orientation suppression in human visual cortex. J Neurophysiol 106:2108–2119.
57. Olsen SR, Bhandawat V, Wilson RI (2010): Divisive normalization in olfactory population codes. Neuron 66:287–299.
58. Olsen SR, Wilson RI (2008): Lateral presynaptic inhibition mediates gain control in an olfactory circuit. Nature 452:956–960.
59. Sato TK, Haider B, Häusser M, Carandini M (2016): An excitatory basis for divisive normalization in visual cortex. Nat Neurosci 19:568–570.
60. Katzner S, Busse L, Carandini M (2011): GABAA inhibition controls response gain in visual cortex. J Neurosci 31:5931–5941.
61. Rosenberg A, Patterson JS, Angelaki DE (2015): A computational perspective on autism. Proc Natl Acad Sci U S A 112:9158–9165.
62. Foss-Feig JH, Tadin D, Schauder KB, Cascio CJ (2013): A substantial and unexpected enhancement of motion perception in autism. J Neurosci 33:8243–8249.
63. Tadin D, Lappin JS, Gilroy LA, Blake R (2003): Perceptual consequences of centre-surround antagonism in visual motion processing. Nature 424:312–315.
64. Glasser DM, Tadin D (2013): Reliable non-veridical perception of brief moving stimuli. J Vis 13:764–764.
65. Glasser DM, Tadin D, Pack CC (2014): Motion reversal reveals mechanisms of perceptual suppression. J Vis 14:472–472.
66. Zenger-Landolt B, Heeger DJ (2003): Response suppression in v1 agrees with psychophysics of surround masking. J Neurosci 23: 6884–6893.
67. Petrov Y, Carandini M, McKee S (2005): Two distinct mechanisms of suppression in human vision. J Neurosci 25:8704–8707.
68. Cascio CJ, Moana-Filho EJ, Guest S, Nebel MB, Weisner J, Baranek GT, Essick GK (2012): Perceptual and neural response to affective tactile texture stimulation in adults with autism spectrum disorders. Autism Res 5:231–244.
69. Haigh SM, Minshew N, Heeger DJ, Dinstein I, Behrmann M (2016): Over-responsiveness and greater variability in roughness perception in autism. Autism Res 9:393–402.
70. Gowen E, Hamilton A (2013): Motor abilities in autism: A review using a computational context. J Autism Dev Disord 43:323–344.
71. Haigh SM, Heeger DJ, Dinstein I, Minshew N, Behrmann M (2015): Cortical variability in the sensory-evoked response in autism. J Autism Dev Disord 45:1176–1190.
72. Dinstein I, Heeger DJ, Lorenzi L, Minshew NJ, Malach R, Behrmann M (2012): Unreliable evoked responses in autism. Neuron 75:981–991.
73. Milne E (2011): Increased intra-participant variability in children with autistic spectrum disorders: Evidence from single-trial analysis of evoked EEG. Front Psychol 2:1–12.
74. Dinstein I, Heeger DJ, Behrmann M (2015): Neural variability: Friend or foe? Trends Cogn Sci 19:322–328.
75. MacDonald SWS, Nyberg L, Bäckman L (2006): Intra-individual variability in behavior: Links to brain structure, neurotransmission and neuronal activity. Trends Neurosci 29:474–480.
76. Ölveczky BP, Otchy TM, Goldberg JH, Aronov D, Fee MS (2011): Changes in the neural control of a complex motor sequence during learning. J Neurophysiol 106:386–397.
77. Clarke DD, Sokoloff L (1999): Chapter 31: Circulation and energy metabolism of the brain. In: Siegel GJ, Agranoff BW, Albers RW, Fisher SK, Uhler MD, editors. Basic Neurochemistry: Molecular, Cellular, and Medical Aspects. Philadelphia: Lippincott-Raven, pp 637–670.
78. Attwell D, Laughlin SB (2001): An energy budget for signaling in the grey matter of the brain. J Cereb Blood Flow Metab 21:1133–1145.
79. Abeles M (1991): Corticonics: Neural Circuits of the Cerebral Cortex, vol. 6. New York: Cambridge University Press. Available at. https://books.google.com/books?id=v46SDOLJrLcC&pgis=1; Accessed February 16, 2016.
80. Lennie P (2003): The cost of cortical computation. Curr Biol 13:493–497.
81. Heeger DJ, Ress D (2002): What does fMRI tell us about neuronal activity? Nat Rev Neurosci 3:142–151.
82. Cardoso MMB, Sirotin YB, Lima B, Glushenkova E, Das A (2012): The neuroimaging signal is a linear sum of neurally distinct stimulus- and task-related components. Nat Neurosci 15:1298–1306.
83. Ames A, Maynard KI, Kaplan S (1995): Protection against CNS ischemia by temporary interruption of function-related processes of neurons. J Cereb Blood Flow Metab 15:433–439.
84. Harris JJ, Jolivet R, Attwell D (2012): Synaptic energy use and supply. Neuron 75:762–777.
85. Levy WB, Baxter RA (1996): Energy efficient neural codes. Neural Comput 8:531–543.
86. Ascoli GA, Alonso-Nanclares L, Anderson SA, Barrionuevo G, Benavides-Piccione R, Burkhalter A, *et al*. (2008): Petilla terminology: Nomenclature of features of GABAergic interneurons of the cerebral cortex. Nat Rev Neurosci 9:557–568.
87. McBain CJ, Fisahn A (2001): Interneurons unbound. Nat Rev Neurosci 2:11–23.
88. Lee S-H, Kwan AC, Zhang S, Phoumthipphavong V, Flannery JG, Masmanidis SC, *et al*. (2012): Activation of specific interneurons improves V1 feature selectivity and visual perception. Nature 488:379–383.
89. Wehr M, Zador AM (2003): Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex. Nature 426:442–446.
90. Taub AH, Katz Y, Lampl I (2013): Cortical balance of excitation and inhibition is regulated by the rate of synaptic activity. J Neurosci 33: 14359–14368.
91. Polack P-O, Friedman J, Golshani P (2013): Cellular mechanisms of brain state-dependent gain modulation in visual cortex. Nat Neurosci 16:1331–1339.
92. Marder E, Goaillard J-M (2006): Variability, compensation and homeostasis in neuron and network function. Nat Rev Neurosci 7:563–574.
93. Etherton MR, Blaiss CA, Powell CM, Südhof TC (2009): Mouse neurexin-1alpha deletion causes correlated electrophysiological and behavioral changes consistent with cognitive impairments. Proc Natl Acad Sci U S A 106:17998–18003.
94. Tabuchi K, Blundell J, Etherton MR, Hammer RE, Liu X, Powell CM, Südhof TC (2007): A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. Science 318:71–76.
95. Kron M, Howell CJ, Adams IT, Ransbottom M, Christian D, Ogier M, Katz DM (2012): Brain activity mapping in Mecp2 mutant mice reveals functional deficits in forebrain circuits, including key nodes in the default mode network, that are reversed with ketamine treatment. J Neurosci 32:13860–13872.