



Discussion forum

Does attenuated divisive normalization affect gaze processing in autism spectrum disorder? A commentary on Palmer et al. (2018)



Ari Rosenberg^{a,*} and Adhira Sunkara^b

^a Department of Neuroscience, School of Medicine and Public Health, University of Wisconsin - Madison, Madison, WI, USA

^b Department of Surgery, Stanford University School of Medicine, Stanford, CA, USA

Autism spectrum disorder (ASD) is associated with substantial behavioral heterogeneity. Differences in the behavioral expression of ASD can manifest both qualitatively and quantitatively. Qualitative differences reflect the presence or absence of certain behavioral characteristics, such as a language impairment (American Psychiatric Association, 2013), and allow for the division of ASD into subgroups defined by distinct phenotypic constellations. Quantitative differences reflect the degree of symptom severity, such as the developmental trajectory and endpoint of verbal ability in individuals with a language impairment (Anderson et al., 2007).

1. Divisive normalization (DN) theory of autism

Although physiological and behavioral aspects of ASD are widely studied, less attention has been given to how changes in physiology affect computations performed by neural circuits, resulting in heterogeneous ASD phenotypes. We recently proposed that circuit-specific reductions in the strength of a canonical (i.e., occurring throughout the brain) computation called DN underlies certain behaviors observed in ASD (Rosenberg, Patterson, & Angelaki, 2015a). DN contributes to the balance of neural excitation and inhibition, and is implicated in many aspects of neural processing (Beck, Latham, & Pouget, 2011; Carandini & Heeger, 2012; Louie, Khaw, & Glimcher, 2013; Ni, Ray, & Maunsell, 2012; Ohshiro, Angelaki, & DeAngelis, 2011; Qamar et al., 2013; Reynolds & Heeger, 2009; Seilheimer, Rosenberg, &

Angelaki, 2014). Reduced DN increases the excitatory to inhibitory ratio, consistent with observations in humans with ASD and murine models of the disorder (Han, Tai, Jones, Scheuer, & Catterall, 2014; Rubenstein & Merzenich, 2003; Yizhar et al., 2011). Alterations in DN can explain ASD heterogeneity since different neural systems rely on different mechanisms and physiological pathways to implement DN (Carandini & Heeger, 2012; Katzner, Busse, & Carandini, 2011; Magnusson, Park, Pecka, Grothe, & Koch, 2008; Olsen, Bhandawat, & Wilson, 2010). The DN theory of ASD proposes that qualitative differences reflect which pathways are affected, and thus the brain region(s) impacted. Likewise, quantitative differences reflect the extent to which DN is attenuated, and thus how much specific pathways are affected. Indeed, reduced DN in specific neural systems is consistent with diverse ASD findings ranging from changes in low-level visual functions (Foss-Feig, Tadin, Schauder, & Cascio, 2013) to high-level cognitive processes (De Martino, Harrison, Knafo, Bird, & Dolan, 2008).

Elucidating the neuro-computational underpinnings of ASD can benefit from the interplay of empirical and computational approaches (Pellicano & Burr, 2012; Qian & Lipkin, 2011; Rosenberg, Patterson, & Angelaki, 2015b; Sinha et al., 2014). Given a behavior that differs between typically developing (TD) and ASD participants, a neuromimetic model of the computations underlying the behavior provides a valuable tool for gaining insights into the disorder. For example, a model can be used to determine how computations must be altered to account for the behavioral difference. Such approaches may be especially valuable for understanding

* Corresponding author.

E-mail address: ari.rosenberg@wisc.edu (A. Rosenberg).

<https://doi.org/10.1016/j.cortex.2018.06.017>

0010-9452/© 2018 Elsevier Ltd. All rights reserved.

behaviors of key relevance to diagnosing ASD, such as gaze processing (Palmer et al., 2018).

2. Gaze processing in autism

Impairments in the social use of eye contact are a criterion used for diagnosing ASD (American Psychiatric Association, 2013), and research has identified several aspects of gaze processing that are affected in the disorder. For example, in TD participants, viewing another person's eccentric gaze (e.g., 25° to the right of straight-ahead) biases subsequent judgments of gaze directions on the adapted (e.g., right) side towards straight-ahead. This aftereffect is weaker in ASD (Lawson, Aylward, Roiser, & Rees, 2018; Pellicano, Rhodes, & Calder, 2013), consistent with a broad set of findings on sensory habituation (Sinha et al., 2014). Using a gaze adaptation model (Palmer & Clifford, 2017), Palmer and colleagues investigated if reduced DN can account for weaker gaze aftereffects in ASD (Palmer et al., 2018). As in earlier work, the authors found a 'repulsive' effect in which perception of gaze directions on the adapted side were biased away from the adapter. However, they did not find the previously observed TD/ASD group difference in the size of gaze aftereffects (Lawson et al., 2018; Pellicano et al., 2013). Two possible explanations for this discrepancy are differences in task structure and differences in stimulus parameters.

Earlier work used a categorization task in which gaze direction was reported as 'leftward', 'straight-ahead', or 'rightward' (Lawson et al., 2018; Pellicano et al., 2013), whereas the Palmer et al. (2018) study used a continuous indicator. As the authors discussed, if adaptation differentially affects the higher-level process of gaze categorization in TD and ASD participants, but not the lower-level sensory coding of gaze direction, this may account for the discrepancy between studies. To help distinguish disruptions in sensory gaze processing from gaze categorization, the same participants could complete continuous indicator and categorization versions of the gaze adaptation study. This would eliminate concerns about comparing results from experiments that draw different samples from a heterogeneous ASD population. A deficit in gaze categorization would be indicated if group differences exist only in the categorization version. Assuming this result, attenuated DN in the gaze categorization circuit could be tested by conducting a follow-up categorization study which includes different levels of stimulus noise. Computational work building on previous models could then assess if attenuated DN accounts for group differences in the rates at which performance falls off with increasing noise (Qamar et al., 2013; Rosenberg et al., 2015a).

A previous study using a 25° gaze adapter found a TD/ASD group difference in aftereffects for a test gaze of 5° but not 10° (Pellicano et al., 2013). Therefore, the stimulus parameters (gaze adapter = 25°, smallest test gaze = 10°) used in Palmer et al. (2018) may not be capable of detecting a group difference, and the data may be insufficient for evaluating whether DN is preserved in the sensory processing of gaze direction in ASD. Combining smaller test gazes with the continuous indicator task would allow for a stronger test of attenuated DN in sensory gaze processing. If a group difference is found at small gaze directions, it would suggest a disruption in sensory gaze

processing, and computational work building on previous models could evaluate if attenuated DN accounts for the difference (Palmer et al., 2018; Rosenberg et al., 2015a).

In addition to repulsive effects, Palmer and colleagues identified an 'attractive' effect that biases perception of large gaze directions on the non-adapted side towards the adapter. The gaze adaptation model used in the study does not account for this novel finding, and the neural basis of the attractive effect deserves further study. For example, a more neuromimetic model of gaze processing that incorporates the relationship between the adapter and neuronal tuning properties into the DN term may account for both repulsive and attractive effects in gaze adaptation (Schwartz, Sejnowski, & Dayan, 2009).

3. Interpretation of the Palmer et al. (2018) study

An implication of the Palmer et al. (2018) findings is that how gaze processing is disrupted in ASD remains uncertain. Existing data are consistent with at least two (not mutually exclusive) possibilities: (i) a deficit in the sensory coding of gaze direction and (ii) a deficit in gaze categorization. Gaze-dependent behaviors rely on evaluating conditions such as, "Is this person making eye contact with me?" Thus, it is possible that the sensory processing of gaze is intact, but its categorization is disrupted in ASD. The Palmer et al. (2018) findings are consistent with this possibility, and are compatible with neural network modeling that shows a loss of DN worsens categorization performance (Qamar et al., 2013). Some aspects of atypical gaze-dependent behaviors in ASD could thus arise from attenuated DN in the gaze categorization circuit.

Reflecting the similarity of TD and ASD gaze aftereffects observed in the Palmer et al. (2018) data, their fitted model parameters for the two groups were indistinguishable. Based on this result, the authors conclude that their data conflict with the attenuated DN theory of ASD. This conclusion rests on their assertion that a "widespread reduction" of DN is a "systemic feature" of ASD (Palmer et al., 2018), and thus, any evidence for intact DN would be interpreted as evidence against the theory. However, this is an incorrect premise. Reduced DN in ASD is not likely to be widespread across the brain since DN is implemented using different mechanisms and physiological pathways across neural systems. Indeed, the theory attributes ASD heterogeneity to reduced DN in select systems and to varying degrees across individuals (Rosenberg et al., 2015a). Therefore, a reasonable prerequisite for testing the theory is the use of behavioral protocols that reveal significant TD/ASD group differences, unlike the paradigm used in Palmer et al. (2018). If DN were reduced system wide, the prevalence of ASD and epilepsy comorbidity (Spence & Schneider, 2009; Volkmar & Nelson, 1990) would likely be higher, and there would be fewer qualitative differences in the behavioral expression of the disorder.

4. Synergy between computational and empirical studies

Neuro-computational theories are likely to have an increasingly greater role in our understanding of ASD. Thus, it is important to

establish scientific paradigms for conducting empirical research that reliably test those theories. Protocols that reveal significant differences between TD and ASD groups are necessary to combat errors that can arise as a consequence of random sampling from a heterogeneous ASD population. A neuro-computational theory should also account for behaviors that are associated with key diagnostic criteria (Palmer et al., 2018). This need implies a critical role for the development of neuro-mimetic models that can accurately reproduce complex behaviors. Support for or against a theory can then be gained through modeling work that evaluates if changes in the hypothesized computation account for observed behavioral differences. Through rigorous testing of neuro-computational theories, the synergistic interplay of empirical and computational approaches can provide valuable insights into ASD as well as other neuro-developmental and mental health disorders.

Acknowledgments

This work was supported by the Alfred P. Sloan Foundation and University of Wisconsin Institute for Clinical and Translational Research Pilot Grant UL1TR000427 (NIH/NCATS).

REFERENCES

- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-V*. American Psychiatric Pub.
- Anderson, D. K., Lord, C., Risi, S., DiLavore, P. S., Shulman, C., Thurm, A., et al. (2007). Patterns of growth in verbal abilities among children with autism spectrum disorder. *Journal of Consulting and Clinical Psychology*, 75, 594–604.
- Beck, J. M., Latham, P. E., & Pouget, A. (2011). Marginalization in neural circuits with divisive normalization. *Journal of Neuroscience*, 31, 15310–15319.
- Carandini, M., & Heeger, D. J. (2012). Normalization as a canonical neural computation. *Nature Reviews Neuroscience*, 13, 51–62.
- De Martino, B., Harrison, N. A., Knafo, S., Bird, G., & Dolan, R. J. (2008). Explaining enhanced logical consistency during decision making in autism. *Journal of Neuroscience*, 28, 10746–10750.
- Foss-Feig, J. H., Tadin, D., Schauder, K. B., & Cascio, C. J. (2013). A substantial and unexpected enhancement of motion perception in autism. *Journal of Neuroscience*, 33, 8243–8249.
- Han, S., Tai, C., Jones, C. J., Scheuer, T., & Catterall, W. A. (2014). Enhancement of inhibitory neurotransmission by GABAA receptors having alpha2,3-subunits ameliorates behavioral deficits in a mouse model of autism. *Neuron*, 81, 1282–1289.
- Katzner, S., Busse, L., & Carandini, M. (2011). GABAA inhibition controls response gain in visual cortex. *Journal of Neuroscience*, 31, 5931–5941.
- Lawson, R. P., Aylward, J., Roiser, J. P., & Rees, G. (2018). Adaptation of social and non-social cues to direction in adults with autism spectrum disorder and neurotypical adults with autistic traits. *Developmental Cognitive Neuroscience*, 29, 108–116.
- Louie, K., Khaw, M. W., & Glimcher, P. W. (2013). Normalization is a general neural mechanism for context-dependent decision making. *Proceedings of the National Academy of Sciences of the USA*, 110, 6139–6144.
- Magnusson, A. K., Park, T. J., Pecka, M., Grothe, B., & Koch, U. (2008). Retrograde GABA signaling adjusts sound localization by balancing excitation and inhibition in the brainstem. *Neuron*, 59, 125–137.
- Ni, A. M., Ray, S., & Maunsell, J. H. (2012). Tuned normalization explains the size of attention modulations. *Neuron*, 73, 803–813.
- Ohshiro, T., Angelaki, D. E., & DeAngelis, G. C. (2011). A normalization model of multisensory integration. *Nature Neuroscience*, 14, 775–782.
- Olsen, S. R., Bhandawat, V., & Wilson, R. I. (2010). Divisive normalization in olfactory population codes. *Neuron*, 66, 287–299.
- Palmer, C. J., & Clifford, C. W. G. (2017). Functional mechanisms encoding others' direction of gaze in the human nervous system. *Journal of Cognitive Neuroscience*, 29, 1725–1738.
- Palmer, C. J., Lawson, R. P., Shankar, S., Clifford, C. W. G., & Rees, G. (2018). Autistic adults show preserved normalisation of sensory responses in gaze processing. *Cortex*, 103, 13–23.
- Pellicano, E., & Burr, D. (2012). When the world becomes 'too real': A Bayesian explanation of autistic perception. *Trends in Cognitive Science*, 16, 504–510.
- Pellicano, E., Rhodes, G., & Calder, A. J. (2013). Reduced gaze aftereffects are related to difficulties categorising gaze direction in children with autism. *Neuropsychologia*, 51, 1504–1509.
- Qamar, A. T., Cotton, R. J., George, R. G., Beck, J. M., Prezhdo, E., Laudano, A., et al. (2013). Trial-to-trial, uncertainty-based adjustment of decision boundaries in visual categorization. *Proceedings of the National Academy of Sciences of the USA*, 110, 20332–20337.
- Qian, N., & Lipkin, R. M. (2011). A learning-style theory for understanding autistic behaviors. *Frontiers in Human Neuroscience*, 5, 77.
- Reynolds, J. H., & Heeger, D. J. (2009). The normalization model of attention. *Neuron*, 61, 168–185.
- Rosenberg, A., Patterson, J. S., & Angelaki, D. E. (2015a). A computational perspective on autism. *Proceedings of the National Academy of Sciences of the USA*, 112, 9158–9165.
- Rosenberg, A., Patterson, J. S., & Angelaki, D. E. (2015b). Reply to Lawson et al.: A synergistic approach to mental health research. *Proceedings of the National Academy of Sciences of the USA*, 112, E5227.
- Rubenstein, J. L., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior*, 2, 255–267.
- Schwartz, O., Sejnowski, T. J., & Dayan, P. (2009). Perceptual organization in the tilt illusion. *Journal of Vision*, 9(19), 11–20.
- Seilheimer, R. L., Rosenberg, A., & Angelaki, D. E. (2014). Models and processes of multisensory cue combination. *Current Opinion in Neurobiology*, 25, 38–46.
- Sinha, P., Kjelgaard, M. M., Gandhi, T. K., Tsourides, K., Cardinaux, A. L., Pantazis, D., et al. (2014). Autism as a disorder of prediction. *Proceedings of the National Academy of Sciences of the USA*, 111, 15220–15225.
- Spence, S. J., & Schneider, M. T. (2009). The role of epilepsy and epileptiform EEGs in autism spectrum disorders. *Pediatric Research*, 65, 599–606.
- Volkmar, F. R., & Nelson, D. S. (1990). Seizure disorders in autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, 29, 127–129.
- Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O'Shea, D. J., et al. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*, 477, 171–178.

Received 14 May 2018

Reviewed 28 May 2018

Revised 13 June 2018

Accepted 3 July 2018

Published online 31 July 2018