Journal Club

Can Magnetic Resonance Imaging Aid Diagnosis of the Autism Spectrum?

Jennifer L. Stevenson and Kristina A. Kellett
Department of Psychology, University of Wisconsin–Madison
Review of Ecker et al.

Although neurodevelopmental in origin, autism spectrum disorders are not currently diagnosed by neuroanatomical metrics but rather by behavioral observation. Autistic people differ from other people in their social interactions, communication, movement, and the level to which they focus on interests (American Psychiatric Association, 2000). The neurological basis of these behavioral differences has been of great interest.

Nearly 200 studies over the past 20 years have proposed neuroanatomical markers of autism spectrum disorders; however, these studies have often been in conflict or unreplicated. Some of the conflicting findings can be explained by variation between and within participant samples (e.g., age and IQ) (Stanfield et al., 2008). Furthermore, most previous research has investigated a single morphometric feature of a single neural region, such as the volume of participants' amygdalae, but because several areas have been implicated (e.g., corpus callosum, caudate, cerebellum) (Stanfield et al., 2008) and because identified markers are not limited to a single morphometric feature, future research should consider multiple morphometric features across the brain.

Ecker et al. (2010b) performed a support vector machine (SVM) classification between autistic and non-autistic participants. Linear SVM is a machine learning method that identifies patterns in a dataset by identifying the hyperplane(s) that maximally distinguish different categories. After a classifier is estimated from a training dataset, the classifier can be used to predict category membership. Ecker and colleagues (2010b) trained their classifier based on five morphometric parameters of cortical gray matter: cortical thickness (the distance between white matter and pial surfaces), pial area (surface area of gray matter), metric distortion (Jacobian; the overall degree of cortical folding), average convexity or concavity (sulcal depth and gyral height; primary cortical folding), and mean (radial) curvature (secondary and tertiary cortical folding). All participants were right-handed males, 20–68 years old. The same MRI scans of 20 autistic adults and 20 non-autistic adults (without any known neuropsychiatric disorders) were used to train and validate the classifier using a leave-two-out cross-validation approach, in which all participants except one from each group were used to train the classifier, which was then used to predict the category membership of the left-out participants. The procedure was repeated to predict category membership for all participants. Thus, 20 trials were needed for the cross-validation. Classifiers were trained and validated for each hemisphere using all five morphometric parameters as well as each parameter individually.

Classification accuracy was evaluated by both sensitivity (percentage of autistic participants correctly classified as autistic) and specificity (percentage of non-autistic participants correctly classified as non-autistic). Classification sensitivity and specificity was higher for the left hemisphere than the right hemisphere. When all five morphometric parameters in the left hemisphere were used, 85% of participants were correctly classified with 90% sensitivity and 80% specificity. When parameters were individually examined, the classifier for cortical thickness in the left hemisphere was most accurate, with 90% sensitivity and 90% specificity. Ecker et al. (2010b) also applied their multiparameter classifier to a neurodevelopmental control group of participants with attention deficit hyperactivity disorder (ADHD); the classifier for all five morphometric features in the left hemisphere correctly identified 79% of participants with ADHD as non-autistic, which was a comparable level of specificity to that obtained during cross-validation with the non-autistic participants without a neurodevelopmental disorder.

Validation of Ecker et al.'s (2010b) multiparameter classifier with additional autistic participants is still necessary. Given that imaging findings in autism often are not robust because of the inherent heterogeneity of the autism spectrum and small sample sizes, this study's multiparameter classifier should demonstrate high levels of sensitivity with additional samples of autistic participants that vary in age and autistic characteristics. In many

Table 1. Summary of overlapping regions discriminating between autistic and non-autistic participants on cortical thickness (in alphabetical order)

Region	Hemisphere	Chung et al. (2005)	Ecker et al. (2010b)	Hadjikhani et al. (2006)	Hyde et al. (2010)	Jiao et al. (2010)
Orbitofrontal	Left	⇓ (inferior)		⇓ (BA 11)	⇑ (medial–BA 11)	⇓ (lateral, medial)
	Right		⇑ (medial)	⇓ (BA 11)		⇓ (lateral, medial)
Superior frontal	Left		⇓	⇓ (BA 8)		
	Right		⇓	⇓ (BA 8)	⇑ (BA 10)	
Middle frontal	Left		⇓ (rostral, caudal)		⇑ (BA 9, 10)	
	Right				⇑ (BA 10)	⇓ (rostral)
Inferior frontal	Left		⇓ (BA 44)	⇓ (BA 44)		⇓ (BA 45)
	Right			⇓ (BA 44, 45)	⇑ (BA 44, 45)	⇓ (BA 45)
Precentral	Left			⇓ (BA 4)		
	Right			⇓ (BA 4)	⇓ (BA 4)	
Postcentral	Left			⇓ (SI)		
	Right			⇓ (SI)	⇓ (BA 3)	
Superior parietal	Left			⇓ (BA 7)		⇑
	Right		⇑, ⇓	⇓ (BA 7)		
Precuneus	Left		⇑			⇑
	Right		⇓			
Inferior parietal	Left		⇑	⇓ (BA 39)		⇓
	Right		⇑	⇓ (BA 39)		⇓
Supramarginal	Left		⇑	⇓ (BA 40)		
	Right		⇑	⇓ (BA 40)		
Superior temporal gyrus	Left		⇑		⇑ (BA 41)	
	Right		⇑		⇑ (BA 41)	
Superior temporal sulcus	Left	⇓			⇑ (BA 22)	
	Right		⇑	⇓ (BA 22)	⇑ (BA 22)	
Middle temporal	Left		⇑	⇓ (BA 21)		
	Right		⇑	⇓ (BA 21)		
Fusiform	Left		⇑		⇑ (BA 19, 20)	
	Right		⇑		⇑ (BA 20)	
Parahippocampal	Left		⇑			⇓
	Right		⇑			⇓
Entorhinal cortex	Left		⇑			⇓
	Right		⇑			⇓
Anterior cingulate	Left					⇑
	Right		⇑[a], ⇓	⇓ (BA 24, 32)	⇑ (BA 32)	
Posterior cingulate	Left		⇑		⇑ (BA 24, 31)	
	Right				⇑ (BA 31)	

Note: ⇑ indicates regions where autistic participants exhibited increased cortical thickness, whereas ⇓ indicates regions where autistic participants exhibited decreased cortical thickness relative to non-autistic participants.
[a]It is unclear from Table 5 in Ecker et al. (2010b) whether increased cortical thickness was present in the left or right anterior cingulate.

of the frontal, temporal, and parietal regions identified by the Ecker et al. (2010b) classifier, Raznahan et al. (2010) found that younger autistic participants tend to have lower cortical thickness and older autistic participants tend to have greater cortical thickness compared with non-autistic participants. The role of age in autistic and non-autistic differences in cortical thickness complicates the replicability of the Ecker et al. (2010b) classifier with younger samples.

Ecker and colleagues (2010b) also concluded that their multiparameter classification was responsive to the degree of autistic characteristics because their autistic participants' scores on the Autism Diagnostic Interview-Revised (ADI-R) social and communication subscales were each positively correlated with the participants' distance from the hyperplane that predicted category membership ($r = 0.414$ and 0.620, respectively); but the ADI-R is not intended to reflect severity of autistic characteristics

(University of Michigan Autism and Communication Disorders Center, 2009). Furthermore, neither of two previous SVM studies reported a significant correlation between autistic participants' scores on the ADI-R subscales and distance from the hyperplane (Ecker et al., 2010a; Jiao et al., 2010). Ecker et al. (2010a) previously claimed that group membership classification based on adult morphometric features is primarily determined by current autistic characteristics as measured by the Autism Diagnostic Observation Schedule (ADOS), instead of childhood autistic characteristics as measured by the ADI-R, which contradicts Ecker et al. (2010b)'s more recent result regarding their classifier's relationship with ADI-R scores.

Applying the multiparameter classifier to other non-autistic neurodevelopmental control groups is necessary for further validation of the classifier's specificity, as mentioned by Ecker et al. (2010b). Additionally, because autistic traits are continuously dis-

tributed in the general population (Constantino and Todd, 2003), it would further research to examine how well the multiparameter classifier could predict group membership of non-autistic participants who are relatively high on autistic traits—in particular, whether the degree of autistic traits (measured on a ratio scale) would relate to distance from the hyperplane in non-autistic participants.

Convergence between Ecker et al.'s (2010b) findings and existing data is also limited in terms of specific brain regions. Although Ecker and colleagues (2010b) warned that their results should not be interpreted at the level of individual brain regions due to the multivariate nature of SVM, a comparison with existing data can help determine whether a pattern of consistent markers emerges across studies. The classifier for cortical thickness in the left hemisphere provided the highest accuracy when parameters were examined individually. To date, five studies have ex-

amined cortical thickness by hemisphere in autistic versus non-autistic participants, and two of those studies used SVM (Chung et al., 2005; Hadjikhani et al., 2006; Ecker et al. 2010a; Hyde et al., 2010; Jiao et al., 2010). Across these five studies, differences coalesced mainly in frontal (e.g., inferior frontal gyrus) and temporal (e.g., parahippocampal gyrus) regions, as shown in Table 1. However, the direction of the difference varied across studies. For example, whereas Ecker et al. (2010b) reported autistic participants had increased cortical thickness in bilateral parahippocampal gyri, Jiao et al. (2010) reported the opposite pattern. Therefore, the regions that discriminate between autistic and non-autistic participants in Ecker et al. (2010b) only partially overlap with regions identified by existing research.

Lastly, it is questionable whether SVM pattern classification of neuroanatomical features provides additional diagnostic value beyond that of behavioral criteria. For example, if an individual had a borderline behavioral diagnosis of autism spectrum disorder, estimation of the individual's group membership based on the individual's morphometric features may not help guide diagnosis, because the individual would likely lie close to the hyperplane (i.e., decision boundary) given the positive correlation between ADI-R scores and distance from the hyperplane. Additionally, Ecker et al. (2010b) mention that pattern classification methods could potentially categorize different biological etiologies within the autism spectrum (i.e., subtypes) that have a

similar behavioral phenotype; however, it is unclear how plausible it would be to categorize different biological subtypes within the autism spectrum when using supervised learning techniques (e.g., SVM), given that identifying neuroanatomical markers of the autism spectrum requires training a classifier on group membership defined by behavioral criteria. In other words, diagnostic classification based on neuroanatomical markers would only be as good as the diagnostic behavioral criteria initially used to define group membership.

In summation, Ecker et al. (2010b) provides a pioneering approach for identifying gray matter differences between autistic and non-autistic participants by examining multiple morphometric features within each hemisphere. In particular, their study offers a successful multiparameter classifier for the left hemisphere of right-handed male adults with full-scale IQs > 75. However, successful validation of their SVM classifier is needed with other samples of autistic participants as well as with other neurodevelopmental control groups to fully substantiate any putative clinical value to their laboratory technique.

References

American Psychiatric Association. (2000) Diagnostic and statistical manual of mental disorders, Ed 4. Washington, DC: American Psychiatric.

Chung MK, Robbins SM, Dalton KM, Davidson RJ, Alexander AL, Evans AC (2005) Cortical thickness analysis in autism with heat kernel smoothing. Neuroimage 25:1256–1265.

Constantino JN, Todd RD (2003) Autistic traits in the general population. Arch Gen Psychiatry 60:524–530.

Ecker C, Rocha-Rego V, Johnston P, Mourão-Miranda J, Marquand A, Daly EM, Brammer MJ, Murphy C, Murphy DG, MRC AIMS Consortium (2010a) Investigating the predictive value of whole-brain structural MR scans in autism: a pattern classification approach. Neuroimage 49:44–56.

Ecker C, Marquand A, Mourão-Miranda J, Johnston P, Daly EM, Brammer MJ, Maltezos S, Murphy CM, Robertson D, Williams SC, Murphy DG (2010b) Describing the brain in autism in five dimensions: magnetic resonance imaging-assisted diagnosis of autism spectrum disorder using a multiparameter classification approach. J Neurosci 30:10612–10623.

Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H (2006) Anatomical differences in the mirror neuron system and social cognition network in autism. Cereb Cortex 16:1276–1282.

Hyde KL, Samson F, Evans AC, Mottron L (2010) Neuroanatomical differences in brain areas implicated in perceptual and other core features of autism revealed by cortical thickness analysis and voxel-based morphometry. Hum Brain Mapp 31:556–566.

Jiao Y, Chen R, Ke X, Chu K, Lu Z, Herskovits EH (2010) Predictive models of autism spectrum disorder based on regional cortical thickness. Neuroimage 50:589–599.

Raznahan A, Toro R, Daly E, Robertson D, Murphy C, Deeley Q, Bolton PF, Paus T, Murphy DG (2010) Cortical anatomy in autism spectrum disorder: an in vivo MRI study on the effect of age. Cereb Cortex 20:1332–1340.

Stanfield AC, McIntosh AM, Spencer MD, Philip R, Gaur S, Lawrie SM (2008) Towards a neuroanatomy of autism: a systematic review and meta-analysis of structural magnetic resonance imaging studies. Eur Psychiatry 23:289–299.

University of Michigan Autism and Communication Disorders Center (2009) ADOS/ADI-R FAQs. Retrieved from http://www.umaccweb.com/education/faqs.html.