

new criteria who will be enrolled in our ongoing and future clinical and biomedical research projects.

In conclusion, the results presented by the authors do not support instituting the DSM-5 criteria and can cause harm to our patients and research projects. Furthermore, the proposed changes rest on clinical data, and any changes should be postponed until new, replicable biomedical data warrant such a major undertaking.

## Reference

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*This letter (doi: 10.1176/appi.ajp.2013.12101376) was accepted for publication in January 2013.*

## Response to Ritvo and Ritvo Letter

TO THE EDITOR: The goal of our article (1) was to examine the impact of the new DSM-5 criteria for autism spectrum disorder (ASD) in three large samples of children with DSM-IV-defined ASD and non-ASD disorders. Using items from the Autism Diagnostic Interview–Revised and the Autism Diagnostic Observation Schedule to match DSM-5 criteria, we found that the new criteria correctly classified a large majority of children with ASD (91%), including very young children, girls, and children without language impairments. We also found that the specificity of the new criteria represented an improvement over existing DSM-IV criteria.

Ritvo and Ritvo's commentary about our article and about the upcoming changes to DSM criteria center on two main concerns: 1) that the changes introduced by DSM-5 will affect the sensitivity of the diagnostic criteria and 2) that the changes to DSM-5 criteria will limit the usefulness of ASD data banks.

The possibility of decreased sensitivity in diagnostic criteria is a valid concern. In fact, the initial motivation for our study was to examine whether children with previous DSM-IV diagnoses of any pervasive developmental disorder (PDD) would be incorrectly left out by the new criteria. As Ritvo and Ritvo note, when based on parent-reported symptoms only, approximately 9%–10% of our sample meeting DSM-IV criteria for ASD was not correctly classified by DSM-5 criteria. However, it is important to reiterate that the sensitivity of identification was much more likely affected by the methods of the study—using diagnostic instruments not designed to address the specific revisions in DSM-5—than by the DSM-5 criteria. Our results show that relying on clinical observation in addition to parental report of symptoms improved the sensitivity of the proposed DSM-5 criteria, and in many cases this resulted in sensitivities similar to those for DSM-IV criteria (see Table 2 in our article [1]).

Ritvo and Ritvo expressed particular concern about the sensitivity of the new criteria for Asperger's disorder because of the relatively small proportion of our sample for whom this

DSM-IV diagnosis was used. However, we reiterate that separate analyses were performed with 261 case subjects with Asperger's disorder and 971 case subjects with PDD not otherwise specified (PDD-NOS), and similar results were obtained when both parental report and clinical observation were used. As for previous studies that reported DSM-5 criteria to have poor sensitivity, we refer the reader to Swedo and colleagues' commentary (2) for a full discussion on the limitations of those studies. To assess the true sensitivity of the new criteria, field trials are necessary.

A second and important issue raised by Ritvo and Ritvo involves the effect of the new criteria on the utility of previously collected phenotypic and genetic ASD samples. They speculate that the changes in diagnostic criteria will make these samples "incompatible and unusable." The authors assume that some of the existing cases will lose their ASD classification. However, our study results indicate that this is unlikely to be true. The new DSM-5 criteria now explicitly state that individuals with a well-informed clinical diagnosis of any of the previous PDD subtypes, including PDD-NOS and Asperger's disorder, do not have to be rediagnosed but are assumed to fall under the new larger category of ASD. Importantly, the revisions in DSM-5 provide researchers and clinicians an alternative system for coding dimensions both within ASD and from other areas, including intellectual disabilities, language disorders, and other disorders such as attention deficit hyperactivity disorder, through clinical specifiers. This system should result in more accurate and meaningful descriptions of individuals (see Grzadzinski et al. [3]).

In closing, we remind the reader that the upcoming changes to the DSM criteria reflect the growing body of empirical work showing that the existing classification system needs improvement. Comparisons of DSM-IV subtypes do not reveal consistent differences in clinical presentation (4), and longitudinal studies indicate that these categorical distinctions are not predictive of outcome (5). More recently, research has demonstrated that DSM-IV categorical diagnoses are not reliably made across clinical and research sites (6). With our current classification system, what diagnosis you get (e.g., ASD or Asperger's disorder) is more related to where you go for the diagnosis than to the pattern of presenting symptoms. Thus, while we respect the concerns outlined by Ritvo and Ritvo, the evidence indicates that it is neither scientifically nor clinically justifiable to continue using DSM-IV criteria in the face of data indicating its significant limitations in describing individuals with ASD.

## References

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*The authors' disclosures accompany the original article.*

*This reply (doi: 10.1176/appi.ajp.2013.12101376r) was accepted for publication in January 2013.*

### Treatment Course With Antidepressant Therapy in Late-Life Depression

TO THE EDITOR: We read with great interest the article by Sheline et al. (1) in the November 2012 issue of the *Journal* on the prediction of antidepressant response based on the volume of the hippocampus on MRI. This is a very exciting field that has attracted significant attention in the medical community and from patients. The idea that MRI could finally provide anatomical evidence for some mental disorders could have a significant impact on the general perception and acceptance of some of these diseases. Much progress has been made in this field, but some technological limitations must be considered before getting overexcited about the results of research using MRI quantification.

The resolution of the state-of-the-art MRI scanners is in the range of 0.8 mm, which is excellent. MR imaging data are mainly segmented based on the similarity of signal intensity of neighboring voxels or by selecting regions of interest.

We would like to highlight an important technical limitation that should be considered before accepting these results as conclusive. Sheline et al. observed an average hippocampal volume of 8,298.2 mm<sup>3</sup> in the group of patients who achieved remission from depression and 7,942.3 mm<sup>3</sup> in those who did not achieve remission after treatment. The values are provided in volume (mm<sup>3</sup>), and although the volumetric difference seems large, the difference represents less than 0.3 mm on each dimension of the measured volume. The cubic root of 8,298.2 mm<sup>3</sup> is 20.24 mm and the cubic root of 7,942.3 mm<sup>3</sup> is 19.95 mm, so the approximate difference in each dimension measured of the volume of hippocampus is in the range of 0.3 mm, which is below the resolution of MRI.

We would kindly suggest that the authors check the precision and accuracy of the segmentation process provided by

MRI volumetric quantification on the scanner and workstation chosen for the study before we could accept their results as conclusive.

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*The authors report no financial relationships with commercial interests.*

*This letter (doi: 10.1176/appi.ajp.2013.12121544) was accepted for publication in January 2013.*

### Response to Irion et al. Letter

TO THE EDITOR: In their letter, Irion et al. express concern about the volumetric differences reported, stating that they are below the resolution of MRI. However, we would like to bring to their attention basic statistical principles applied in these circumstances (1), in which examination of group differences depends on the statistical properties of the sample, not on resolution in individual scans. The significance of group differences is based on the sample size, the mean group difference, and the standard deviation of the sample. Thus, even small differences can be significantly different if the measurements are repeatable (with a small standard deviation) as is the case in FreeSurfer segmentation, and if there is a relatively large sample size (N=168 in our study) and a sufficiently large difference in the means. In fact, the total volume difference measured was not small: a mean of 0.3 mm<sup>3</sup>/person × 168 = 50.4 mm<sup>3</sup>.

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*The author's disclosures accompany the original article.*

*This reply (doi: 10.1176/appi.ajp.2013.12121544r) was accepted for publication in February 2013.*

### Adrenergic Receptor Gene Variation and Selective Norepinephrine Reuptake Inhibitors

TO THE EDITOR: A 2010 meta-analysis (1) concluded that reboxetine, a selective norepinephrine reuptake inhibitor approved for the treatment of depression in several countries worldwide, is “an ineffective and potentially harmful antidepressant.” Wide variation in the side effect profiles of