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Reply to: Can the N170 Be Used as an Electrophysiological Biomarker Indexing Face Processing Difficulties in Autism Spectrum Disorder?

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To the Editor:

We appreciate the opportunity to further the discussion regarding the N170 in autism spectrum disorder (ASD) (1). We agree that electroencephalography (EEG) holds promise for deriving biomarkers, but that such applications are not straightforward.

The literature indicates variability in the difference in N170 response to face stimuli between individuals with ASD and those with typical development (TD). This inconsistency is precisely why one would undertake a meta-analysis (2): to synthesize across diverse samples. That a modest relative N170 latency effect for faces was found for ASD, even with significant heterogeneity, allowed us to reject the null hypothesis of no difference between populations. This is notable and uncommon in the search for biomarkers of ASD.

Vettori *et al.* (3) suggest that a biomarker must index discriminant validity. This is true of a diagnostic biomarker. However, the N170 is likely not simply a standalone diagnostic biomarker of ASD. Instead, there are multiple biomarkers for distinct purposes: a stratification biomarker may classify individuals with ASD into relevant subgroups; a target engagement biomarker may indicate the response of social brain circuitry to intervention; an early efficacy biomarker may indicate a treatment effect more quickly than subjective reports (4).

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N170 latency variability as seen in the literature and across development, and responsiveness to experience suggest some potential beyond being a diagnostic biomarker—particularly considering our meta-analysis. For instance, the neural response to faces can reflect changes from intervention (5), demonstrating potential as an early efficacy or target engagement biomarker (4). In addition, indexing individual variation in functional processes is useful to be practicable for dissemination (4,6). Indeed, ASD researchers seek biomarkers for symptoms shared with other disorders, such as schizophrenia or social anxiety. N170 face latency is a good candidate in this regard, as it is implicated in many psychiatric disorders. For instance, N170 response to faces indexes continuously distributed processes that subtend social communication, such as perceptual representation of facial expressions or identity, based on structural and social–communicative criteria, such as rapid social–emotional reactions in the observer (7). Thus, N170 can help indicate the processes underlying such capacities transdiagnostically.

Conversely, N170 may be useful as a stratification biomarker across symptom axes, with strata potentially corresponding to unique syndromes. We identified this as a timely topic for investigation: it is necessary to examine the specificity of the applicability of N170 to ASD versus other populations now that the specificity to face stimuli (vs. nonfaces) in the difference in N170 latency between ASD and TD has been established meta-analytically. Several recent studies have examined this question (8,9)—often with mixed results. This is appropriate to the current development of the literature and demands more nuanced and sophisticated questions regarding when, how, and for whom the N170 face latency difference may function as a biomarker and what sort of biomarker it may be.

Biomarkers should also be sensitive to changes across development, given normative and necessary ontogenetic dynamics of neural systems. ASD is a developmental disorder, and therefore a biomarker would need to capture such variability over time to demarcate discrete stages of developmental canalization (6). N170 largely meets this criterion, as its morphology reflects developmental maturation and can be applied consistently throughout the lifespan with well-established response patterns (6,10). While the variation in N170 morphology across participants and age groups can complicate objective determination of latency and amplitude, atypical developmental morphology is reliably quantifiable with diligent attention across studies even with methodological variability (11). Moreover, differences that become more prominent between ASD and TD across ages (e.g., the amplitude difference found in our meta-analysis) might simply reflect a more consistently evoked ERP, rather than developmental differences in underlying neurophysiology. This is precisely an area for study now that a benchmark population difference has been identified, and this calls for future studies in stricter accordance with guidelines for acquiring and interpreting EEG data in ASD (12,13).

There are several more general points that require some clarification. First, while increased N170 amplitude to facial stimuli is well established, the current literature also supports faster latency to faces than nonfaces in TD (9,11,14). Therefore, the relative delay in ASD to faces (but not to nonfaces) is likely to reflect divergent neural mechanisms of face processing. Second, while the effect size for nonsocial stimuli was medium, it was a nonsignificant effect (95% confidence interval −0.14 to 1.16). This indicates that the

null hypothesis should not be rejected (15,16), suggesting that the notion that N170 delay may reflect slower general processing of visual stimuli is not supported on the basis of substantive or statistical significance. Third, we examined the P1 component that reflects basic sensory processes and found that it did not differ between ASD and TD. Therefore, the literature to date suggests that differential processing in ASD does not emerge until the N170 stage (11). Fourth, we wish to clarify that our study compared N170 latency delay in individuals with ASD to age-matched TD control subjects, suggesting that relative N170 latency is delayed in ASD despite an absolute N170 latency decrease. This reveals that the rate of maturation lags behind TD adults, adding support to theories of experience-expectant development of face processing (17,18) and highlighting the N170 as a candidate marker with protracted maturation whose deviation from typical neural activity may reflect a quantitative developmental delay of normative processes that may exacerbate over time.

Finally, we wish to highlight that relative to the current evaluative standards of the field, EEG-based assessment of the N170 offers the promise of a more accessible and efficient evaluation. For instance, EEG-based evaluation offers a more rapid assessment thanks to EEG's wide applicability (i.e., to a wide developmental and intellectual range), low cost, high accessibility, acute sensitivity, and objectivity in measurement (4). Other practical advantages are evident as well. ASD is presently best diagnosed and treated based on the subjective evaluation of clinical experts or the use of structured tools—both of which exhibit limited availability and potential subjectivity (6). However, biological differences that may be clinically relevant may not be present in overt behaviors, and observable manifestations are not consistently expressed across development. Therefore, any tool that increases objectivity or access would represent a dramatic clinical advance with practical value for investigation, assessment, and treatment of ASD.

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