

AUTISM SPECTRUM DISORDER

Stratifying the autistic phenotype using electrophysiological indices of social perception

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Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by difficulties in social communication, but also great heterogeneity. To offer individualized medicine approaches, we need to better target interventions by stratifying autistic people into subgroups with different biological profiles and/or prognoses. We sought to validate neural responses to faces as a potential stratification factor in ASD by measuring neural (electroencephalography) responses to faces (critical in social interaction) in $N = 436$ children and adults with and without ASD. The speed of early-stage face processing (N170 latency) was on average slower in ASD than in age-matched controls. In addition, N170 latency was associated with responses to faces in the fusiform gyrus, measured with functional magnetic resonance imaging, and polygenic scores for ASD. Within the ASD group, N170 latency predicted change in adaptive socialization skills over an 18-month follow-up period; data-driven clustering identified a subgroup with slower brain responses and poor social prognosis. Use of a distributional data-driven cutoff was associated with predicted improvements of power in simulated clinical trials targeting social functioning. Together, the data provide converging evidence for the utility of the N170 as a stratification factor to identify biologically and prognostically defined subgroups in ASD.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition associated with difficulties in social interaction and communication and the presence of restricted or repetitive behaviors or interests and sensory hypo/hypersensitivity (1). The causes of ASD are highly heterogeneous, with multiple identified genetic factors (2) and several possible environmental factors that likely interact with genetic background (3). Symptom presentation is also highly variable, both in core symptomatology and in the presence or absence of a range of associated conditions, such as anxiety, depression, intellectual disability, or language delay (4). To move toward individualized interventions/support strategies, we need to stratify

this heterogeneous population into more biologically and prognostically homogeneous subgroups.

Difficulties in engaging with the social world are central to the symptom profile of ASD. Social difficulties in ASD can compromise everyday adaptive functioning (5). Social withdrawal and associated loneliness are major risk factors for conditions experienced at higher-than-expected rates in autistic people, including depression and anxiety (6–8). Developing support strategies for social functioning is critical to boosting mental well-being, adaptive functioning and independence skills, and life quality in autistic people (9). However, social difficulties may be associated with many different neurobiological alterations; identifying “stratification factors”—objective measures used to identify more biologically or prognostically homogeneous subgroups—is crucial. Despite decades of research on ASD, there remain no validated stratification markers (10). Key steps include identifying metrics that are individually reliable, mechanistically sensitive, relevant to a known biological system, predictive of prognosis, and that have a clear potential context of use for clinical settings (11).

Here, we focus on the N170 neural response to faces as a candidate stratification factor for social functioning in ASD (12). Social interactions are complex and fast-moving, and as such, expertise with faces is central to mature social interaction (13). The N170 (14) is a face-sensitive event-related potential of negative polarity peaking around 170 ms after stimulus onset over occipito-temporal electrodes [representing the coordinated firing of groups of neurons in lateral occipital areas (15), including the fusiform gyrus (16)]; it likely reflects face expertise (15), built through experience (17–19), and is sensitive to configural processing measured via stimulus inversion (20). Its amplitude and latency have moderate to good intraindividual reliability [0.6 to 0.8; (21–23)]. In a meta-analysis, autistic people

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showed on average a longer N170 latency (slower) to faces (Hedges' $g = 0.36$) but not to nonface control stimuli, relative to neurotypical controls (24). Within ASD, faster N170 latency relates to better holistic face processing (25), stronger adaptive socialization (26), and fewer social difficulties. Prognostically, N170 latencies have been related to trajectories of social symptoms from childhood to adolescence (16, 27).

We examined whether the N170 could be used for stratification according to social functioning in a large heterogeneous population of 436 individuals with ASD and controls tested in a multisite European longitudinal study [the Longitudinal European Autism Project (LEAP) (28)]. First, we examined whether differences in N170 latency related to clinical phenotype (categorical ASD diagnostic status). Second, we examined mechanistic sensitivity by testing whether N170 latency associated with measures of expertise-sensitive processing [the magnitude of the face inversion effect in electroencephalography (EEG) (14)]. Third, we tested whether N170 latency was associated with ASD-relevant biological pathways by examining its correlation with the magnitude of brain responses to faces in core social brain areas measured through functional magnetic resonance imaging (fMRI) (29), and to variation in ASD polygenic scores (PGS)—the aggregated effect of many common variants previously associated with ASD. Fourth, we examined prognostic utility by testing whether N170 latency could predict later social functioning (on the Vineland-II Socialization scale and its constituent subdomains) within the ASD group. To further probe clinical utility, we then examined whether the subdomains of the Vineland socialization scale at follow-up that associated with the N170 were themselves related with broader measures of clinical change [Clinical Global Impressions (30)] and quality of life [Child Health and Illness Profile (31)]. Last, to explore putative context of use, we used Monte Carlo simulations to model the potential gain in power from using an exemplar distributional-defined N170 cutoff [derived by creating a normative model of N170 latency change with age and then computing the position of each individual with autism within that distribution (32)] to enrich a clinical trial for participants who are more likely to show no spontaneous improvements in their social functioning over time.

RESULTS

N170 latency and categorical diagnosis

Table 1 characterizes the phenotype of the sample. As expected, N170 latency (N170L) to upright faces decreased with age ($F_{2,430} = 49.78$, $P < 0.001$, $\eta_p^2 = 0.188$; fig. S1) and was on average slower in the ASD group than in the control group ($F_{1,430} = 9.43$, $P = 0.002$, $\eta_p^2 = 0.021$; Fig. 1). N170L did not differ across hemispheres ($F_{1,430} = 0.68$, $P = 0.41$, $\eta_p^2 = 0.002$), and diagnosis, age, and hemisphere did not interact (all F s < 1.7 , all P s > 0.2 , η_p^2 s < 0.004).

Adding site and sex and their interactions with the diagnostic group did not alter the statistical pattern [main effect of group on latency ($F_{1,426} = 7.03$, $P = 0.02$, $\eta_p^2 = 0.013$; fig. S4); diagnostic group effects did not significantly vary by site ($F_{1,426} = 1.36$, $P = 0.25$, $\eta_p^2 = 0.003$) or sex ($F_{1,426} = 0.16$, $P = 0.69$, $\eta_p^2 < 0.001$), and sex had no overall effect on N170L ($F_{1,426} = 0.07$, $P = 0.80$, $\eta_p^2 < 0.001$)].

Consistent with our expectations, N170L did not show strong promise as a diagnostic marker. Using leave-one-out cross validation, a logistic regression predicting ASD status from N170L was significant (est = 9.57, SE = 3.30, $z = 2.9$, $P = 0.0037$; fig. S2). However, the area under the curve (AUC) was 0.56, indicating relatively poor

prediction, with a sensitivity of 0.19 and a specificity of 0.81. Separating the group by sex suggested slightly better performance in males (est = 11.92, SE = 4.1, $z = 2.91$, $P = 0.0036$, AUC = 0.57, $n = 301$, sens = 0.13, spec = 0.88) than in females (est = 5.31, SE = 5.7, $z = 0.93$, $P = 0.35$, AUC = 0.46, $n = 135$, sens = 0.61, spec = 0.33).

N170 amplitude

The sample overall showed a normative pattern of larger responses to faces in the right than the left hemisphere ($F_{1,430} = 28.61$, $P < 0.001$; Fig. 1). Likewise, amplitudes decreased with age ($F_{2,430} = 64.163$, $P < 0.001$; fig. S1). The groups did not differ on N170 amplitudes across both hemispheres ($F_{1,430} = 0.358$, $P = 0.550$; Fig. 1), and there was no significant interaction between hemisphere and group ($F_{1,430} = 0.707$, $P = 0.401$; Fig. 1).

Relation between N170 latency and symptomatology

Correlations with symptomatology were computed within the ASD group and controlled for age. Faster N170L related to fewer examiner-rated social symptoms [Autism Diagnostic Observation Schedule (ADOS) Social Affect] ($r_{209} = 0.20$, $P = 0.003$; fig. S3) but not restricted and repetitive behaviors ($r_{209} = 0.064$, $P = 0.36$). No associations were observed with associated symptoms [internalizing, externalizing, or intelligence quotient (IQ)], indicating specificity (table S6 and fig. S3). If sex was added to the model, then there were no significant sex differences in the magnitude of the association between N170L and ADOS Social Affect (analysis of variance including sex, age, N170L, and sex*N170L as predictors and ADOS Social Affect as the dependent variable; interaction between sex and N170L $F_{1,207} = 0.66$, $P = 0.42$, $\eta_p^2 = 0.003$; fig. S3).

Mechanistic relevance: The inversion effect

Inverting a face disrupts processing of its configuration and extraction of identity; thus, if case-control differences in the N170L represent altered face processing, then we should see corresponding differences in the modulation of the N170 by face inversion. The ASD group indeed showed diminished inversion effects for N170L (fig. S4) relative to the control group (interaction: $F_{1,430} = 7.67$, $P = 0.006$, $\eta_p^2 = 0.018$; ASD: $F_{1,243} = 0.02$, $P = 0.9$, $\eta_p^2 = 0.000$; controls: $F_{1,187} = 15.86$, $P < 0.001$, $\eta_p^2 = 0.078$). The magnitude of the group difference in the inversion effect did not vary by sex ($F_{1,427} = 0.27$, $P = 0.61$, $\eta_p^2 = 0.001$; fig. S4). Consistent with N170 sensitivity to configural processing, within the ASD group, N170 latency to upright faces correlated with the magnitude of the effect of inversion on N170 amplitude and latency (age-controlled, latency inversion $r_{246} = 0.49$, $P < 0.001$; amplitude inversion $r_{246} = -0.23$, $P < 0.001$; fig. S5).

Internal reliability of the N170 latency and amplitude

Across the whole sample, the internal reliability of the N170 component was either good or excellent in both hemispheres (table S9). Observed intraclass correlation coefficient (ICCs) were higher for latency (0.95) than for amplitude (0.84 to 0.88). ICCs for subgroup analyses (by diagnosis, age, and presence of mild-ID) were all either good or excellent except for amplitude in the left hemisphere in the mild-ID group, which was moderate (ICC = 0.69).

Relation to face-sensitive fMRI responses

Face-sensitive responses of the fusiform face area (FFA) were assessed as differential blood oxygenation level-dependent (BOLD) response to a face-matching condition compared to a shape-matching

Table 1. Clinical and diagnostic profile of individuals with EEG data within the LEAP sample. Data are means (SD). Participants at the Cambridge site for whom EEG was not attempted were excluded. Clinical and diagnostic information at follow-up only presented for those with valid baseline and follow-up scores. VABS was not administered to controls at follow-up. IQ, intelligence quotient; VABS, Vineland Adaptive Behavior Scales-II; ADI-R, Autism Diagnostic Interview-Revised 4 to 5 years/ever algorithm scores; ADOS CSS Total, SA, RRB, Autism Diagnostic Observation Schedule Calibrated Severity Scores for Total, Social Affect, and Restricted and Repetitive Behaviors; DAWBA, Development and Well-Being Assessment. WASI; Wechsler Abbreviated Scale of Intelligence, WISC; Wechsler Intelligence Scale for Children, NA; Not applicable.

Baseline visit	Autism Spectrum Disorder (n = 246)	Control (n = 190)
Sex (males:females) (% of females)	66:180 (27%)	69:121 (36%)
Age, years	17.0 (5.6)	17.5 (5.7)
Verbal IQ (WASI/WISC)	96.0 (19.4)	102.3 (20.6)
Performance IQ (WASI/WISC)	97.1 (21.0)	102.0 (20.0)
Full-scale IQ (WASI/WISC)	96.6 (19.0)	102.3 (19.0)
VABS Communication Standard Score	74.9 (16.8)	85.7 (24.6)
VABS Daily Living Standard Score	73.7 (16.2)	86.5 (22.4)
VABS Socialization Standard Score	70.6 (16.6)	93.2 (24.0)
VABS Play and Leisure Time V-Score	10.3 (3.4)	13.2 (3.7)
VABS Coping Skills V-Score	11.5 (3.5)	14.6 (4.4)
IVABS Interpersonal Relationships V-Score	8.5 (3.1)	13.5 (4.2)
ADI-R Social	16.0 (7.2)	NA
ADI-R Communication	12.7 (5.8)	NA
ADI-R Restricted and Repetitive Behaviors	4.2 (2.7)	NA
ADOS-CSS Total	5.3 (2.7)	NA
ADOS-CSS SA	6.0 (2.6)	NA
ADOS-CSS RRB	4.7 (2.7)	NA
DAWBA externalizing	1.9 (1.7)	0.9 (1.1)
Follow-up visit	Autism Spectrum Disorder (n = 223)	Control (n = 155)
Sex (males:females) (% of females)	62:161 (28%)	59:96 (38%)
Age, years	18.2 (5.6)	18.2 (5.4)
VABS Communication Standard Score	74.0 (17.9)	NA
VABS Daily Living Standard Score	75.6 (16.3)	NA
VABS Socialization Standard Score	74.4 (17.6)	NA
VABS Play and Leisure Time V-Score	11.2 (3.3)	NA
VABS Coping Skills V-Score	12.1 (3.7)	NA
VABS Interpersonal Relationships V-Score	9.5 (3.3)	NA
ADOS-CSS Total	5.3 (2.8)	NA
ADOS-CSS SA	5.8 (2.6)	NA
ADOS-CSS RRB	5.1 (2.8)	NA

control condition. Across the ASD ($n = 99$) and control groups with data available ($n = 100$), N170 latency was associated with the face-sensitive response in the right fusiform gyrus {peak voxel at Montreal Neurological Institute (MNI) [30 -64 -10] ($t = 3.93$, $P_{SVC} = 0.032$; $R^2 = 0.131$, N170 $b = 0.285$, $P < 0.001$; Fig. 2, A and B) with fair regional specificity (figs. S6 and S7); this effect was not modulated by diagnostic group ($F_{1,190} \leq 7.38$, $P_{SVC} \geq 0.860$) or age ($F_{1,188} \leq 9.09$, $P_{SVC} \geq 0.619$).

Relation to common genetic variation

Longer N170 latency was associated with higher PGS for ASD (33) (Fig. 2C; Spearman's $r^2 = 0.026$; $P = 0.0031$; participants with ASD $r^2 = 0.022$; $P = 0.039$; controls $r^2 = 0.024$; $P = 0.074$) but not with

schizophrenia (34), brain volume (35), intelligence (36), or body mass index (fig. S8). The correlation between N170L and ASD-PGS remained significant when the latter was computed with the new SBayesR method ($P = 0.035$) (37). There was also a significant positive correlation with the PGS for attention deficit hyperactivity disorder (ADHD) (33) ($r^2 = 0.01$; $P = 0.039$) and a negative correlation with a recent PGS computed for scores on the "Reading the Mind in the Eyes" test (38) ($r^2 = 0.01$; $P = 0.03$), a measure of cognitive empathy that can be more challenging for autistic participants (39).

Dimensional relation to Vineland socialization

To determine whether the N170L may have prognostic utility, we examined relations between N170 at the first assessment wave with

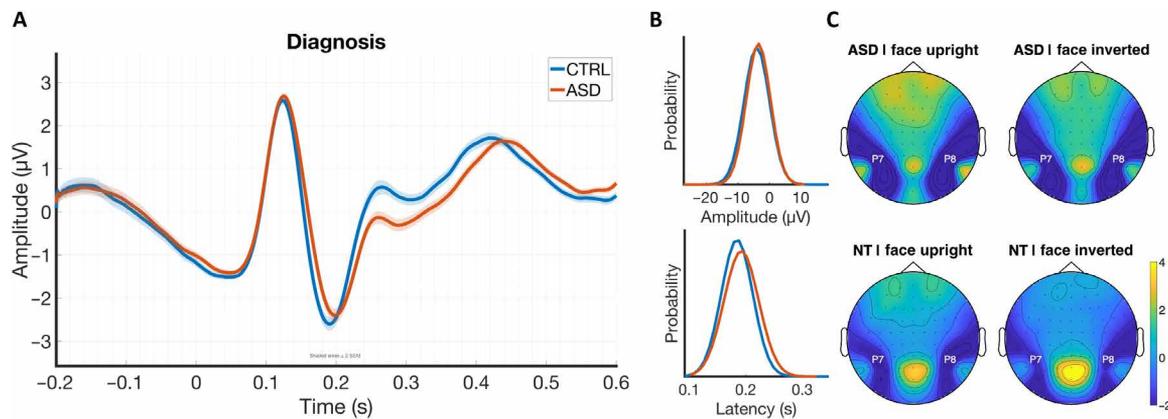


Fig. 1. N170 event-related potentials and topological maps elicited by upright face stimuli. (A) Grand-average event-related potential waveform with solid lines indicating the mean waveform and ± 2 SE shaded, in ASD ($n = 246$) and control ($n = 190$) groups, general linear model; $F_{1,430} = 9.43$, $P = 0.002$, $\eta_p^2 = 0.021$. (B) Probability density function for differences in amplitude and latency. (C) Topo-map of activation from 150 to 250 ms post-face onset, electrodes P7 and P8 marked.

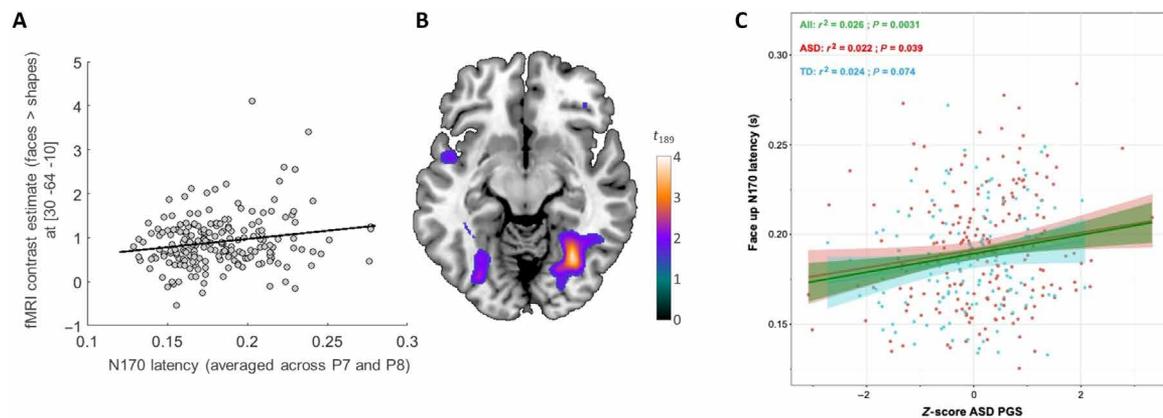


Fig. 2. Associations with functional magnetic resonance imaging and polygenic scores and N170 latency. (A) Dimensional association between face-sensitive functional responses in the fusiform gyrus and N170 latencies (ASD $n = 99$, control $n = 100$; general linear model; $t = 3.93$, $P_{SVC} = 0.032$; $R^2 = 0.131$, N170 $\beta = 0.285$, $P < 0.001$); right: t values plotted on a brain slice. (B) Correlation between ASD polygenic scores and N170 latency responses (full sample: Spearman's $r^2 = 0.026$; $P = 0.0031$; participants with ASD $n = 198$, $r^2 = 0.022$; $P = 0.039$; controls $n = 133$, $r^2 = 0.024$; $P = 0.074$). The samples are 198 ASD and 133 controls of European ancestry.

changes in Vineland Socialization and its subdomains at the second wave. Within the ASD group, and controlling for age and baseline scores, simple partial correlation showed that faster N170 latency at baseline was associated with greater improvement in the Vineland Socialization domain's Play and Leisure Time subdomain V-scale scores between baseline and the follow-up visit ($r_{141} = -0.235$, $P = 0.005$; Bonferroni corrected for four comparisons $\alpha = 0.02$; fig. S9). The association between N170L and change in Play and Leisure V-scores did not vary in strength by sex [analysis of covariance (ANCOVA); $F_{1,139} = 0.055$, $P = 0.82$, $\eta_p^2 = 0.00$]. Other scales did not show a predictive relation ($P_s > 0.5$; table S7).

A regression controlling for age at baseline and the time in days between baseline and follow-up assessments also showed a significant effect of N170 latency (overall model $F_{3,144} = 3.05$, $P = 0.031$, $r^2 = 0.06$; N170L beta = -0.020 , $t_{144} = -2.15$, $P = 0.033$), and using the rate of change of V-scale scores as the dependent variable (score difference divided by time gap) and controlling for age at baseline also showed the same effect (overall model $F_{3,144} = 3.04$, $P = 0.031$, $r^2 = 0.06$; N170L beta = -0.021 , $t_{144} = -2.26$, $P = 0.026$; fig. S9), indicating that time between baseline and follow-up did not confound results.

Using leave-one-out cross validation and controlling for baseline score and age, a linear regression confirmed a significant predictive relation between N170L and change in Vineland Play and Leisure V-scores (est. = -24.39 , SE = 8.48, $t_{143} = -2.88$, $P = 0.0046$). Controlling for the effect of site ($t_{142} = 1.59$, $P = 0.11$) did not remove the overall effect (est. = -21.80 , SE = 8.58, $t_{143} = -2.54$, $P = 0.01$). Confirming its clinical relevance, Play and Leisure V-scores at follow-up significantly varied across the five outcome categories of the Clinical Global Impressions scale (caregiver judgment of change between baseline and follow-up expressed as "a lot/a little worse," "about the same," "a little/lot better"; $F_{4,180} = 3.78$, $P = 0.006$, $\eta_p^2 = 0.079$; controlling for age $F_{4,180} = 3.49$, $P = 0.009$, $\eta_p^2 = 0.074$; fig. S10), and higher scores at follow-up were cross-sectionally associated with higher scores for achievement ($r_{162} = 0.36$, $P < 0.001$; controlling for age $r_{158} = 0.38$, $P < 0.001$), satisfaction ($r_{176} = 0.21$, $P = 0.004$; controlling for age $r_{173} = 0.23$, $P = 0.002$), comfort ($r_{176} = 0.17$, $P = 0.023$; controlling for age $r_{173} = 0.17$, $P = 0.028$), and resilience ($r_{176} = 0.20$, $P = 0.007$; controlling for age $r_{173} = 0.23$, $P = 0.001$), as measured by the Child Health and Illness Profile.

Cluster analysis of grand-average EEG responses

We examined whether a Gaussian mixture model cluster analysis computed on individual EEG averages concatenated and down-sampled across four key electrodes (P7, P8, O1, and O2) would reveal underlying “subgroups” of participants. The most parsimonious model used three clusters (Bayesian information criterion = 33,483, Akaike information criterion = 33,294); the model converged after 26 iterations with a negative log-likelihood of 16,603. Table S8 shows diagnostic and clinical profiles of the three clusters within the ASD group (cluster 1, $n = 118$, 48%; cluster 2, $n = 27$, 11%; and cluster 3, $n = 101$, 41%); briefly, clusters did not differ in symptom severity, IQ, or sex but were significantly different in age ($F_{2,245} = 57.29$, $P < 0.001$, $\eta_p^2 = 0.320$; cluster 1: mean = 20.6 years, SD = 4.3 years; cluster 2: mean = 15.1 years, SD = 4.8 years; cluster 3: mean = 12.1 years, SD = 4.7 years). A significant difference was observed between the three clusters in N170 latency ($F_{2,245} = 64.32$, $P < 0.001$, $\eta_p^2 = 0.975$; Fig. 3; controlling for age $F_{2,245} = 31.991$, $P < 0.001$, $\eta_p^2 = 0.209$). Bonferroni-corrected post hoc tests confirmed that cluster 2 had significantly longer latencies than cluster 1 ($P = 0.021$) or 3 ($P < 0.001$); cluster 3 had shorter latencies than cluster 1 ($P < 0.001$). This analysis confirms that the N170 latency captures a meaningful proportion of variance in the multidimensional EEG waveform.

Clusters differed in Play and Leisure Time scores ($F_{2,144} = 4.41$, $P = 0.014$, $\eta_p^2 = 0.06$; Fig. 3), although this effect was not significant when controlling for age ($F_{2,144} = 2.21$, $P = 0.11$, $\eta_p^2 = 0.03$). Cluster 2 (with the slower N170 latency) had significantly smaller changes in Play and Leisure Time V-scores between baseline and follow-up

than cluster 3 ($P = 0.019$). Within cluster 2, the association between N170 latency to upright faces at P7 and P8 explained over 25% of the variance in the change in the same subdomain Vineland Socialization (Play and Leisure Time) scores between baseline and 18-month follow-up visit ($r_{19} = -0.517$, $P = 0.023$; controlling for age $r_{16} = -0.56$, $P = 0.015$; Fig. 3).

Clusters also differed in number of improvers/nonimprovers on Vineland PLT score. A total of 68% ($n = 13$ of 19) of individuals in cluster 2 did not improve/declined (change scores of ≤ 0), compared with 58% ($n = 42$ of 73) in cluster 1 and 42% ($n = 22$ of 53) in cluster 3 ($\chi^2 = 5.23$, $P = 0.07$).

Creating age-adjusted zN170L scores for use as inclusion criteria

We used a normative model to transform raw N170 latency in the ASD group to zN170L, a score representing age-corrected deviance from the NT group mean. The root mean square error (RMSE) of the model was 24.4 ms, with 22.3% of the variance in N170 latency explained by age. For comparison, a linear fit of age on N170 latency has an RMSE of 25.4 ms and explains 17.0% of the variance—an increase in variance explained by the normative model of 5.3% over a linear fit (fig. S11).

Monte Carlo simulation of a clinical trial enriched using a zN170L cutoff

To provide a simplified worked example of the potential utility of the zN170L in a clinical trial, we used Monte Carlo-based clinical trial simulations to compare the statistical power by sample size in trials with and without N170 latency enrichment (figs. S12 and S13). With an example cutoff of $+0.5SD$ in the present sample, 72% ($n = 42$ of 58) of the ASD did not improve/decline, compared to 40% ($n = 35/87$) of those below the $+0.5SD$ cutoff ($\chi^2 = 14.5$, $P < 0.001$). We simulated 2500 randomized (1:1), placebo-controlled, 12-week clinical trials with and without enrichment using an estimated fixed effect size of intervention of Cohen's $D = 0.45$. On the basis of interpolation across the simulations, about 78 subjects per arm would be required in a nonenriched placebo-controlled clinical trial to detect a beneficial drug effect of equivalent magnitude with an 80% probability (type II error or $\beta = 0.20$) at $\alpha = 0.025$ [one-sided, or (equivalently) $\alpha = 0.05$ two-sided]. Conversely, the same 80% probability of detecting an analogous drug effect at the same α is achieved with about 48 subjects per arm in an enriched clinical trial. This represents a reduction in sample size of about 38% (fig. S13A). Figure S14 illustrates bootstrapped methods (1000 iterations) for optimizing cutoffs to maximize either sensitivity in the context of a reasonable level of specificity (A) or specificity in the context of a reasonable level of sensitivity (B). Using

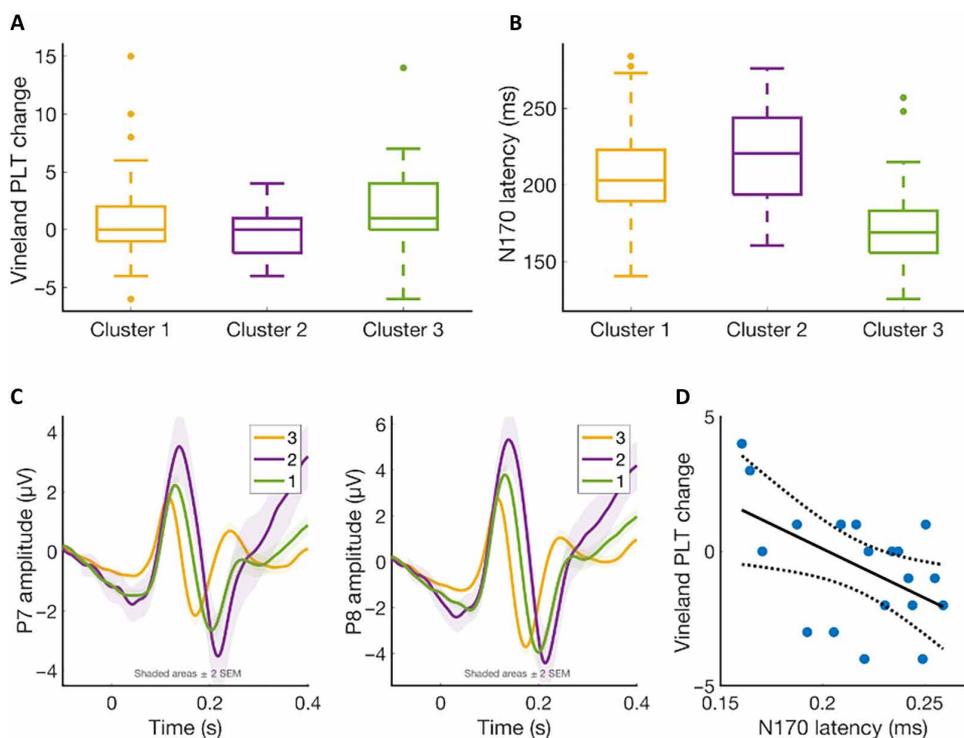


Fig. 3. Cluster analysis of EEG data within the ASD group. (A) Change in play and leisure time scores within each cluster (general linear models; cluster 1 $n = 73$, cluster 2 $n = 19$, cluster 3 $n = 53$; $F_{2,144} = 4.41$, $P = 0.014$, $\eta_p^2 = 0.06$). (B) N170 latency per cluster (cluster 1 $n = 118$, cluster 2 $n = 27$, cluster 3 $n = 101$; $F_{2,245} = 64.32$, $P < 0.001$, $\eta_p^2 = 0.975$). (C) Waveforms per cluster for P7 (top) and P8 (bottom) with solid lines indicating the mean amplitude and the shaded area depicting ± 2 SE. (D) Association between N170L and change in play and leisure time scores within cluster 2 ($n = 19$; Pearson's $r_{19} = -0.517$, $P = 0.023$).

leave-one-out cross-validation and logistic regression to predict improvement versus declining *V*-scores from an optimized zN170L cutoff (est. -0.56 , $SE = 0.18$, $z = -3.1$, $P = 0.002$) yielded an AUC of 0.65, at a sensitivity of 0.66 and specificity of 0.59 (males only: est. -0.54 , $SE = 0.21$, $z = -2.61$, $P = 0.009$, $AUC = 0.66$, $sens = 0.67$, $spec = 0.60$; females only: est. -0.65 , $SE = 0.38$, $z = -1.73$, $P = 0.08$, $AUC = 0.57$, $sens = 0.61$, $spec = 0.5$).

DISCUSSION

We provide evidence that the N170 is a promising stratification marker that may have utility in clinical trials. One option would be for individuals with a relatively longer N170 latency to be selectively enrolled in a trial because they would be (probabilistically) less likely to show spontaneous improvement in their social adaptive functioning over time than those with a shorter N170; an alternative would be to use the N170 as a baseline covariate. First, we show sensitivity to a clinical phenotype in our cohort: as a group, individuals with ASD showed slower N170 responses to upright faces, replicating a recent meta-analysis (24). This effect did not vary with age, sex, or collection site and was not confounded by IQ or associated conditions such as ADHD or anxiety. Second, variation in N170 latency was associated with a marker of configural processing (the face inversion effect). Third, we showed relation to other biological variables: variation in N170 latency across the cohort was associated with higher polygenic liability for ASD and with the fMRI response of a core brain region involved in face processing, the fusiform gyrus (40). Fourth, we demonstrated potential prognostic utility. Variation in N170 latency was associated with social clinical prognosis (change in Vineland Socialization Play and Leisure Time scores, a subdomain that at follow-up was associated with overall global impressions of change between baseline and follow-up and concurrently relates to key measures of quality of life) over an 18-month period in both dimensional and subtype analyses. Last, we further defined a potential context of use: We showed that data-derived cutoff scores could increase efficiencies in clinical trials, reducing the magnitude of potential placebo effects. Together, we contend that the N170 meets core criteria for consideration as a stratification factor for ASD.

Our work replicates and extends previous demonstrations that groups of individuals with ASD show slower latency N170 responses than controls (of whom a proportion had mild intellectual disability of varied etiology) (24). In our cohort, this was not confounded by associated internalizing or externalizing symptoms, or IQ; the only baseline association was with observed social symptoms, a core aspect of the ASD phenotype. Delays in N170 latency are not specific to ASD—groups with conditions like schizophrenia also show alterations in N170 amplitude that relate to general face recognition ability (41). However, schizophrenia shows substantial genetic overlap with ASD (42), and this is associated with common molecular brain-based phenotypes (43). Thus, markers that carve heterogeneity within ASD are likely to operate transdiagnostically (44). This observation might affect utility as, for example, a putative diagnostic marker (see below) but does not reduce the utility of the N170 as a potential stratification marker that may help us parse heterogeneity within cohorts with ASD. However, our ability to draw inferences about the degree to which the current findings regarding stratification are specific to ASD or would generalize to other conditions is limited because we did not include a control group with another

developmental condition, and this will be an important step for future work.

We did not observe sex differences in N170L or in the magnitude of group differences in N170L, or in the relation between N170L and concurrent or future measures of social behaviors. Previous observations of faster N170L in neurotypical females than males (45) and slower N170L in autistic females than males (46) may have led to the expectation of greater group differences in females than in males, but this was not borne out in the present sample. However, the predictive relations between N170 latencies and both diagnosis and change in socialization scores were numerically stronger in males. These analyses should be considered in light of our 3:1 sex ratio, which may have affected our ability to detect meaningful differences in the profile of autistic females and males or to detect effects within autistic females analyzed separately. Future investigation in more balanced samples is warranted to establish whether markers need to be sex stratified. Furthermore, we did not measure gender identity, which may have a different influence on social processing than sex. Caution should thus be exercised when generalizing our results to populations less well represented in our dataset.

We show that polygenic ASD scores computed from a genome-wide association study (GWAS) including over 18,000 people with ASD and 27,000 controls (47) correlated with variation in N170 latency. A previous twin study reported a genetic contribution to the N170 (48). Our study suggests that this N170L heritability is positively correlated with the heritability of ASD (and possibly to other psychiatric heritability because ASD is genetically correlated with other conditions). It is interesting that the strongest observed correlation is with the ASD PGS, because individuals with ASD display replicable differences in the N170 response to faces relative to controls (24). One limitation is that the proportion of variance explained by the current polygenic ASD score is relatively low ($\sim 2\%$) (47). Further work could complement this approach by examining the N170 in participants carrying large-effect genetic mutations conferring liability to autism that act on putatively more subscribed neural pathways. A recent study showed an association between PGS for ASD and an infant precursor of the N170 at 8 months that also relates to later diagnosis (49), suggesting that effects of genes linked to ASD on the neural correlates of face processing may emerge very early in development and could play a role in causal paths to symptom emergence. This may be consistent with other evidence that the genetic etiology of dimensional variation in autistic traits is similar to the etiology of autism diagnoses (50) and the proposal that dimensional variation in autistic traits is underpinned by the combined effects of multiple dimensional developmental alterations (51), one of which may be indexed by a longer N170L.

N170L also associated with PGS derived from a GWAS from 89,553 people who completed a measure of cognitive empathy called the Reading the Mind in the Eyes test (38). The test requires interpretation of emotional expressions from viewing isolated pictures of eyes and is something with which some autistic people have difficulty (39). Although replication is needed before strong conclusions can be drawn, given the slowed N170L in autistic people versus controls is strongest when attention is directed to the eye region of faces (52), this may point to shared neurobiological pathways via the role of eye gaze on advanced emotion recognition and early-stage face processing. Further, N170L was associated with the PGS for ADHD¹¹ (but not with behavioral measures of externalizing).

Although again replication is necessary, our results may thus suggest there are concurrent genetic contributions to N170L from both a relatively ASD-specific mechanism and a more general liability to broad psychopathology, which may begin in early development (49).

How does the N170 inform the mechanisms underlying social difficulties in some individuals with autism? The rich neurotypical data on the N170 provide us with many avenues for investigation. First, N170 response to faces may index the action of a dedicated face processing system that is innately programmed and selectively and exclusively engaged in the processing of faces (53). If so, our results may indicate some very early-stage alteration in face processing systems that could compromise subsequent social development (54, 55). When taking an individual differences approach, face-selective responses in the temporal lobe (such as the fusiform gyrus) are highly correlated with the N170 component (56), as is the case in the present study. Alternatively, it may not be the years that matter, but the “mileage”—that is, the N170 may be more influenced by experience than maturation (29). In the present sample, faster N170 latencies were associated with the magnitude of face inversion effects over both the latency and amplitude of the N170, supporting its relation to configural processing (57, 58). Configural processing develops more gradually than featural processing (59). The face sensitivity of the N170 may thus reflect the outcome of an expertise-based process of learning about faces (60). Distinguishing between these possibilities is an important step for future work.

We provide evidence that variation in N170 latency predicts change in social adaptive behavior over an 18- to 24-month period. This is consistent with reports of concurrent relations between the toddler precursor of the N170 (the N290) and social adaptive behaviors (26), and predictive relations between N290 latency and trajectories of observation-measured social symptoms on the ADOS (27). We observed dimensional relations between N170 latency and less progress in the Vineland Socialization Play and Leisure Time subscale; relations were stronger within a data-driven subset of individuals who had particularly slow N170 latencies and no or negative change in Vineland scores. Play and Leisure Time scores were associated with measures of Quality of Life, suggesting their clinical relevance. Furthermore, we provided a worked example of how such insights could be used to yield benefits within a clinical trial context.

Limitations include that these results require replication. We did not predict that predictive relations would be specific to the Play and Leisure Time subscale. This scale asks about turn-taking, understanding of rules, and independent social activity, which have face validity for activities that may reflect expertise in processing information from faces and people more broadly. Unlike for the broader Vineland scales, no estimates of minimal clinically meaningful changes are available for subscales (61), and this is an important task for future work (in addition to establishing whether the items included are relevant and meaningful as endpoints for autistic people). Furthermore, although we used leave-one-out validation to verify the predictive relation between the N170L and the Vineland subscale, an external replication dataset remains important. Although this was a multisite study and site did not explain the variance in prognosis or N170L, each site did not recruit sufficiently large or representative samples with prognostic data to test the generalizability of predictive models at individual sites. We must also explain why associations with this Vineland scale were solely prognostic and not concurrent. This pattern was also observed in a longitudinal study from childhood to adolescence that found associations between the

latency of the developmental precursor to the N170 and the slope of change in ADOS social symptoms over development, but not the intercept (concurrent symptoms) (27). Changes in the brain may precede the emergence of changes in behavior if changes in perception or attention affect learning from the environment, which over time has cumulative effects that subsequently manifest in behavior (62). Predicting future trajectories may also prove more powerful than relating brain measures to concurrent behavioral measures, in part because measuring change in a single variable within a participant can add information if the baseline and follow-up measures are strongly correlated, as in this case (63). However, large-scale rigorous tests of underpinning models will be required to make progress in this area. Furthermore, we did not include groups with other diagnoses, which could have probed specificity of prognostic validity to autistic people. No estimates of minimal clinically meaningful changes are available for Vineland subscales, making it difficult to identify an appropriate cutoff for change over time. We did not have access to an external dataset in which to replicate our prognostic associations. Although our sample was large, the sample size at individual sites was insufficient to test formal replication of findings across locations. We did not consider both sex and gender, which will be important in future work. We did not include an assessment of the meaningfulness of the Play and Leisure Time subscale to autistic people, which will be critical to judging its value as a putative intervention target.

In conclusion, the utility of the N170 as a putative marker has been widely debated (23, 64–66). Individual differences in N170L are moderately reliable in test-retest assessments (21–23) and were strongly split-half reliable in the present cohort. Utility as a diagnostic biomarker is clearly limited by the substantial population overlap between individuals with ASD and controls illustrated in the present study, and the presence of N170 delays in other conditions like schizophrenia (41). Use as a proxy end point for clinical trials would require more rigorous data on phenotypic association than is available to date (23). However, the N170 may be more appropriate for consideration as a trial enrichment marker. This would entail the use of the N170 to select a subset of a population of individuals with ASD for entry into trials targeted toward social functioning. Such “trial enrichment” markers (67) are used at the discretion of those designing support strategies. In this context, perfect sensitivity and specificity to diagnostic category would not be expected. If the N170 in part reflects an index of social expertise, then individuals with ASD who have a slower N170 latency may be statistically more likely to have a poorer prognosis in their social functioning and benefit more from targeted social support strategies. Our study provides evidence for prognostic value on a subdomain of the Vineland through both dimensional and categorical analysis approaches. We also show proof of principle that data-driven cutoffs can identify inclusion criteria that could be used to target clinical trials to those less likely to spontaneously improve, boosting power and efficiency. This is important not only in reducing the magnitude of expected placebo effects (68) but also in reducing the risk-benefit ratio and increasing the ability to make informed choices for individuals, although it is also important to note that restricting trial inclusion based on an N170 criteria would make recruitment even more challenging. The cutoff we chose to model was arbitrary, and investigators may choose a range of cutoffs depending on their goals. To be fully validated for clinical use, particular cutoffs would need to be replicated in an independent sample. An alternative

approach that does not require an arbitrary selection may be to use the N170L as a baseline covariate in a clinical trial to improve the precision of statistical estimates of effects. Future work should test whether the subgroups we identify may also be more likely to benefit from particular support strategies targeted to relevant biological or social systems. In summary, the promise of stratification biomarkers in psychiatry has long been recognized but not yet realized. Our work may provide a blueprint for the next generation of research studies to move from biomarker discovery to validation to deliver optimal outcomes for autistic people.

METHODS

Study design

Data were taken from the LEAP, a European multisite longitudinal observational study with two complete waves of assessment and an ongoing third assessment; for a comprehensive clinical characterization of the full LEAP cohort, see (4). The Supplementary Materials provide full inclusion/exclusion criteria and broader methodological details. At each site, an independent ethics committee approved the study; all participants (where appropriate) and their parent/legal guardian provided written informed consent. The objectives of the LEAP study are to identify stratification biomarkers for autism; in this analysis, we predicted that the N170 derived from EEG responses to faces would predict social trajectories, based on previous literature (26, 27). Participants were not randomized to a particular arm or condition, and neither participants nor experimenters were blind to diagnostic status. All analysis stages were performed blind to age, site, and diagnostic status.

Participants

We included the total sample of 436 participants with and without autism with valid EEG data, ranging in age from 6 to 31 years and with full-scale IQs between 50 and 148 (table S1 and Table 1). No outliers were excluded. See Supplementary Materials for inclusion and exclusion criteria.

Electroencephalography

Five sites acquired EEG data at baseline, following international standards (69) using three different systems. Details of the EEG acquisition, cleaning, processing averaging, and peak detection and extraction are described in the Supplementary Materials.

Using TaskEngine (70)/Presentation, participants were presented with three upright or inverted faces [Caucasian, African-American, and Asian (71), subtending 12.4°], repeated 168 times over four blocks (fig. S1, left). Each trial began with a randomly selected fixation icon (2.9° of visual angle positioned where the eye region of the face would subsequently appear in both upright and inverted conditions).

Data were uploaded from each site to a central repository in their raw, manufacturer-specific, proprietary formats and preprocessed in EEGLab (72) to harmonize data in a common format (62-channel montage, referenced to FCz with sampling rate of 1 kHz). Visual stimulus timing was measured and corrected at all sites except for UCBM using a photodiode. In Fieldtrip (73), raw EEG data were epoched from -200 to 800 ms after stimulus onset; band-pass filtered 0.1 to 30 Hz with 2000-ms padding; and resampled to 500 Hz. Artifacts were identified and removed with a custom-written automatic algorithm and whole-scalp artifacts (voltages $\geq 100 \mu\text{V}$ or a range of >150 or $0 \mu\text{V}$) were detected and interpolated using a

spherical spline algorithm where at least three neighboring channels were artifact free. Electrooculography (EOG) artifacts were detected on frontal electrodes FP1/z/2, AF7/8, and contaminated trials were removed. Grand averaged data were corrected to baseline (mean amplitude from -200 to 0 ms) and average rereferenced. Last, N170 (P7 and P8) peak amplitude and latency were extracted through an automatic algorithm with hand supervision. See table S2 for a breakdown of data loss by group, and table S3 for differences in clinical scores between those participants who provided usable data and those who did not.

Clinical measures, visual fMRI, and genetics

To test specificity of phenotypic associations with the N170L, we collected clinical measures of core [ADOS (74)], Autism Diagnostic Interview (ADI) (75) and associated symptoms [IQ, Development, and Wellbeing Assessment for internalizing and externalizing (76)], and adaptive function [Vineland (77)]. A proportion of the sample ($n = 145$ with EEG) returned for a follow-up visit 14 months to 2 years after the original assessment; change in social functioning was assessed using the Vineland Socialization domain and constituent subscales given in previous work (26). Quality of life was assessed using the Child Health and Illness Profile (31), and general change using the Clinical Global Impressions Scale. Functional brain responses were acquired on three Tesla MRI scanners as part of the LEAP protocol using a well-established face matching task (78), with alternating blocks of faces (showing angry and fearful emotions) and control conditions. Functional imaging data were preprocessed and statistically analyzed using standard analysis routines implemented in SPM12. To establish whether EEG N170 latency was related to core face-sensitive brain regions, we used fMRI to assess the BOLD response within a bilateral, a priori-defined anatomical mask of the FFA [2318 voxel, small volume correction; fig. S3 (79)]. FFA is a brain region considered as one of the primary sources of the N170 response (16). Single-nucleotide polymorphism genotyping was performed at the “Centre National de Recherche en Génomique Humaine (CNRGH)” using the Infinium OmniExpress-24v1 BeadChip (>700 K markers) from Illumina. After quality control and ancestry correction, a range of PGS scores (including ASD) were computed for 198 individuals with autism and 133 controls from European descent with EEG data using PRSice-2 tool (80).

Statistical approach

Analyses were run in SPSS24 and R1.3.959 and corrected for multiple comparisons within each core question; statistical thresholds were set at two-sided $P < 0.05$ unless otherwise noted: (i) relation to clinical phenotype: We used linear modeling of the latency of the N170 on face upright trials by diagnosis (ASD/control) \times hemisphere (left [O1/P7]/right [O2/P8]) \times age group (children 6 to 11/adolescents 12 to 17/adults 18 to 30). We additionally tested stability of the group effect when adding “sex” as a fixed effect and “site” as a covariate. We examined specificity to the N170 latency by repeating this model with N170 amplitude. We tested efficacy as a diagnostic marker using logistic regression with leave-one-out cross-validation (R package caret). We examined concurrent associations between N170 and core (ADOS Social Affect, ADOS Restricted and Repetitive Behavior Scale, Social Responsiveness Scale-2, Vineland Socialization domain and constituent subscales) and associated (DAWBA externalizing and internalizing scales) symptoms and IQ, controlling for age. (ii) Mechanistic utility: We used a series of partial correlations corrected for age within each diagnostic group to examine the

relation between N170 latency and inversion effect magnitude (N170 amplitude to upright-inverted faces). (iii) Relation to biology: For genetics, Spearman's rank correlation tests were performed to study the relation between the ASD PGS (47) and N170 latency (averaged across P7 and P8). For fMRI, individual contrast images were subjected to a voxel-wise group-level analysis using a general linear model to assess the association of fMRI responses with the EEG-derived N170 latency. We additionally assessed effects of diagnosis and age while controlling for effects of sex and site. Effects were evaluated at a statistical threshold of $P = 0.05$, family-wise error corrected (FWE) at the voxel level within a bilateral mask of the fusiform gyrus (2318 voxel) based on the Anatomical Automatic Labeling Atlas (see fig. S8), using small volume correction (SVC). (iv) Prognostic utility: We used partial correlations (SPSS) and regression models with leave-one-out cross-validation (R package caret) to examine the relation between N170 latency and the domain and subdomain scores of the Vineland socialization scale at the follow-up visit, controlling for age and score on the same measure at the baseline visit and to explore whether relations varied by sex or were affected by controlling for site. We used Pearson's correlation to examine the relation between any Vineland scores that significantly ($P < 0.05$) associated with the N170 and five domain scores of the CHIP (Quality of Life). Then, we used a data-driven decomposition approach to examine whether meaningful variance in the EEG data related to future social behavior. To identify clusters, we took individual event-related potentials from four electrodes over which brain responses to faces are seen (O1, O2, P7, and P8) and ran a spatial principal components analysis (PCA; see the Supplementary Materials) on the downsampled signal (to prevent collinearity—167 Hz) in Matlab. We took the loadings of each individual participant on the top seven PCA components and subjected the scores to a Gaussian mixture model-based cluster analysis (regularization value 0.1, diagonal covariance matrix, 10 replicates) across the whole sample. We then examined whether the N170 latency, change in Vineland Socialization subscale scores between baseline and follow-up, and their interrelation varied across clusters using general linear models. (v) Context of use/potential utility in a clinical context: To examine the potential utility of the N170 in a clinical trial context, we first fit a normative model of N170 latency on age and used the derived z scores in a leave-one-out cross-validated logistic regression with AUC calculation (R package caret) to examine predictive validity for individuals likely to improve or be stable/decline in their Vineland Socialization subscale scores. We then identified possible cutoff points optimized for sensitivity or specificity for subsequent change in Vineland Socialization subscale scores using bootstrapping (1000 runs) in R package cutpointr. Using an exemplar zN170L cutoff selected to have good sensitivity for detecting and excluding "improvers," we then used Monte Carlo simulations to determine the effect of restricting clinical trial entry to those predicted to have stable or decreasing Vineland Socialization subscale scores over time.

SUPPLEMENTARY MATERIALS

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Supplemental Methods

Figs. S1 to S14

Tables S1 to S9

References (81–85)

[View/request a protocol for this paper from Bio-protocol.](#)

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Stratifying the autistic phenotype using electrophysiological indices of social perception

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Exploiting face processing in patients with ASD

The heterogeneity observed in patients with autism spectrum disorder (ASD) highlights the need for better patient stratification methods. Here, Mason *et al.* evaluated the use of the speed of early-stage face processing (N170 latency) for clinical stratification and prognosis in ASD and age-matched healthy individuals. N170 latency was slower in individuals with ASD and correlated with response to faces measured with fMRI and with polygenic risk score. Among participants with ASD, the N170 values stratified patients according to socialization prognosis and improved power in a simulated clinical trial. The results suggest that including N170 evaluation in clinical stratification might help the design and development of patient-specific therapies for ASD.

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