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The Unfulfilled Promise of the N170 as a Social Biomarker

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ABSTRACT

BACKGROUND: Greater affordability and accessibility of noninvasive brain imaging techniques have led to an increased interest in identifying biomarkers of various cognitive processes, particularly in the field of neurodevelopmental disabilities. Autism spectrum disorder (ASD) is one area of research in which strong claims in support of brain-based biomarkers, such as the face-sensitive N170 event-related potential response, are currently emerging. This study systematically examined the possibility of the N170 amplitude and latency measures serving as a biomarker of social information processing in ASD.

METHODS: The N170 response to faces and houses was recorded during passive picture viewing in 77 children with ASD, 7 to 16 years of age, at 2 time points (before and after a social skills intervention) 3 months apart. Social functioning was assessed using standardized behavioral tests, caregiver reports, and observational measures of naturalistic social interactions.

RESULTS: The results replicated prior findings of larger N170 amplitudes in response to faces than to houses, but the associations with the behavioral measures of social functioning were modest and not consistently present across the 2 assessment time points. Neither the amplitude nor the latency of the N170 response to faces was sensitive to the effects of a social skills intervention that produced behavioral improvements.

CONCLUSIONS: The N170 is a reliable event-related potential response reflecting the sensory-perceptual stage of face processing, but it does not fit the definition of a biomarker of social deficits in ASD because it is not sufficiently informative about heterogeneity of social functioning and is not sensitive to treatment effects.

Keywords: Autism, Biomarker, Face, N170, Social, Treatment

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Greater affordability and accessibility of noninvasive brain imaging techniques have led to a dramatic increase in the interest to identify biomarkers of various cognitive processes. The appeal of an objective brain-based measure that could predict risk, assist with a diagnosis, or evaluate treatment effects is particularly strong in the field of neurodevelopmental disorders, in which standardized behavioral assessment options are often limited (e.g., owing to intellectual, motor, or language difficulties) and access to clinical expertise for diagnosis and management is not always readily available.

Autism spectrum disorder (ASD) is one area in which strong claims in support of brain-based biomarkers are currently emerging. ASD is a neurodevelopmental disorder characterized by impairment in social competence; restricted, repetitive behavior; and sensory processing problems (1), involving cognitive, neural, behavioral, and functional components (2). Behavioral studies in ASD often noted atypical social information processing, mainly using face stimuli in tasks of detection, recognition, or emotion identification (3–6). However, the results were highly variable, leading some to question whether face processing is uniformly impaired in ASD (7,8). The need for a reliable measure that could be used across ages and functioning levels makes biological data highly attractive. Indeed, biological differences that may be clinically relevant are not always detected in overt behaviors (9) but could be captured in measures of brain activity and/or peripheral physiology (10).

Event-related potentials (ERPs) offer an affordable and widely accessible means to noninvasively monitor information processing with millisecond-level precision. Among the ERP responses, a negative peak occurring over the occipitotemporal scalp at 170 ms (N170) has been established in typical populations as sensitive to faces that elicit larger amplitudes than nonsocial stimuli (11,12). Following the initial reports of atypical N170 characteristics in ASD (13), the past 10 years have seen a 10-fold increase in the number of empirical studies and opinion articles considering the possibility of the N170 response serving as a biomarker of social information processing in ASD, from 15 articles between 2000 and 2009 to 149 articles between 2010 and 2019 (Google Scholar search with keywords of *ASD*, *N170*, *biomarker*).

Recently, Kang *et al.* (14) conducted the first meta-analysis of the N170 studies comparing persons with ASD with typical

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individuals. They identified no consistent group differences in the N170 amplitude but noted a small but significant effect size for delays in the N170 latency in ASD. Age, sex, cognitive ability, or diagnostic process differences did not explain variability in the timing of the N170 response to faces. These findings led the authors to conclude that the N170 latency could serve as a possible biomarker of social information processing in ASD (14).

However, this conclusion was challenged by Vettori *et al.* (15), who pointed out that a slower-than-typical N170 latency to faces in ASD may reflect general delays in visual processing speed, because the meta-analysis noted a similar pattern of prolonged latencies (nonsignificant but with medium effect size) for nonsocial stimuli. They further argued that the N170 latency does not fulfill the criteria for a clinically valuable biomarker because of difficulties effectively categorizing individuals and questioned whether it is measuring a specific impairment (face processing) related to a specific clinical profile (e.g., ASD). Considering the latter point, Kang *et al.* (14) highlighted the need for further research connecting the N170 response and the mechanisms of social difficulties in ASD.

This discussion brought to the forefront the conversation about the possible diversity in the types of biomarkers. In the case of ASD, a complex clinical condition with multiple symptoms affecting numerous physiological systems, the current opinion is that a diagnostic biomarker is not yet available (16). In the meantime, the N170 response is often suggested as a promising sample stratification or a target engagement biomarker of social deficits (9,17). Nevertheless, even in this more limited context, a measure aiming for classification as a biomarker needs to be sensitive to heterogeneity within the target population, developmental differences, and treatment effects (17). To date, this has not been clearly demonstrated for the N170 response.

Most studies examining the N170 response in persons with ASD did not test the associations between its amplitude or latency and behavioral measures of social functioning. The few studies that performed explicit correlational analyses yielded inconsistent results. Some reported that more accurate performance on face recognition tasks in persons with ASD was associated with slower left hemisphere N170 responses (Wechsler Memory Scale–III Faces subtest) (13) or faster right hemisphere N170 (Benton Facial Recognition Test) (18). The strength of such correlations (e.g., with the Diagnostic Analysis of Nonverbal Accuracy–Second Edition) diminished after controlling for age and IQ (19). Others reported no significant associations between the N170 amplitude or latency and performance on the Wechsler Face Recognition test (20,21) or Diagnostic Analysis of Nonverbal Accuracy–Second Edition (22). Furthermore, small-to-medium correlations between the N170 latency and a subset of Diagnostic Analysis of Nonverbal Accuracy–Second Edition items (e.g., child angry faces) were attenuated when a behavioral measure of social motivation was included in the statistical model (22). The N170 amplitude or latency also did not correlate with autism diagnostic scores, IQ, language, adaptive behavior (23), or measures of social motivation (22), social cognition, and social behavior (24). In adults with ASD, the N170 amplitude or latency did not change following intensive face recognition training that produced significant improvements in behavioral performance (25).

This variability in the results across studies could be attributable to differences in the sample size, age, ASD diagnostic procedures and severity, equipment, choice of tasks, analyses, and data quality. Nevertheless, it highlights the need for further research that would validate the N170 response as a biomarker of social deficits in ASD.

In the current study using a large sample of children with ASD, we aimed to systematically examine whether the N170 face response fits the definition of a stratification or a treatment effect biomarker by evaluating its sensitivity to 1) individual differences in social functioning and 2) the effects of a behavioral intervention targeting social skills. Specifically, based on the suggestions by Kang *et al.* (14) that the N170 response reflects neural processes relevant to social functioning in ASD, we hypothesized that larger amplitudes and shorter latencies in response to faces would be associated with more optimal performance on the standardized behavioral measures and during real-life social interactions. Improvements in social functioning following treatment would be associated with acceleration of N170 latency and/or increase in amplitude in response to faces. Additionally, we examined psychometric properties of the N170 response, such as test–retest stability of its amplitude and latency as well as of its associations with behavioral measures of social functioning. Given our focus on heterogeneity within the ASD population and not on group differences from typical peers, this study did not include a typical comparison group.

METHODS AND MATERIALS

Participants

Seventy-seven youths with ASD, 7 to 16 years of age, representing 3 consecutive cohorts of participants in a randomized clinical trial of a social skills treatment (SENSE Theatre [Vanderbilt Kennedy Center, Nashville, Tennessee]; NCT02276534) contributed ERP data for this study. The sample included 44 individuals randomized into the treatment (EXP) group and 33 participants placed into the waitlist control (WLC) group. Participants were recruited from the university clinic, support groups, and schools. The diagnosis of ASD was made in accordance with the DSM-5 (1) based on 1) a previous diagnosis by a psychologist, psychiatrist, or pediatrician with autism expertise; 2) current clinical judgment (B.A.C.); and 3) the Autism Diagnostic Observation Schedule (26), administered by research-reliable personnel. The Social Communication Questionnaire (27) further corroborated the diagnosis (scores $\geq$15). Co-occurring conditions included attention-deficit/hyperactivity disorder (19.5%); learning disability (1.3%); language disorder (1.3%); and sensory (3.9%), anxiety (6.5%), and medical diagnosis (13.0%), and were evenly distributed across the 2 groups ($\chi^2_6 = 2.69$, $p = .85$). All participants had an IQ of 70 or greater, as measured by the Wechsler Abbreviated Scale of Intelligence (28). The demographic information is presented in Table 1.

All participants had normal or corrected-to-normal vision and no medical history of seizures, traumatic head injury, or other serious medical conditions affecting the central nervous system (confirmed during screening). Parents/guardians of the participants provided written informed consent, and participants provided assent. The study was approved by the

Table 1. Demographic and Diagnostic Characteristics of the Treatment (EXP) and Waitlist Control (WLC) Groups

	EXP Group	WLC Group	*p* Value
Psychotropic Medications, Any	18	14	
Psychotropic Medications, >1	11	7	
Age, Years	11.12 (2.54)	10.58 (2.32)	.34
Female/Male	11/32	8/25	.82
ADOS Algorithm	10.57 (4.73)	11.83 (5.43)	.32
WASI	104.18 (19.27)	96.49 (17.50)	.07
SCQ	20.95 (6.70)	20.69 (7.18)	.87

Values are *n* or mean (SD).

ADOS, Autism Diagnostic Observation Schedule; SCQ, Social Communication Questionnaire; WASI, Wechsler Abbreviated Scale of Intelligence.

institutional review board of Vanderbilt University Medical Center.

Procedures

Participants completed ERP, neuropsychological, and social behavior measures at baseline and at the end of a treatment period, approximately 3 months later. All assessments for the EXP and the WLC groups were conducted concurrently.

N170 ERP Acquisition

Following the procedures of Key and Corbett (29), participants viewed a sequence of 51 color photographs of unfamiliar young adult faces [Radboud Faces Database (30)] mixed with 51 color photographs of unfamiliar house façades (obtained from realtor websites). Unbeknownst to the participants, one of the stimuli in each category was randomly selected and repeated 50 times throughout the experiment, yielding a unique set of 50 repeated faces and houses for each person. The remaining stimuli were presented once. The participants were instructed to watch the screen "like TV" and had no stimulus-specific task. To verify attention, a button press was required in response to a drawing of a yellow smiley face (10 probes). All stimuli were presented in random order for 1500 ms with a varied interstimulus interval of 1300 to 1600 ms to prevent habituation. The on-screen size of faces and houses was 30 cm × 25 cm (visual angle of 19° × 16° from the viewing distance of 90 cm). The attention probe was 14.5 cm (9.21°) in diameter. E-Prime version 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA) controlled stimulus presentation. The entire task included 210 trials and lasted approximately 12 minutes. If participants became inattentive or restless, stimulus presentation was suspended until the participant was ready to continue with the task.

A 128-channel Geodesic Sensor Net (Electrical Geodesics, Inc., Eugene, OR) was used to record the ERPs. Data were sampled at 250 Hz with impedance levels at or below 50 kΩ. All electrodes were referred to vertex and then re-referenced during data analysis to an average reference (31).

Neuropsychological Assessments

The NEPSY Memory for Faces subtest (32) assessed face perception. Participants viewed a series of 16 pictures of children's faces presented for 5 seconds each and then were asked to identify them amid an array of 3 nonpresented choices, immediately and following a 20-minute delay. The scaled scores for immediate and delayed memory for faces (average: 7–13) were used in the analyses.

The Social Responsiveness Scale (SRS) (33) is a 65-item questionnaire completed by caregivers to measure social functioning (e.g., communication, cognition). The Total T-score was used in the analyses. T-scores between 60 and 75 are clinically significant, with scores above 76 indicating more severe ASD symptoms.

The Adaptive Behavior Assessment System (34) is a caregiver questionnaire that assesses 10 areas of adaptive functioning. For this study, the Adaptive Behavior Assessment System ascertained adaptive functioning related to social skills. Scaled scores between 7 and 13 fall within the average range, scores between 3 and 6 are clinically relevant.

Social Behavior Assessment

The Peer Interaction Paradigm (35) is a 20-minute playground interaction in which the participant with ASD engages in play with 2 unfamiliar, trained, sex- and age-matched typically developing confederates who provide behavioral structure to the play by initiating interactive sequences (i.e., cooperative and group play) in an otherwise natural setting. The Observer XT (36) was used for the analysis of observational data.

Continuous timed-event coding of 2 primary behaviors (cooperative play, verbal bout) was conducted by coders blinded to group membership and study time periods. Cooperative play was defined as the percentage of time the participant with ASD was engaged in a reciprocal activity for enjoyment that involved participation of other children. Verbal bout was defined as an interaction between the participant with ASD and 1 or more children that began with a verbal overture and continued in reciprocal to-and-fro communication. Interrater reliability was comparable to previous studies (35) with κ = .82 and .88 for cooperative play and verbal bout, respectively.

Social Skills Treatment

The SENSE Theatre social skills intervention (37–39) was implemented over ten 4-hour group sessions. It used theatre games, role-play, improvisation, and character development activities in the context of putting on a play. Trained peer actors served as expert models of reciprocal social communication, flexible thinking, and behavior (40). Prior studies examining the efficacy of SENSE Theatre showed significant and sustained gains in behavioral (e.g., social communication), cognitive (e.g., theory of mind), and neurophysiological measures of social functioning (e.g., face memory) (37–39).

ERP Data Analysis

Continuous electroencephalography recordings were filtered using a 0.1- to 30-Hz bandpass filter and segmented on stimulus onset to include a 100-ms prestimulus baseline interval and a 900-ms poststimulus interval. Trials contaminated by ocular and movement artifacts were excluded from analysis using an automated screening algorithm in NetStation 5.3 (Electrical Geodesics, Inc., Eugene, OR) followed by a manual review. Data for electrodes with poor signal quality were reconstructed using spherical spline interpolation (41). If more

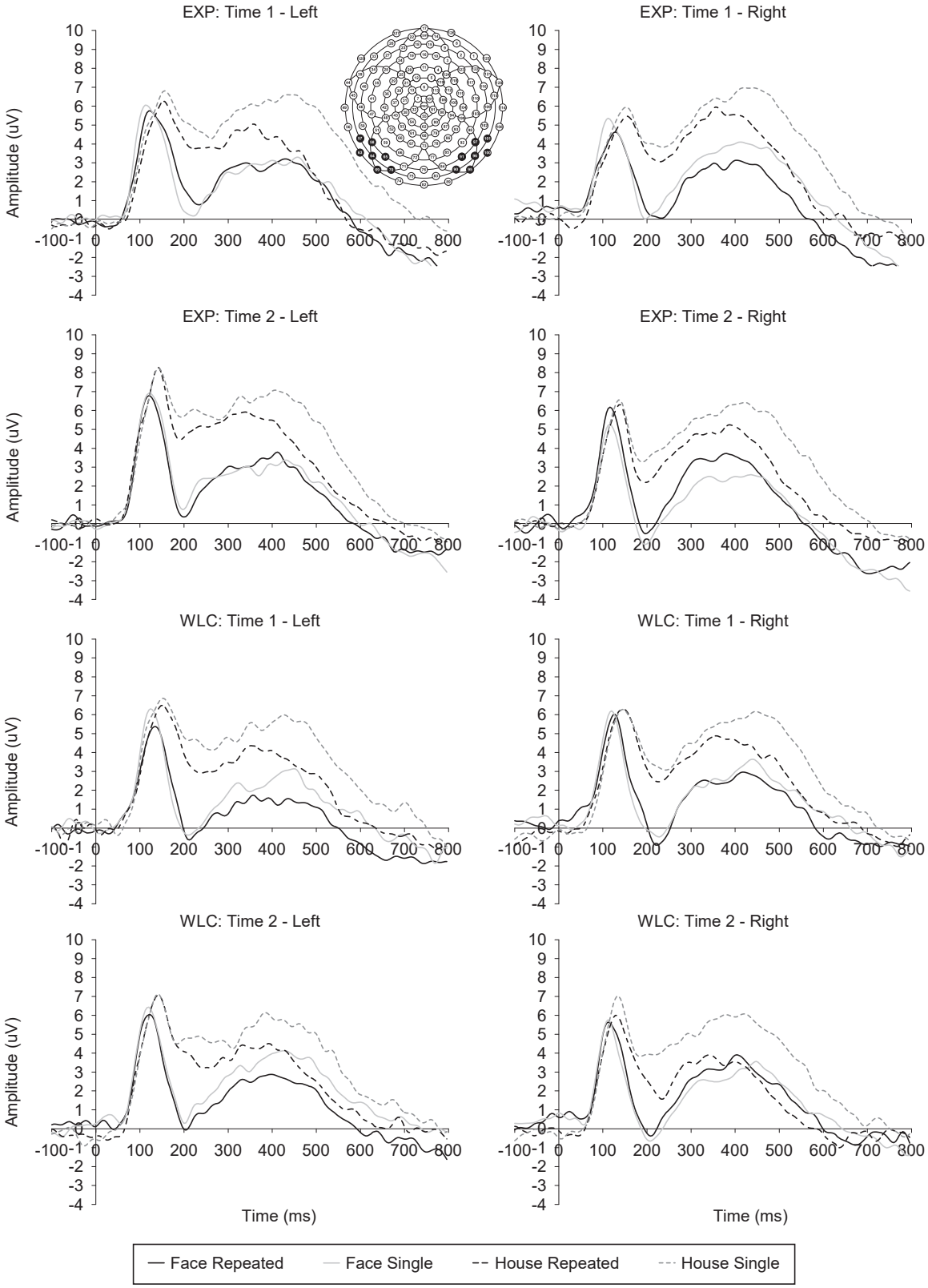

Figure 1. Event-related potential waveforms in response to repeated and single stimuli at left and right occipitotemporal clusters for youths with autism spectrum disorder in the treatment (EXP) and waitlist control (WLC) groups at baseline (time 1) and posttest (time 2).

than 20% of the electrodes within a trial required interpolation, the entire trial was discarded. The retention rates were comparable across conditions, groups, and test sessions (EXP group, baseline: mean = 20.22, SD = 6.20; posttest: mean = 21.26, SD = 7.21; WLC group, baseline: mean = 20.71, SD = 7.19; posttest: mean = 19.09, SD = 7.04; all p values $>.05$) and similar to those reported in prior studies using the same paradigm (29,42,43).

Following artifact removal, individual ERPs were averaged for repeated and single presentations of faces and houses, re-referenced to an average reference, and baseline-corrected by subtracting the average microvolt value across the 100-ms prestimulus interval from the post-stimulus segment. Next, mean N170 amplitudes and peak latencies were derived within the 150- to 240-ms interval for occipitotemporal electrodes within each hemisphere (left: 57, 58, 63, 64, 65, 69, 70; right: 90, 91, 95, 96, 97, 100, 101) (Figure 1). These scalp locations and time intervals were selected a priori based on published N170 studies in children with autism (29,44) and confirmed by visual inspection of the grand-averaged waveforms. The resulting values were averaged across the electrodes within each cluster and entered into separate $2 \times 2 \times 2 \times 2 \times 2$ repeated-measures analyses of variance with group (EXP, WLC) as the between-subjects factor and time (baseline, posttest), stimulus (faces, houses), memory condition (single, repeated), and hemisphere (left, right) as within-subjects factors with Huynh-Feldt correction. Significant interactions were further explored using 1-way analyses of variance and pairwise comparisons with Bonferroni correction.

Exploratory analyses examined correlations among the N170 characteristics, age, ASD symptoms, and social functioning, as well as test–retest reliability. To provide the least conservative evaluation of possible brain–behavior associations, no correction for multiple significance testing was applied for this analysis.

RESULTS

Summary data for the neuropsychological and social behavior assessments are presented in Table 2. The N170 amplitude and latency data are presented in Table 3.

N170 Amplitude

There were main effects of stimulus ($F_{1,74} = 117.197$, $p < .001$, $\eta_p^2 = .613$), memory ($F_{1,74} = 6.856$, $p = .011$, $\eta_p^2 = .085$), and hemisphere ($F_{1,74} = 10.202$, $p = .002$, $\eta_p^2 = .121$), as well as stimulus $\times$ memory ($F_{1,74} = 12.977$, $p = .001$, $\eta_p^2 = .149$), stimulus $\times$ hemisphere ($F_{1,74} = 4.115$, $p = .046$, $\eta_p^2 = .053$), and time $\times$ stimulus $\times$ memory $\times$ hemisphere ($F_{1,74} = 5.516$, $p = .022$, $\eta_p^2 = .069$) interactions. There was no significant group effect. Follow-up analysis of the 4-way interaction first contrasted the N170 responses at baseline versus posttest and revealed no significant differences in the left or right hemisphere for any of the stimulus conditions ($p = .031$–$.999$). Therefore, the remaining analyses were performed on data pooled across the 2 test sessions.

Paired t tests indicated that in the repeated and single-presentation conditions, faces elicited larger (more negative) N170 responses than houses in both hemispheres ($t_{75} = 6.475$–11.196, $p < .001$, $d = 0.74$–1.28). Larger N170 responses over the right than the left hemisphere were

Table 2. Baseline and Posttest Performance on Behavioral Measures of Social Functioning in the Treatment (EXP) and Waitlist Control (WLC) Groups

		WLC Group		EXP Group	
Measure	Time	Mean	SD	Mean	SD
NEPSY MF-I	Baseline	7.46	3.69	8.50	3.66
	Posttest	9.52[a]	2.98	10.35[a]	3.30
NEPSY MF-D	Baseline	7.88	3.57	8.96	3.59
	Posttest	9.42[a]	4.30	11.05[a]	3.55
ABAS-Social	Baseline	3.16	3.00	2.80	2.26
	Posttest	3.28	2.62	3.77[a]	2.93
SRS Total	Baseline	78.28	9.41	78.82	6.60
	Posttest	76.97	9.66	75.36[a]	9.12
SCQ Total	Baseline	20.69	7.18	20.95	6.90
	Posttest	19.64	7.39	19.12[a]	7.21
PIP T2[b] Verbal Bout	Baseline	49.52	38.53	65.63	30.99
	Posttest	53.62	37.25	61.80	31.63
PIP T4[b] Verbal Bout	Baseline	57.38	39.57	56.39	37.28
	Posttest	49.05	36.24	64.37	31.50
PIP T2 Cooperative Play	Baseline	33.74	33.22	59.45	28.18
	Posttest	31.51	33.83	34.54[a]	34.85
PIP T4 Cooperative Play	Baseline	33.62	33.24	41.47	27.06
	Posttest	34.29	32.05	56.87[a]	29.35

See Corbett *et al.* (50) for further details regarding the treatment and its outcomes.

ABAS, Adaptive Behavior Assessment System; MF-D, Memory for Faces—delayed; MF-I, Memory for Faces—immediate; PIP, Peer Interaction Paradigm; SCQ, Social Communication Questionnaire; SRS, Social Responsiveness Scale.

[a]Posttest values that are significantly different from baseline in each group.

[b]T2/T4, Peer Interaction Paradigm periods with elicited social interactions.

Table 3. Mean Amplitude and Peak Latency for the N170 in the Left and Right Hemisphere for All Stimulus Conditions at Baseline (Time 1) and Posttest (Time 2)

		N170 Amplitude						N170 Latency					
		WLC Group (n = 33)		EXP Group (n = 44)		Total (N = 77)		WLC Group (n = 33)		EXP Group (n = 44)		Total (N = 77)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline													
Face													
Single	Left	0.03	4.23	0.01	3.82	0.02	3.98	207.65	18.61	206.64	20.32	207.07	19.49
	Right	−0.39	3.16	−0.38	3.57	−0.39	3.37	208.45	23.54	201.01	23.61	204.20	23.72
Repeated	Left	0.24	3.92	0.86	4.36	0.60	4.16	211.22	17.19	206.74	25.89	208.66	22.55
	Right	0.05	3.39	−0.26	3.75	−0.13	3.58	211.58	24.79	202.78	27.64	206.55	26.65
House													
Single	Left	4.62	5.33	4.03	4.46	4.29	4.83	202.70	26.93	203.51	25.79	203.16	26.11
	Right	3.46	3.86	3.02	4.54	3.21	4.24	207.08	26.20	201.71	28.66	204.01	27.59
Repeated	Left	3.69	5.06	3.16	4.15	3.39	4.54	206.75	25.97	202.73	23.26	204.45	24.37
	Right	3.02	4.48	2.50	3.96	2.72	4.17	212.45	18.89	203.56	28.27	207.37	24.94
Posttest													
Face													
Single	Left	0.49	3.50	0.64	5.01	0.58	4.39	200.59	23.40	202.79	17.44	201.83	20.12
	Right	−0.70	2.64	−0.62	3.26	−0.65	2.99	201.30	21.56	196.81	22.73	198.76	22.20
Repeated	Left	−0.03	3.38	0.26	4.23	0.13	3.86	203.58	20.22	199.67	21.48	201.37	20.90
	Right	−0.36	3.39	−0.51	3.46	−0.44	3.41	202.58	25.48	195.92	22.90	198.81	24.12
House													
Single	Left	4.00	4.68	4.12	5.75	4.07	5.28	201.06	22.47	197.70	22.16	199.16	22.21
	Right	3.24	4.04	2.43	3.43	2.78	3.71	200.10	25.86	194.91	25.37	197.17	25.54
Repeated	Left	3.55	4.61	3.38	6.14	3.45	5.49	212.43	21.84	199.40	24.86	205.06	24.33
	Right	1.75	4.70	1.44	3.41	1.57	4.00	209.44	24.78	198.67	21.98	203.35	23.69

EXP, treatment; WLC, waitlist control.

observed for repeated and single presentations of faces and house, but only the latter remained statistically significant after correction for multiple comparisons (single houses [t_{75} = 3.224, p = .002, d = 0.37], repeated houses [t_{75} = 3.445, p = .001, d = 0.40]). Differences between the single and repeated presentations were present only for the house images, with the repeated stimuli eliciting more negative amplitudes both in the left (t_{75} = 3.695, $p < .001$, d = 0.42) and right (t_{75} = 3.470, p = .001, d = 0.40) hemisphere.

N170 Latency

The analyses identified main effects of time ($F_{1,74}$ = 7.186, p = .009, η_p^2 = .089) and memory ($F_{1,74}$ = 11.619, p = .001, η_p^2 = .136), as well as a memory × group interaction ($F_{1,74}$ = 7.194, p = .009, η_p^2 = .089). Follow-up paired t tests noted slightly faster N170 latencies at posttest (200 ms) compared with baseline (205 ms) (t_{75} = 2.735, p = .008, d = 0.31). Across the 2 time points, the latencies were slightly longer for the repeated than single presentations for all stimulus types (204 ms vs. 201 ms [t_{75} = 2.963, p = .004, d = 0.34]). This result was driven primarily by the WLC group (208 ms vs. 203 ms [t_{32} = 4.539, $p < .001$, d = 0.79]), while the EXP group did not show a significant difference (201 ms vs. 200 ms; p = .611). The between-groups 1-way analysis of variance indicated that the groups were not significantly different in the N170 latency for the single presentations (p = .357), while the N170 response to all repeated stimuli was delayed in the WLC group compared with the EXP group (p = .029).

Brain-Behavior Associations

Exploratory analyses of the brain–behavior associations at baseline and posttest revealed low-to-moderate concurrent and predictive correlations between the N170 amplitude and latency and behavioral metrics of age, autism severity, and intellectual and social functioning (Table 4). Similar strength of associations was also noted between the N170 characteristics and real-life social behaviors during naturalistic social interactions (Table 5). Of note, a large portion of the observed correlations involved nonsocial stimuli.

Test–Retest Reliability

Exploratory intraclass correlations examined test–retest reliability of the N170 metrics in the EXP and WLC groups as well as in the combined sample. The results suggested moderate-to-high reliability for the N170 amplitude in response to faces and houses, while the latency was moderately reliable for faces only (Table 6).

DISCUSSION

This study evaluated the N170 response as a potential biomarker of social deficits in ASD. We examined its sensitivity to individual differences in social functioning (measured using standardized and naturalistic tools), developmental stage (age), and treatment effects of an established social skills intervention in a large (N = 77) sample of youths with ASD.

Table 4. Concurrent and Predictive Brain–Behavior Associations in the Left and Right Hemisphere Between the Standardized Measures of Social Functioning and the N170 Amplitude and Latency at Baseline and Posttest

	Baseline								Posttest							
	Face				House				Face				House			
	Single		Repeated		Single		Repeated		Single		Repeated		Single		Repeated	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Amplitude																
Age	0.06	0.10	0.12	0.16	−0.22	−0.15	−0.12	−0.02	−0.05	0.21	0.19	0.17	−0.02	−0.14	−0.19	−0.01
ADOS communication	−0.25[a]	−0.23	−0.23	−0.21	−0.06	−0.11	−0.15	−0.12	−0.13	0	−0.14	−0.11	−0.11	−0.17	−0.02	0.06
ADOS social interaction	0.14	−0.06	−0.01	−0.08	0.18	0.21	0.16	0.15	−0.01	−0.06	−0.06	−0.09	0.01	−0.02	0.04	0.06
ADOS stereotyped behaviors	0.11	0.06	0.06	−0.05	0.15	−0.01	0.13	0.06	0.01	−0.02	−0.04	−0.07	−0.08	−0.06	−0.07	−0.17
ADOS total	−0.03	−0.14	−0.11	−0.19	−0.01	−0.01	−0.03	0.02	−0.04	−0.03	−0.15	−0.19	−0.07	−0.10	−0.01	−0.07
ADOS algorithm score	0.13	−0.02	−0.01	−0.12	0.23	0.19	0.13	0.18	0.09	0.02	0	0.03	0.08	0.15	0.11	0.17
WASI composite IQ	0.11	0.15	0.05	0.07	0.19	0.19	0.23[a]	0.03	0.07	−0.07	−0.03	−0.02	0.30[b]	0.15	0.27[a]	0.11
WASI verbal IQ	0.04	0.11	0.03	0.08	0.11	0.15	0.12	−0.06	0.13	0.01	0.03	0.07	0.29[a]	0.17	0.26[a]	0.10
WASI performance IQ	0.18	0.22	0.07	0.10	0.24[a]	0.24[a]	0.31[b]	0.17	0.02	−0.09	−0.03	−0.09	0.25[a]	0.12	0.25[a]	0.14
NEPSY MF-I (baseline)	−0.08	0.10	−0.17	0.06	−0.07	0.11	−0.04	0.01	−0.18	−0.08	−0.06	0.13	−0.06	0.12	−0.04	0.22
NEPSY MF-I (posttest)	−0.08	0.10	−0.01	0.16	−0.15	0.15	−0.11	−0.03	−0.06	0	−0.09	0.11	0.04	0.25[a]	0.09	0.26[a]
NEPSY MF-D (baseline)	−0.10	0.03	−0.14	−0.06	−0.02	0.01	−0.10	−0.08	−0.12	−0.14	−0.10	−0.02	−0.07	0.10	−0.10	0.15
NEPSY MF-D (posttest)	−0.11	−0.03	−0.04	0.04	−0.13	0.02	−0.12	−0.12	−0.06	−0.04	−0.11	0.04	−0.01	0.09	0.03	0.20
SCQ total (baseline)	0.07	0.02	0.02	0.05	0.10	−0.01	0.29[a]	0.17	0.07	0.09	−0.01	0.01	−0.03	0.02	−0.03	−0.07
SCQ total (posttest)	0.16	−0.01	0.06	0.01	0.21	0.07	0.29[a]	0.32[b]	0.15	0.07	0.07	0.01	0.10	0.11	0.10	0.07
ABAS social (baseline)	−0.20	−0.03	−0.19	−0.01	−0.04	−0.05	−0.12	−0.03	−0.11	0.03	−0.04	−0.01	0.07	0.13	−0.02	0.09
ABAS social (posttest)	0.01	0.13	0.03	0.07	0.01	0.02	−0.10	−0.07	−0.07	−0.05	0.02	0.06	0.05	0.03	−0.04	0.07
SRS total (baseline)	0.10	−0.11	0.12	−0.01	0.17	0.14	0.23[a]	0.15	0.10	0.07	0.05	0.05	−0.05	0.07	0.03	0
SRS total (posttest)	0.15	−0.09	0.15	0.07	0.19	0.16	0.29[a]	0.34[b]	0.26[a]	0.15	0.23[a]	−0.05	0.12	0.09	0.21	0.03
Latency																
Age	−0.13	−0.13	−0.15	−0.32[b]	−0.06	−0.13	−0.09	−0.18	−0.20	−0.34[b]	−0.29[a]	−0.39[b]	−0.13	−0.14	−0.18	−0.25[a]
ADOS communication	0.11	0.10	−0.04	−0.02	0.25[a]	0.28[a]	0.28[a]	0.25[a]	0.08	0.26[a]	0.20	0.17	0.22	0.23	0.17	0.19
ADOS social interaction	0.21	0.04	0.19	0.09	0.19	0.05	0.21	0.13	0.28[a]	0.19	0.32[b]	0.28[a]	0.30[a]	0.29[a]	0.13	0.21
ADOS stereotyped behaviors	0.10	−0.02	0.12	0.13	0.21	0.18	0.21	0.14	0.20	0.02	0.36[b]	0.20	0.22	0.22	0.21	0.13
ADOS total	0.24[a]	0.14	0.14	0.16	0.24[a]	0.25[a]	0.30[a]	0.29[a]	0.24[a]	0.24[a]	0.34[b]	0.33[b]	0.29[a]	0.33[b]	0.19	0.25[a]
ADOS algorithm score	0.23	0.15	0.13	0.15	0.19	0.14	0.14	0.07	0.11	0.21	0.26[a]	0.14	0.24	0.25[a]	0.12	0.24
WASI composite IQ	−0.07	−0.03	−0.06	−0.06	−0.34[b]	−0.27[a]	−0.46[b]	−0.17	−0.03	−0.01	−0.05	−0.06	−0.20	−0.22	−0.24[a]	−0.21
WASI verbal IQ	−0.01	0.05	0.04	0.05	−0.27	−0.20	−0.36[b]	−0.15	−0.04	0.03	−0.06	0.01	−0.19	−0.19	−0.22	−0.11
WASI performance IQ	−0.07	−0.08	−0.16	−0.12	−0.39[b]	−0.33[b]	−0.50[b]	−0.17	−0.05	−0.03	−0.04	−0.10	−0.16	−0.22	−0.25[a]	−0.27[a]
NEPSY MF-I (baseline)	−0.26[a]	−0.16	−0.10	−0.08	−0.24[a]	−0.24[a]	−0.10	−0.08	−0.05	0.03	−0.09	−0.03	−0.09	−0.13	−0.14	−0.17
NEPSY MF-I (posttest)	−0.21	−0.15	−0.01	−0.16	−0.30[b]	−0.32[b]	−0.20	−0.15	−0.03	0.02	−0.08	−0.05	−0.08	−0.08	−0.05	−0.14
NEPSY MF-D (baseline)	−0.11	−0.06	0.04	−0.07	−0.11	−0.10	−0.24[a]	−0.02	−0.12	0.01	−0.01	−0.02	0.07	−0.06	0.08	−0.09
NEPSY MF-D (posttest)	−0.13	−0.06	0.08	−0.14	−0.22	−0.13	−0.18	−0.04	−0.05	0.01	−0.02	−0.06	−0.02	0.01	0.10	−0.14
SCQ total (baseline)	−0.09	−0.17	−0.15	−0.12	−0.07	−0.04	−0.11	−0.11	−0.01	−0.22	0.05	−0.17	−0.05	−0.05	−0.11	−0.07
SCQ total (posttest)	−0.02	−0.04	−0.11	0.03	−0.08	0.03	−0.05	−0.18	0.05	−0.11	0	−0.14	−0.07	−0.06	−0.12	−0.02
ABAS social (baseline)	−0.07	0.10	−0.16	0	−0.04	−0.02	−0.18	−0.03	0.07	0.23[a]	−0.04	0.15	−0.16	−0.11	0.17	0.10

Table 4. Continued

	Baseline								Posttest							
	Face				House				Face				House			
	Single		Repeated		Single		Repeated		Single		Repeated		Single		Repeated	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
ABAS social (posttest)	−0.07	0.06	−0.06	−0.09	−0.22	−0.26[a]	−0.20	−0.14	−0.02	0.15	−0.12	0.10	−0.14	0.04	0.01	−0.09
SRS total (baseline)	−0.14	−0.02	−0.11	−0.04	0.09	−0.06	−0.11	−0.03	−0.22	−0.14	−0.10	−0.09	−0.16	0.03	−0.13	0.04
SRS total (posttest)	−0.02	0.06	−0.10	0.02	0.09	−0.03	0.02	−0.09	−0.07	−0.07	−0.12	−0.09	−0.09	0.15	−0.24[a]	0.12

ABAS, Adaptive Behavior Assessment System; ADOS, Autism Diagnostic Observation Schedule; MF-D, Memory for Faces—delayed; MF-I, Memory for Faces—immediate; SCQ, Social Communication Questionnaire; SRS, Social Responsiveness Scale; WASI, Wechsler Abbreviated Scale of Intelligence.

[a] $p < .05$.

[b] $p < .01$.

Participants were diagnosed using the gold-standard tools and represented a wide range of ages (7–16 years), intellectual ability (IQ: 70–141), and Autism Diagnostic Observation Schedule scores (total: 6–25). We also assessed test–retest stability of the N170 amplitude and latency across 2 visits conducted approximately 3 months apart.

N170 to Faces Versus Nonsocial Stimuli

Our results replicated prior findings of larger N170 amplitudes to faces than houses in both repeated and single stimulus presentation conditions, consistent with the interpretation of the N170 amplitude as a face-sensitive response in typical populations (11) and in persons with ASD (45,46). We also observed the expected hemisphere differences, with larger N170 amplitudes in response to faces over the right occipitotemporal region than over the left occipitotemporal region (11,46,47). Test–retest stability analysis of the N170 amplitude replicated prior evidence (48) of its good reliability for both faces and houses, suggesting that it is a robust perceptual response that can be obtained in typical and atypical populations across ages, ability levels, testing settings, and equipment types.

Within-session repetition-related amplitude enhancement was detected for the houses only, replicating our previous findings (29) and possibly reflecting increased perceptual experience owing to repeated exposures to the same image (49). The lack of a comparable enhancement for the repeated faces suggests that face perception in ASD may be less modifiable by short-term exposure, with the N170 amplitude reflecting a stable trait characteristic. It is also possible that face perception mechanisms in participants with ASD were consistently engaged regardless of face familiarity [see also Webb *et al.* (46)]. This interpretation is further supported by the lack of significant differences in the N170 amplitude between the baseline and posttest assessments for any of the stimulus conditions or hemisphere sites. The meta-analysis findings (14) of absent group differences in the N170 amplitude to faces between participants with ASD and typical peers further support the interpretation that it may not be the optimal measure of social perception deficits in ASD.

The N170 latency did not appear to differentiate between social and nonsocial stimuli in children with ASD at either of the 2 time points [see McPartland *et al.* (18) for similar findings]. It did show slight acceleration (5 ms) from baseline to posttest for all stimuli, but the effect size was small, raising concerns about its clinical significance. Within-session stimulus repetition was associated with slight delays in the N170 latency compared with the stimuli presented once, but this finding was not specific to faces. Test–retest reliability of the N170 latency was moderate. Our results are consistent with the comments by Vettori *et al.* (15) that the N170 latency may be less face-specific than its amplitude.

Sensitivity to Heterogeneity in Social Functioning

After replicating the established N170 response characteristics in our passive viewing paradigm, we examined sensitivity of the N170 to individual differences in social functioning. The extensive battery of standardized behavioral measures included gold-standard assessments of autism

Table 5. Concurrent and Predictive Associations in the Left and Right Hemisphere Between the N170 Amplitude/Latency and Real-Life Social Behaviors During Elicited Social Interaction Periods (T2/T4) of the Peer Interaction Protocol at Baseline and Posttest

	Baseline								Posttest							
	Face				House				Face				House			
	Single		Repeated		Single		Repeated		Single		Repeated		Single		Repeated	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
Amplitude																
T2 PRE verbal bout	0.019	0.124	0.033	0.107	0.131	0.133	−0.004	−0.010	0.068	0.003	0.028	0.050	0.148	0.167	0.120	0.074
T4 PRE verbal bout	0.024	0.112	0.110	0.056	0.084	0.146	0.068	0.117	0.022	0.076	−0.022	0.139	0.143	0.256[a]	0.128	0.031
T2 PRE cooperative play	−0.235[a]	−0.090	−0.153	0.044	−0.215	−0.068	−0.209	−0.185	−0.180	0.004	−0.059	−0.050	−0.157	−0.192	−0.131	−0.119
T4 PRE cooperative play	−0.159	−0.102	−0.037	−0.067	−0.243[a]	−0.130	−0.254[a]	−0.120	−0.242[a]	0	−0.164	0.061	−0.215	−0.047	−0.231[a]	−0.070
T2 POST verbal bout	−0.024	0.074	0.075	0.071	−0.047	0.051	−0.035	0.054	0.073	0.122	0.091	0.036	0.098	0.125	0.135	0.030
T4 POST verbal bout	−0.030	0.081	0.034	−0.020	−0.005	0.035	0.052	0.036	0.036	0.002	0.024	0.007	0.118	0.028	0.152	−0.007
T2 POST cooperative play	−0.227[a]	−0.142	−0.239[a]	−0.145	−0.123	−0.148	−0.039	−0.218	−0.068	−0.232[a]	−0.061	−0.212	−0.021	−0.246[a]	−0.048	−0.071
T4 POST cooperative play	−0.038	0.146	0.121	0.133	−0.116	−0.093	−0.128	−0.144	−0.027	0.171	0.019	0.108	0.029	0.045	−0.001	0.042
Latency																
T2 PRE verbal bout	−0.058	0.044	−0.041	−0.036	0.150	−0.003	0.003	−0.113	−0.123	0.024	−0.034	0.003	−0.153	−0.048	−0.123	0.065
T4 PRE verbal bout	−0.106	0.107	0.026	−0.016	−0.052	−0.05	−0.303[b]	−0.029	−0.093	0.044	−0.080	0.002	−0.175	0.005	−0.056	0.003
T2 PRE cooperative play	−0.338[b]	−0.167	−0.198	−0.208	0.040	0.002	0.018	−0.123	0.087	−0.187	0.064	−0.067	−0.130	−0.170	−0.144	−0.166
T4 PRE cooperative play	0.037	0	0.063	−0.138	0.239[a]	0.154	0.088	0.057	−0.082	−0.120	−0.053	−0.095	0.018	−0.032	−0.001	0.032
T2 POST verbal bout	−0.211	−0.161	−0.194	−0.343[b]	−0.227[a]	−0.213	−0.179	−0.229[a]	−0.311[b]	−0.281[a]	−0.413[b]	−0.271[a]	−0.201	−0.059	−0.320[b]	−0.221
T4 POST verbal bout	−0.246[a]	−0.187	−0.208	−0.221	−0.183	−0.091	−0.180	−0.036	−0.191	−0.076	−0.363[b]	−0.232[a]	−0.188	−0.078	−0.254[a]	−0.107
T2 POST cooperative play	−0.081	−0.028	0.02	0.067	−0.058	0.184	0.014	0.084	0.048	0.015	0.007	−0.062	0.103	−0.220	−0.046	−0.114
T4 POST cooperative play	−0.106	−0.143	−0.182	−0.297[b]	0.019	−0.014	−0.015	−0.126	−0.278[a]	−0.276[a]	−0.158	−0.274[a]	−0.112	−0.273[a]	−0.066	−0.268[a]

PRE, baseline; POST, posttest.
[a]$p < .05$.
[b]$p < .01$.

Table 6. Intraclass Correlations Indexing Test–Retest Reliability Between Baseline and Posttest Values for the N170 Amplitude and Latency in the Treatment (EXP) Group, Waitlist Control (WLC) Group, and Combined Sample

	EXP Group		WLC Group		Combined Sample	
	Left	Right	Left	Right	Left	Right
Amplitude						
Face single	0.72 (0.49 to 0.85)	0.73 (0.50 to 0.85)	0.73 (0.45 to 0.87)	0.53 (0.05 to 0.77)	0.72 (0.56 to 0.83)	0.66 (0.47 to 0.79)
Face repeated	0.58 (0.23 to 0.77)	0.81 (0.64 to 0.89)	0.70 (0.40 to 0.85)	0.57 (0.13 to 0.79)	0.63 (0.41 to 0.76)	0.72 (0.56 to 0.82)
House single	0.76 (0.55 to 0.87)	0.78 (0.59 to 0.88)	0.71 (0.40 to 0.85)	0.53 (0.05 to 0.77)	0.74 (0.58 to 0.83)	0.68 (0.50 to 0.80)
House repeated	0.64 (0.33 to 0.80)	0.58 (0.22 to 0.77)	0.79 (0.57 to 0.89)	0.36 (−0.29 to 0.69)[a]	0.70 (0.53 to 0.80)	0.47 (0.16 to 0.66)
Latency						
Face single	0.24 (−0.40 to 0.59)[a]	0.52 (0.11 to 0.74)	0.54 (0.08 to 0.77)	0.58 (0.14 to 0.79)	0.40 (0.05 to 0.62)	0.55 (0.30 to 0.72)
Face repeated	0.17 (−0.53 to 0.55)[a]	0.49 (0.07 to 0.73)	0.64 (0.27 to 0.82)	0.59 (0.16 to 0.80)	0.36 (−0.01 to 0.60)[a]	0.55 (0.29 to 0.72)
House single	0.50 (0.08 to 0.73)	0.59 (0.24 to 0.78)	0.37 (−0.27 to 0.69)[a]	0.13 (−0.77 to 0.57)[a]	0.44 (0.12 to 0.65)	0.44 (0.11 to 0.64)
House repeated	0.48 (0.03 to 0.72)	0.48 (0.03 to 0.72)	0.28 (−0.45 to 0.65)[a]	0.40 (−0.21 to 0.71)[a]	0.42 (0.08 to 0.63)	0.49 (0.19 to 0.67)

Values in parentheses are 95% confidence interval.
[a]Nonsignificant value.

symptomatology, direct testing of social information processing (face memory), and caregiver reports of social skills and adaptive functioning. Real-life social behavior was systematically characterized using the naturalistic Peer Interaction Paradigm (35).

The exploratory correlational analysis involving the N170 amplitude for repeated and single presentations of faces and houses revealed sporadic and mostly weak ($r < .4$) brain–behavior associations at baseline and posttest. Applying statistical correction for multiple significance testing to these results would have further reduced the number of detected associations. The N170 amplitude was not significantly associated with age at baseline, while at posttest, a small partial correlation was observed after controlling for the EXP group membership, with increasing age being associated with smaller N170 responses to faces and larger responses to houses. The most consistent pattern of significant effects across the 2 testing times was between the smaller N170 amplitude to houses and higher IQ scores, particularly the performance IQ. Of particular note, few correlations were observed between the N170 amplitude and standardized measures of social cognition (NEPSY Memory for Faces subtest) or daily social functioning (SRS, Social Communication Questionnaire) at baseline: smaller N170 responses to houses were associated with higher scores on all of these measures. The same correlations were not present at posttest, in which only reduced N170 amplitude to faces was related to higher SRS scores.

Compared with the amplitude measures, the N170 latency appeared to be more sensitive to individual differences in social functioning at baseline. Yet, similar to patterns observed for the amplitude, most of the significant correlations were with the N170 latency to the nonsocial stimuli. Delayed N170 response to houses was related to higher Autism Diagnostic Observation Schedule scores, while faster latencies were associated with higher IQ scores and better NEPSY Memory for Faces subtest scores. Similar to the amplitudes, most of these associations were not observed at posttest.

Correlations between the N170 amplitude and real-life social interactions revealed largely the same pattern of a few weak associations that were not consistently present across baseline and posttest. Correlations with the N170 latency reached significance mainly at posttest, when faster responses to faces and houses were associated with longer periods of verbal interaction and cooperative play.

In combination, these results suggest that the N170 amplitude and latency in ASD may be weakly associated with distinct aspects of social and adaptive functioning: the amplitudes reflected more general nonverbal intelligence, while the latencies showed associations with autism symptomatology, memory for faces, and real-life social behavior. Importantly, for both measures, the observed correlations were not specific to faces—the greatest number of brain–behavior associations were with the nonsocial stimuli. Furthermore, the correlations were small and generally not repeatable across 2 time points. Thus, while the N170 characteristics appear to be sensitive to some aspects of individual differences in social functioning, the reliability of such connections may be low.

Sensitivity to Treatment Effects

In the context of a social skills training program with known efficacy (37–39), analyses revealed no clear evidence of sensitivity to treatment effects (no time × group interactions) for the N170 amplitude or latency. Yet, there were significant increases in behavioral performance on the NEPSY Memory for Faces subtest (immediate and delayed) in both groups, and the EXP group also showed improvements on the SRS, Social Communication Questionnaire, and Adaptive Behavior Assessment System. Previously, Faja *et al.* (25) reported a similar lack of the N170 sensitivity to treatment effects following a perceptual expertise training that resulted in behavioral improvements in adults with ASD. Thus, the N170 metrics may not be sensitive to changes in social functioning, and instead reflect a stable perceptual trait in ASD.

This observation extends support for the idea that purely perceptual deficits may not fully explain social difficulties in ASD (7,8). We previously identified a parietal "old/new" response elicited within 250 to 500 ms after stimulus onset that indexed spontaneous recognition of stimulus repetition (29). That response was specific to faces (no effect for houses),

greater in typical children than those with ASD, and correlated with the aforementioned behavioral measures of social functioning. It was also sensitive to treatment effects [i.e., increased in the EXP group, unchanged in the WLC group (39)], including in the current sample (50). Consideration of the electroencephalography/ERP metrics indexing face recognition [see also Vettori *et al.* (51)] as potential biomarkers of social information processing in ASD would fit with the social motivation theory of ASD (20,52). Social salience can be indexed by incidental memory for faces, a cognitive ability dependent on sufficient engagement with the stimuli and allocation of adequate cognitive processing resources (i.e., beyond initial sensory-perceptual processes associated with stimulus detection).

Conclusions

This study aimed to examine whether the N170 response could serve as a stratification or treatment effects biomarker of social functioning in ASD. Many ERP responses have known neural sources and well-established functional interpretations: in case of the N170, it reflects activity of the fusiform gyrus associated with expert visual processing and is typically larger for faces than for other stimuli. In the current study, the N170 response was successfully recorded using a passive viewing task in youths with ASD and varied intellectual and adaptive functioning. We replicated the larger N170 amplitude to faces than nonsocial stimuli and observed moderate test–retest stability across 2 time points.

However, the N170 amplitude and latency showed limited sensitivity to individual differences in social functioning in youths with ASD. The observed correlations were small, not consistently repeatable across the 2 time points, and often involved the N170 response to houses rather than to faces. Therefore, the N170 response does not fit the definition of a social deficit biomarker in ASD that could be used for sample characterization or stratification. Of note, our exploratory correlational analyses included a variety of behavioral assessments commonly used in ASD research and deliberately minimized type II error. Our sample ($N = 77$) was at least twice the size of those in the previous studies that reported significant correlations between N170 latency and face processing in ASD [e.g., $n = 15$ in McPartland *et al.* (13); 36 in McPartland *et al.* (18); 34 in Lerner *et al.* (19)] and therefore provided sufficient power to detect even small correlations. Thus, the lack of strong and consistent brain–behavior associations for the N170 response is not likely to be explained by low statistical power. Replication of the canonical N170 characteristics (larger amplitude for faces than for houses, particularly in the right hemisphere) also rules out the possibility that our passive viewing paradigm or the selected electrode clusters were not optimal for eliciting the N170 response.

Our data also did not support the use of the N170 as a biomarker of treatment effects. Neither amplitude nor latency measures were sensitive to change following a social skills intervention that resulted in improved behavioral performance on standardized measures and in real-life social interactions. It is possible that the N170 response reflects a basic social perceptual process that may not be malleable by a treatment targeting social behaviors rather than basic face detection.

In sum, our results do not support the notion that the N170 latency is a biomarker of social deficits in ASD. It may be a frequently used and psychometrically stable measure of one domain of functioning, basic perceptual face processing, but it is not sufficiently informative about heterogeneity of social functioning and other characteristics of autism. Therefore, the search for a "brain signature" of ASD or social difficulties in general must continue and expand to include other measures to move the field forward.

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ClinicalTrials.gov: SENSE Theatre Intervention for Children With Autism Spectrum Disorder (ASD); https://clinicaltrials.gov/ct2/show/NCT02276534; NCT02276534.

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