Current Biology

A Mechanistic Link between Olfaction and Autism Spectrum Disorder

Highlights

- Olfactory sniffing offers a language and task-free measure of autism and its severity

- Aberrant sniffing implicates sensory-motor loops at the mechanistic heart of autism

- Aberrant sniffing links sensory-motor impairments with social impairments in autism

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In Brief

Sniffs are automatically modulated—vigorous sniffs for pleasant and truncated sniffs for unpleasant odors. Rozenkrantz et al. find that children with autism do not modulate sniffs, consequently taking vigorous sniffs of odors such as rotten fish. This language and task-free marker puts sensory-motor coordination at the mechanistic heart of autism.

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A Mechanistic Link
between Olfaction and Autism Spectrum Disorder

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SUMMARY

Internal action models (IAMs) are brain templates for sensory-motor coordination underlying diverse behaviors [1]. An emerging theory suggests that impaired IAMs are a common theme in autism spectrum disorder (ASD) [2–4]. However, whether impaired IAMs occur across sensory systems and how they relate to the major phenotype of ASD, namely impaired social communication [5], remains unclear. Olfaction relies on an IAM known as the sniff response, where sniff magnitude is automatically modulated to account for odor valence [6–12]. To test the failed IAM theory in olfaction, we precisely measured the non-verbal non-task-dependent sniff response concurrent with pleasant and unpleasant odors in 36 children—18 with ASD and 18 matched typically developing (TD) controls. We found that whereas TD children generated a typical adult-like sniff response within 305 ms of odor onset, ASD children had a profoundly altered sniff response, sniffing equally regardless of odor valance. This difference persisted despite equal reported odor perception and allowed for 81% correct ASD classification based on the sniff response alone (binomial, $p < 0.001$). Moreover, increasingly aberrant sniffing was associated with increasingly severe ASD ($r = -0.75$, $p < 0.001$), specifically with social ($r = -0.72$, $p < 0.001$), but not motor ($r < -0.38$, $p > 0.18$), impairment. These results uncover a novel ASD marker implying a mechanistic link between the underpinnings of olfaction and ASD and directly linking an impaired IAM with impaired social abilities.

RESULTS

Autism spectrum disorder (ASD) is associated with impaired sensory-motor coordination [13]. One type of brain mechanism subserving sensory-motor coordination is referred to as internal action models (IAMs). IAMs are brain templates that allow action initiation based on sensory expectations alone and ongoing refinement of motor output based on sensory input flow [1]. Hu-man olfaction is subserved by the sniff response where unpleasant and intense odors are sampled with low-magnitude sniffs, but pleasant and mild odors are sampled with high-magnitude sniffs [8–10]. Because the sniff response entails fine adjustment of a motor process (the sniff) in precise accordance with sensory input (the odor), it can be considered an IAM. Here, we set out to test the hypothesis that the sniff response will be altered in children with ASD. Notably, we do not hypothesize that children with ASD will be unable to sniff, but rather that they will generate an inappropriate sniff given a particular odor. In other words, we do not hypothesize a motor impairment per se, but rather impairment in IAM-dependent sensory-motor coordination.

To measure the sniff-response in children, we built a computer-controlled air-dilution olfactometer equipped with a custom-designed double-barreled pediatric nasal cannula that allowed us to simultaneously deliver odors and measure nasal airflow (Figure 1). We used this apparatus to precisely measure the sniff response following pleasant (rose or shampoo) and unpleasant (sour milk or rotten fish) odors in 18 children with ASD (17 boys, mean age = 7 ± 2.3) and 18 age- and gender-matched typically developing (TD) children (17 boys, mean age = 6.7 ± 2.1) as controls (Table 1). The 10-min procedure consisted of 20 trials (10 of each valence), each 1–2 s in duration, separated by a 30-s intertrial interval. During the paradigm, participants watched a cartoon.

The Sniff Response Was Profoundly Altered in ASD

To characterize the TD and ASD sniff responses, we extracted four sniff parameters: sniff volume, peak airflow rate, mean airflow rate, and duration. A multivariate repeated-measures ANOVA applied to all parameters revealed a significant interaction between odorant valence (pleasant versus unpleasant) and group (TD versus ASD) ($F_{1,34} = 4.47$, $p < 0.05$), reflecting larger sniffs for pleasant versus unpleasant odors in TD alone. This was evident in a point-by-point comparison of the sniff traces revealing that TD children altered their sniff to account for odorant properties within 305 ms of sniff onset (at 305 ms, flow pleasant = 0.918 ± 0.32 normalized flow units [nfu], flow unpleasant = 0.665 ± 0.22 nfu, $t_{17} = 3.68$, $p < 0.0019$, equivalent to $p < 0.05$ Bonferroni corrected for the multiple t tests) and maintained this or greater difference 680 ms into the sniff response (dotted line, Figure 2A). In contrast, ASD sniffs did not significantly differ by odor at any point along the sniff trace (Figure 2B).
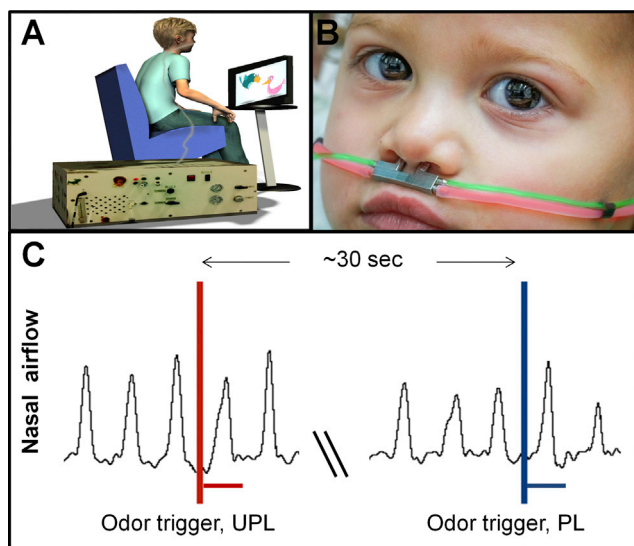
Figure 1. A Pediatric Olfactometer Delivered Odors and Measured Sniffs

(A) The subject was comfortably seated in front of a computer monitor viewing a cartoon, linked by nasal cannula to the olfactometer.

(B) A double-barreled nasal cannula delivering odorants (red) and measuring nasal airflow (green) (child is TD).

(C) A schematic of nasal airflow recording with odorant onsets denoted by vertical lines and odor duration by horizontal lines.

In addition, a three-way interaction between sniff parameters, odorant valence, and group ($F_{3,102} = 6.16$, p < 0.001) revealed the same effect materialized individually in three of the four parameters we extracted (e.g., volume = $F_{1,34} = 4.2$, p < 0.05; TD: normalized sniff volume: pleasant = 1.07 ± 0.3 normalized volume units [nvu], unpleasant = 0.79 ± 0.22 nvu, $t_{17} = 4.73$, p < 0.0005; ASD: pleasant = 0.95 ± 0.33 nvu, unpleasant = 0.99 ± 0.64 nvu, $t_{17} = 0.36$, p = 0.72; same effects for mean and peak airflow, both $F_{1,34} > 4.2$, both p < 0.05) (Figure 2C). No other significant main effects or interactions were found (all p > 0.11). In other words, consistent with our hypothesis, TD children exhibited an adult-like sniff response, but ASD children did not activate the olfactory IAM to adjust their sniff in accordance with odorant properties.

A key characteristic of this approach is that it does not depend on verbal comprehension. Nevertheless, we later used a child-friendly visual-analog scale (VAS) to obtain odorant pleasantness estimates from the participants. Whereas 17 of the 18 TD children provided such estimates directly after testing, only 3 of the 18 ASD subjects agreed to do the same. An additional nine of the ASD children agreed to provide these estimates when approached at a later date. In TD, the sniff response was a strong predictor of perceived explicitly reported pleasantness (r = 0.74, p < 0.001; Figure 2D, green). In turn, although there were no differences in reported pleasantness between TD and ASD (U = 81, p = 0.37), the sniff response was unrelated to perceived explicitly reported pleasantness in ASD (r = −0.31, p = 0.34; Figure 2D, orange). The VAS reports obtained from children, both TD and ASD, are not highly reliable in our view. Nevertheless, these reports implied that both TD

and ASD children perceived the pleasant and unpleasant odors as intended, but only the TD children modulated their sniff accordingly.

The Sniff Response Was Linked to Social, but Not Motor, Impairment in ASD

The above analyses revealed a pronounced group difference. We next tested whether the altered sniff response in ASD can differentiate ASD from TD children at a single-subject level. We used a multivariate normal density classifier applied to the sniff parameters and found that a classifier relying on the differences in pleasant versus unpleasant sniff duration combined with the sniff volume for unpleasant odors effectively distinguished TD from ASD children. Using a leave-one-out analysis, the classifier correctly identified 17 of 18 TD children as well as 12 of 18 ASD children, i.e., one false positive and six false negatives (81% accuracy, binomial p < 0.001) (Figure 3A). In contrast to a group difference alone, this power at the single-subject level implies that an altered sniff response is a genuine part of ASD.

Finally, to determine whether the sniff response informs on ASD beyond classification alone, we correlated the sniff response with independently obtained autism severity scores (Autism Diagnosis Observation Schedule [ADOS]) [14]. We found a strong correlation in several sniff-response parameters, most notably in sniff duration, reflecting that within the ASD group, more aberrant sniffing (longer sniff durations for unpleasant versus pleasant odors) was associated with an increase in autism severity (r = −0.75, p < 0.0005) (Figure 3B). Notably, this correlation between the sniff-dependent measure and ADOS scores is very similar to the ADOS test retest correlation [15].

To further investigate this link between autism severity and the sniff response, we looked at separate components of the non-olfactory tests we conducted. We found that the sniff response remained highly predictive of the social affect component of ADOS (r = −0.72, p < 0.001) (Figure 3C), but it was unrelated to the restricted and repetitive behavior component of ADOS (r = 0.18, p = 0.47). Notably, there was a trend toward a correlation between social affect component of ADOS and IQ (r = −0.42, p < 0.09) and, indeed, an ensuing trend toward a correlation between the sniff response and IQ (r = 0.55, p < 0.06). In other words, the sniff-response measure is reflective of the mechanism involved with the social impairment that is at the heart of ASD.

Finally, to determine whether the sniff response merely reflected a generalized motor impairment, we first compared it to the separately obtained motor score from the Vineland Adaptive Behavior Scale (VABS) [16] and found no relation at all (r = −0.12, p = 0.68) (Figure 3D). Altered sniffing was unrelated to the other VABS subscales as well (communication: r = 0.22, p = 0.39; daily living: r = −0.22, p = 0.39; social: r = 0.07, p = 0.78). Given that the VABS depends on parental reports rather than direct testing, and its social score was unrelated to the ADOS social score in our study (r = −0.13, p = 0.61) and several previous studies [17, 18], we further assessed the relation to basic motor performance by conducting direct testing. We re-approached the children with ASD using a previously described [19] battery of simple motor tests including a finger tapping test (FTT), strength of grip (SOG), and a modified pegboard test (MPT). Like the VABS

Table 1. Non-olfactory Characteristics of the ASD and TD Groups

Subject	Gender	Age	IQ	VABS	ADOS Social	RRB	Severity	ADI Interaction	Communication	RRB	Subject	Gender	Age	SCQ
ASD 1	m	7.08	–	82	11	5	9	4	5	4	TD 1	m	7.50	1
ASD 2	m	6.33	71[a]	77	15	4	8	11	12	8	TD 2	m	5.58	2
ASD 3	m	4.17	–	68	10	3	6	17	12	2	TD 3	m	4.58	10
ASD 4	m	10.00	90[a]	78	13	3	9	20	15	9	TD 4	m	9.42	10
ASD 5	m	5.58	118[b]	97	11	3	8	23	12	7	TD 5	m	5.25	8
ASD 6	m	6.33	104[b]	85	6	3	6	6	3	2	TD 6	m	7.25	0
ASD 7	m	4.92	104[b]	78	7	4	6	19	20	12	TD 7	m	4.33	5
ASD 8	m	6.83	94[b]	71	7	6	6	12	9	3	TD 8	m	7.08	1
ASD 9	m	7.33	134[b]	83	7	3	6	7	3	2	TD 9	m	7.33	1
ASD 10	f	9.67	73[a]	75	19	0	10	23	14	2	TD 10	f	7.00	2
ASD 11	m	4.92	102[b]	89	11	4	8	11	9	5	TD 11	m	4.58	2
ASD 12	m	4.33	130[b]	74	2	4	3	18	19	10	TD 12	m	4.08	6
ASD 13	m	5.92	83[b]	76	15	3	10	21	19	12	TD 13	m	5.67	1
ASD 14	m	11.58	40[a]	63	9	4	8	15	12	4	TD 14	m	10.42	1
ASD 15	m	6.17	–	94	9	3	7	9	3	4	TD 15	m	6.50	0
ASD 16	m	9.33	–	69	12	6	8	11	20	8	TD 16	m	8.83	0
ASD 17	m	11.08	106[a]	88	5	3	5	4	9	4	TD 17	m	10.08	6
ASD 18	m	4.92	–	92	6	0	3	12	4	3	TD 18	m	4.08	0
Averages and SDs														
Average (%)	94	7.00	96.08	79.94	9.72	3.39	7.00	13.50	11.11	5.61		94	6.65	3.11
SD		2.33	25.57	9.52	4.17	1.58	2.06	6.26	5.98	3.45			2.05	3.46

ASD measures are from the diagnostic procedure at the Autism Center, which typically includes the following: full-scale IQ using the Wechsler Scales of Intelligence (WISC-IV) [47] or Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III) [48] (four of the five missing IQ scores reflect large gaps across the IQ subscales that prevented derivation of a final score; note that the subscale data implied average IQ for these children); Vineland Adaptive Behavior Scales (VABS) [16]; Autism Diagnosis Observation Schedule (ADOS; a semi-structured, interactive schedule designed to assess social and communicative functioning [49]; to assess autism symptom severity, we used the standardized ADOS severity score [14]); and Autism Diagnostic Interview-Revised (ADI-R; a semi-structured interview administered to parents [50]). Values of severity range between 1 and 10, with a cutoff of 3 for inclusion in ASDs. All TD participants were screened for ASD using the Social Communication Questionnaire (SCQ) [46], a 40-item parent-report questionnaire for brief screening. A dash ("–") indicates that the test was not preformed or could not be evaluated.
[a]WISC-IV.
[b]WPPSI-III.

motor subscale, we found that performance on these tests was unrelated to the sniff response (FTT: r = −0.11, p = 0.71; SOG: r = −0.1, p = 0.72; MPT: r = −0.38, p = 0.18; Figure 3E). In other words, the degree of alteration in the ASD sniff response was unrelated to the level of basic motor performance.

DISCUSSION

These results imply an altered olfactory response that is evident in children with ASD and is more pronounced with increased autism severity. This implies that olfaction, which may serve in ASD intervention [20], may also provide for a novel early non-verbal non-task-dependent ASD marker. Previous studies of olfaction in ASD came to mixed results [21–30]. Moreover, even when altered olfaction was detected in ASD, whether it was present early in the ASD cascade or was the result of life with ASD was unknown. One possible reason for the differences across previous ASD olfaction studies and for the unknown developmental time course is the verbal and task-dependent nature of standard olfactory tests. These typically entail following verbal or written

time-locked instructions and providing verbal or written answers. This clearly prevents testing at pre-verbal ages and is further susceptible to ASD-related differences in comprehension, motivation, and general task-related parameters. The sniff response is largely devoid of these limitations, as it consists of a language-free task-free automatic odor-specific response. This allowed us to answer the above questions as follows: olfaction is genuinely altered in ASD, this alteration is evident early in the ASD cascade (childhood), and it is related to autism severity. Notably, the sniff response is similar across humans and rodents [31]. Given this, the language-free task-free nature of this paradigm also renders it a promising benchmark candidate for future testing of ASD animal models that can directly be compared to humans in this respect.

The implications of these findings include a potential novel early marker for ASD. That said, several limitations prevent current application of this marker. First, the current study was far in scope from a clinical trial. Second, an important open question of whether this marker is specific to ASD or common across various developmental disorders remains. Third, we did not
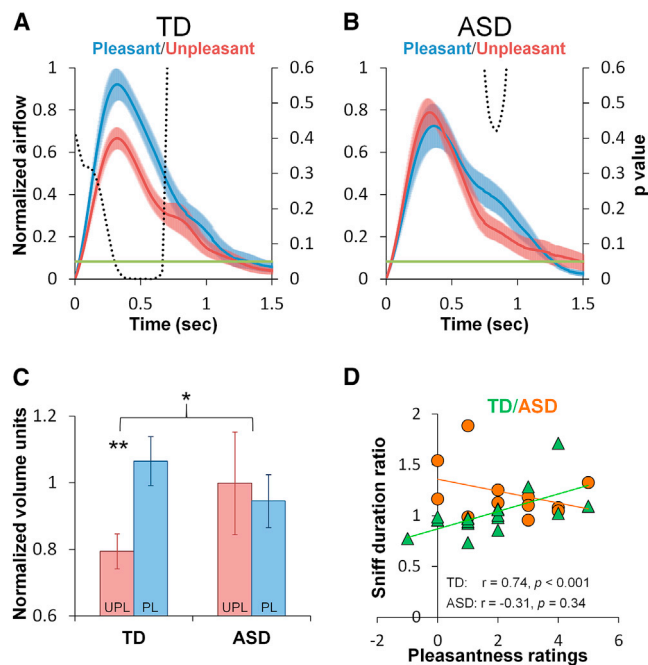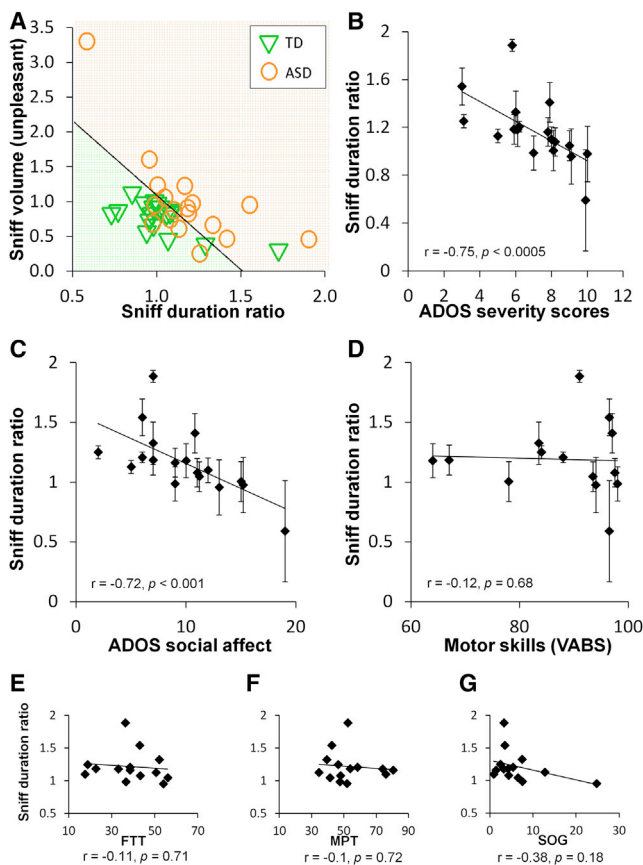
Figure 2. An Altered Sniff Response in ASD

(A and B) The averaged normalized sniff trace of TD (A) and ASD (B) children (n = 18) in response to pleasant (blue) versus unpleasant (red) odors. The black dotted line is the Bonferroni-corrected p value on the paired t test of airflow for pleasant versus unpleasant; green horizontal line marks the Bonferroni-corrected 0.05 significance level.

(C) The averaged normalized sniff volume in response to pleasant (blue) versus unpleasant (red) odors in ASD versus TD children. *p < 0.05, **p < 0.0005. Error bars represent SEM.

(D) Correlation of sniff duration ratio with pleasantness rating differences (pleasant minus unpleasant) in the TD group (green rectangles) and ASD group (orange circles). Odor pleasantness ratings are correlated with sniff duration ratio in TD, but not in ASD.

Figure 3. The Sniff Response Reflects Social Impairment in ASD

(A) The results of a leave-one-out classification scheme based on sniff-response parameters (ASD in orange, TD in green). The graph reveals one false positive classification and six false negatives.

(B) Correlation of sniff duration ratio with autism severity (ADOS) (overlapping ADOS values were jittered to prevent overlay). Each dot is a subject. Error bars represent SEM.

(C) Correlation of sniff duration ratio with the social affect component of the ADOS test (overlapping ADOS values were jittered to prevent overlay). Each dot is a subject. Error bars represent SEM.

(D) Correlation of sniff duration ratio with the motor skills score of the VABS test (overlapping VABS values were jittered to prevent overlay). Each dot is a subject. Error bars represent SEM.

(E–G) Correlation of sniff duration ratio with a battery of motor tests: finger tapping test (FTT), modified pegboard test (MPT), and strength of grip (SOG).

obtain full IQ scores for the TD cohort. Given the trend toward a correlation between IQ and sniff response in the ASD group, this link deserves further investigation. Finally, several technical issues (such as compliance) need to be addressed before this could become a useful tool in clinics. In turn, these findings also support an emerging theory regarding the mechanisms of ASD and potentially link this theory to the hallmark symptom of ASD. Specifically, the impaired-IAM theory of ASD has been linked to altered brain connectivity in ASD [2] (although the extent of altered connectivity in ASD remains unclear [32, 33]). Indeed, the sniff response likely depends on large-scale connectivity between ventral temporal olfactory cortex where odor valence is processed [34, 35] and cerebellar circuits where the sniff response is likely actuated [36, 37]. Coincidently, these ventral temporal and cerebellar substrates of olfaction are in fact neural substrates specifically implicated in ASD [38, 39]. Thus, the results obtained here are supportive of the notion that impaired IAMs are at the mechanistic root of ASD. Impaired IAMs subserving visual gaze and socially relevant eye fixation targets may partially underlie the social impairments in ASD [40], giving rise to an ASD-type theory of mind [41]. Here, we end in speculating that our results offer a novel additional possible link between impaired IAMs and the social impairment

of ASD. Specifically, increasing evidence implies that social chemosignaling is a meaningful component of human social interaction [42, 43]. Critically, olfaction and odor are used to gage [44] and influence [45] the emotions of others and thus play a meaningful role in social communication. We propose that the altered IAM that is the sniff response leads to altered olfaction, which contributes to impaired social communication. Consistent with this hypothesis, the degree of alteration in sniff response was predictive of impaired social communication (Figure 3C), but not of generalized motor impairment (Figures 3D–3G). In other words, we end in hypothesizing that the measure we have uncovered links a proposed mechanism of ASD (impaired IAMs) with the primary phenotype of ASD (impaired social communication).

EXPERIMENTAL PROCEDURES

Legal guardians (all were parents) of all participants signed informed consent to procedures approved by both the Assaf Harofe Medical Center and Israeli National Helsinki Committees.

Participants

Exclusion criteria for all children were organic smell disturbances or acute respiratory infection and for TD children a Social Communication Questionnaire (SCQ) score of above 11 [46]. To estimate the number of participants to enroll, we conducted a power analysis based on means and SDs in healthy adults (healthy controls in [37]). Given previous odorant-dependent changes in sniff volume from 60.65 to 55.54 ± 5 nvu, at power = 0.8 and alpha = p < 0.05, power analysis implied at least 17 participants in each group. We therefore studied 18 children with ASD (17 boys, mean age = 7 ± 2.3) (this gender bias reflected the underlying population at the Autism Center) and 18 TD controls (17 boys, mean age = 6.7 ± 2.1). The TD and ASD groups did not significantly differ in age (t_{34} = 0.51, p = 0.61), gender (Fisher's exact test p = 1.0), or parental education (t_{63} = 1.22, p = 0.23). Table 1 lists all non-olfactory measures obtained. Notably, only about one in four children approached at the Autism Center agreed to participate. This raises a selection bias concern whereby perhaps only a specific subset of ASD (those who agreed) was tested. To address this, we obtained all the non-olfactory measures (e.g., ADOS scores, IQ, VABS, etc.) from the children who were approached, but not tested, and compared these to the tested group. We found no differences between the two groups ($F_{9,70}$ = 1.59, p = 0.13).

Procedures

The child was comfortably seated in front of a computer monitor viewing a cartoon and fitted with a custom-designed double-barreled pediatric nasal cannula that both delivered odors from a computer-controlled air-dilution olfactometer and measured the nasal airflow of the sniff response (Figure 1). The 10-min procedure consisted of 20 trials (10 for each valence), each 1–2 s in duration, separated by a 30-s intertrial interval. We used two pairs of odorants, one mono-molecular (pleasant phenyl-ethyl alcohol [PEA], undiluted, CAS 60-12-8, Sigma-Aldrich and unpleasant butyric acid, diluted at 30% in odorless propane-1,2-diol, CAS 107-92-6, Sigma-Aldrich) and one of complex mixtures (pleasant herbal essence and unpleasant rotten fish, both from Senseale, Ramat Gan, Israel). Both pairs of odorants were presented at similar subjective intensity as rated by adult raters. The same result materialized for both odor pairs. To obtain explicit odor ratings, children sniffed the odors from jars and rated their pleasantness using a six-point VAS where each point was also denoted by a "smiley," ranging from a happy face associated with pleasant to a sad face associated with unpleasant. To assess general motor performance in ASD, we conducted three tasks: an FTT, SOG, and MPT [19]. The FTT consisted of using the index finger to tap on a board-mounted manual counter as many times as possible within 10 s. The task was repeated twice with each hand; the totals from all trials were averaged for both hands combined. If the two trials were not within ±5 points, a third trial was completed, and the average of three trials was used. The SOG was measured using a hand dynamometer (NeuLog, SES Scientific Educational Systems) that the subjects held in the palm of their hand and squeezed as tightly as possible. Strength (in kilograms) was recorded in three trials for each hand and averaged. The total SOG score was computed by combining the means of both hands. In the MPT, the participant was required to insert pegs in a grooved board in a specific directionality as quickly as possible using the dominant and non-dominant hand separately. The modification was in the number of pegs used (18 instead of 25) and type of pegs (two-colored wooden pegs). The score was the time required to place all 18 pegs into the holes (timing was not interrupted in the event of a dropped peg). The total MPT score was computed by combining the completion time in both hands.

Analysis

Nasal airflow was measured continuously. To account for variation across subjects stemming from such factors as cannula placement, we normalized each odorant sniff by dividing it by the average of three non-odorant nasal inhalations that preceded it. Data were then analyzed using MATLAB (MathWorks, version R2013a) and STATISTICA (StatSoft, version 7). Differences in sniff response between pleasant and unpleasant odors were first estimated by conducting a t test on every time point of the ongoing respiratory trace (dotted black line in Figure 2). We corrected for the number of t tests as follows: the sniff response in adults materialized within 160 ms [9], so we down-sampled the recording to just above the relevant nyquist range, namely 16.667 Hz. Given an average sniff of about 1.5 s, this translates to 25 comparisons per sniff (16.667 × 1.5). Thus, we Bonferroni corrected for 25 comparisons (green line in Figure 2). Next, differences in sniff response between pleasant and unpleasant odors and specific sniff parameters as a function of group (ASD/TD) were estimated using a multivariate repeated-measures ANOVA with conditions of sniff parameter (mean airflow, airflow peak, sniff duration, and sniff volume), odorant valence (pleasant or unpleasant), and group (ASD or TD). This was followed by repeated-measures ANOVAs and t tests for each sniff parameter alone. When classifying ASD and TD based on this data, each attempt to classify a subject is a Bernoulli trial with even odds of success and failure. Therefore, the probability of correctly classifying 29 out of 36 subjects is given by:

$$p = \left(\frac{1}{2}\right)^{36} \times \binom{36}{29} < 0.001$$

This is therefore the statistical power of our classification result. Finally, correlation between the sniff response and autism measures was assessed using the Spearman correlation coefficient.

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