Routledge
Taylor & Francis Group

Child Neuropsychology

A Journal on Normal and Abnormal Development in Childhood and Adolescence

ISSN: 0929-7049 (Print) 1744-4136 (Online) Journal homepage: http://www.tandfonline.com/loi/ncny20

Olfaction in autism spectrum disorders: A systematic review

Alessandro Tonacci, Lucia Billeci, Gennaro Tartarisco, Liliana Ruta, Filippo Muratori, Giovanni Pioggia & Sebastiano Gangemi

To cite this article: Alessandro Tonacci, Lucia Billeci, Gennaro Tartarisco, Liliana Ruta, Filippo Muratori, Giovanni Pioggia & Sebastiano Gangemi (2015): Olfaction in autism spectrum disorders: A systematic review, Child Neuropsychology, DOI: 10.1080/09297049.2015.1081678

To link to this article: http://dx.doi.org/10.1080/09297049.2015.1081678

Child Neuropsychology, 2015
http://dx.doi.org/10.1080/09297049.2015.1081678

Olfaction in autism spectrum disorders: A systematic review

Alessandro Tonacci[1], Lucia Billeci[1], Gennaro Tartarisco[2], Liliana Ruta[2,3], Filippo Muratori[3], Giovanni Pioggia[2], and Sebastiano Gangemi[4]

[1]National Research Council of Italy – Institute of Clinical Physiology, IFC-CNR, Pisa Unit, Pisa, Italy
[2]National Research Council of Italy – Institute of Clinical Physiology, IFC-CNR, Messina Unit, Messina, Italy
[3]Department of Developmental Neuroscience, Stella Maris Scientific Institute, Calambrone, Pisa, Italy
[4]Department of Clinical and Experimental Medicine, School and Division of Allergy and Clinical Immunology, University Hospital "G. Martino", Messina, Italy

Olfactory function is a well-known early biomarker for neurodegeneration and neural functioning in the adult population, being supported by a number of brain structures that could be dysfunctioning in neurodegenerative processes. Evidence has suggested that atypical sensory and, particularly, olfactory processing is present in several neurodevelopmental conditions, including autism spectrum disorders (ASDs). In this paper, we present data obtained by a systematic literature review, conducted according to PRISMA guidelines, regarding the possible association between olfaction and ASDs, and analyze them critically in order to evaluate the occurrence of olfactory impairment in ASDs, as well as the possible usefulness of olfactory evaluation in such conditions. The results obtained in this analysis suggested a possible involvement of olfactory impairment in ASDs, underlining the importance of olfactory evaluation in the clinical assessment of ASDs. This assessment could be potentially included as a complementary evaluation in the diagnostic protocol of the condition. Methods for study selection and inclusion criteria were specified in advance and documented in PROSPERO protocol #CRD42014013939.

Keywords: ASD; Autism; Autism spectrum disorders; Neurodevelopmental disorders; Olfaction; Smell.

Olfaction is one of the human senses, and until some decades ago it was probably considered the least important one, especially when compared to sight, hearing or touch.

We would like to thank Ms Alison Frank for manuscript revision. Alessandro Tonacci, Lucia Billeci, Giovanni Pioggia and Sebastiano Gangemi contributed equally to this work.

No potential conflict of interest was reported by the authors.

Address correspondence to Giovanni Pioggia, National Research Council of Italy – Institute of Clinical Physiology, IFC-CNR, Messina Unit, Via Consolare Valeria, SNC – 98125 Messina, Italy. E-mail: gpioggia@ifc.cnr.it

Recently, some research has focused on olfactory evaluation as a biomarker of neurodegeneration. Indeed, a clear correlation between loss of olfactory function (or decreased olfactory abilities in some cases) and neurodegenerative conditions, including Alzheimer's (AD) and Parkinson's disorder (PD), amyotrophic lateral sclerosis (ALS), Huntington's chorea (HC) and multiple system atrophy have been reported (Hawkes, 2003).

Other psychiatric disorders, such as schizophrenia, have been also associated with an olfactory dysfunction in some cases (Buschhüter et al., 2008; Moberg et al., 2014; Turetsky et al., 2000). Furthermore, it was recently suggested that olfactory loss could be a strong predictor for 5-year mortality in elderly people (Pinto, Wroblewski, Kern, Schumm, & McClintock, 2014). Olfactory impairment has been reported in child and adolescent psychiatric conditions such as autism spectrum disorders (ASDs; Rozenkrantz et al., 2015; Schecklmann et al., 2013), particularly related to olfactory identification tasks, whereas sensitivity tasks seem to be less affected, as later reported. ASDs are a heterogeneous group of neurodevelopmental conditions characterized by impairment in social interaction and communication and restricted, stereotyped interests and behaviors (American Psychiatric Association, 2013). Furthermore, atypical sensory processing is also part of the diagnostic criteria incorporated in the Diagnostic and Statistical Manual of Mental Disorders-5th version (DSM-5; American Psychiatric Association, 2013), having been identified in 69–100% of people with ASDs in several studies (Baranek, Boyd, Poe, David, & Watson, 2007; Leekam, Nieto, Libby, Wing, & Gould, 2007). These sensory problems contribute to the deficits in more complex social, cognitive, and behavioral symptoms common in ASDs (Boyd et al., 2010; Hilton et al., 2010; Watson et al., 2011).

Anatomically, dysfunction in medial temporal and orbitofrontal areas, often associated with ASDs, may result in olfactory deficits (Amaral, Schumann, & Nordahl, 2008; Suzuki, Critchley, Rowe, Howlin, & Murphy, 2003).

To the best of our knowledge, this is the first review specifically discussing olfactory function in ASDs. Schecklmann et al. (2013) have previously addressed the sense of smell in child and adolescent psychiatric disorders, including ASDs, but without a specific focus on ASDs. Since their review, research in the field has grown and new insights have been found, suggesting the need to address a new, more specific review on the association between olfaction and ASDs.

Cortical Bases of Olfaction

Sensory deficits have been associated with structural and functional abnormalities in the brain that can be characterized using a variety of neuroimaging techniques (Marco, Hinkley, Hill, & Nagarajan, 2011; Owen et al., 2013).

The study of human olfaction is more difficult compared to other sensory functions such as visual or auditory processing that activate larger cerebral areas. The challenge is mainly due to the position and shape of the cortical areas involved in olfactory processing, close to the bone structures and air-filled cavities, as well as because of artifacts induced by breathing.

However, functional neuroimaging techniques, and in particular functional magnetic resonance imaging (fMRI), have been applied to observe olfactory function in the human brain (Tabert et al., 2007; Toledano et al., 2012), and the brain regions involved in the olfactory processing have been directly identified. They include the primary olfactory cortex, entorhinal cortex, hippocampus and parahippocampal cortex, thalamus,

hypothalamus, orbitofrontal cortex, insular cortex, inferior lateral frontal region and the amygdala (Albrecht & Wiesmann, 2006; Toledano et al., 2012; Wang, Eslinger, Smith, & Yang, 2005). In particular, olfactory detection is mediated by lower-order neural pathways, while odor identification, which requires odor recognition and naming, relies on the correct functioning of several cortical areas, including the primary olfactory cortex (Martzke, Kopala, & Good, 1997).

Within the cerebral cortex, the portions directly receiving projections from the olfactory bulb form the olfactory cortex. This area receives inputs without any sort of thalamic relay. Anatomically, such a complex structure is located at the base of the frontal lobe and the medial aspect of the temporal lobe. From the olfactory cortex, the olfactory signal is conducted via the mediodorsal nucleus of the thalamus to the insular and orbitofrontal cortex. These two structures seem to have a basic importance in olfactory processing: the insular cortex is thought to integrate olfactory and taste signals to produce the sensation known as flavor, while the orbitofrontal cortex has a still unknown role in olfactory processing. Furthermore, within the nasal cavity are located free nerve endings of the trigeminal nerve able to respond to irritating substances, these latter rarely employed within specific tests for anosmia.

Areas of the limbic system—the limbic lobe, the hippocampal formation and fornix, the septal area, the amygdala (Majak, Ronkko, Kemppainen, & Pitkanen, 2004), the hypothalamus (Price, Slotnick, & Revial, 1991) and the anterior nuclei of the thalamus—are also involved in olfactory processing. A strong innervation by modulatory inputs from the horizontal limb of the diagonal band of Broca, the locus coeruleus and the raphe nucleus is also present (Shipley & Ennis, 1996), with the limbic and modulatory links permitting behavioral state, arousal, attention and hedonic valence to model cortical responses to odor. A simplified view of the olfactory cortex areas is displayed in Figure 1.

Olfactory Assessment

Olfactory function is usually assessed by administering a specific sensory questionnaire to parents (McIntosh, Miller, & Shyu, 1999) or by using modern psychophysical olfactory tests. In the latter case, a more precise characterization of olfactory sub-functions is possible. Olfactory detection is usually measured by the odor threshold test, which evaluates the lowest concentration of a stimulus (normally n-butanol, having a greater trigeminal component, or phenyl-ethyl-alcohol, with higher prevalence of pure olfactory components) that can be discerned (Deems & Doty, 1987).

Olfactory threshold, a task normally associated with the peripheral portion of the olfactory pathway (Guarneros, Ortiz-Romo, Alcaraz-Zubeldia, Drucker-Colín, & Hudson, 2013), can be measured by means of the T&T olfactometer (Toyota, Kitamura, & Takagi, 1978), the Threshold Test of the Sniffin' Sticks Extended Test (Hummel, Sekinger, Wolf, Pauli, & Kobal, 1997), and the Smell Threshold Test (STT; Doty, 2000).

The odor discrimination test evaluates the ability to differentiate between odorants, without requiring a formal identification of the corresponding stimulus, and asks the person to decide whether two or more stimuli are similar or different (Hummel et al., 1997). Several approaches are used for this category of testing: in one of them, the person has to indicate, on a given trial, whether two given stimuli are the same or different, while in another more frequently used test, the "triangle test" (Frijters, 1980), the person is asked to pick the "odd" stimulus from a set of odors where only the "odd" stimulus

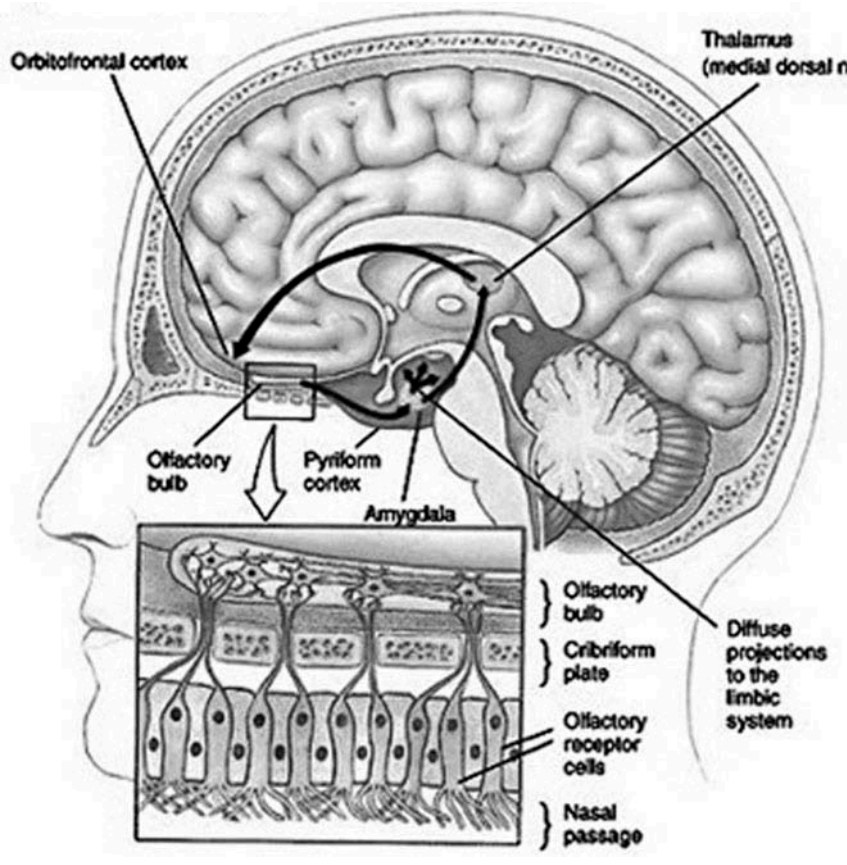

Figure 1 View of the areas defined as the "olfactory cortex".

differs. This is the approach employed, for example, in the Odor Discrimination Test part of the Sniffin' Sticks Extended Test above mentioned, in which 16 triplets of felt-tip pens are presented, each triplet containing two "pair" and one "odd" odor, that the patient should pick after the presentation of the three stimuli.

Odor identification tests are probably the most widely used procedures for the assessment of smell function and are considered the most advanced type of test drawing on higher-order cortical functions (Suzuki et al., 2003; Tanabe, Iino, & Takagi, 1975; Zatorre & Jones-Gotman, 1991). In particular, in multiple-choice identification tests, most commonly used due to their high reliability, the person is asked to identify a stimulus from a list of names or pictures.

The most well-known identification tests include the 40-odorant University of Pennsylvania Smell Identification Test (UPSIT; Doty, Shaman, & Dann, 1984) and the Sniffin' Sticks Identification Test (Kobal et al., 1996), even though several other tools are available, such as the 3-item Quick Smell Identification Test (Q-SIT; Jackman & Doty, 2005), the 12-item Brief Smell Identification Test (B-SIT; Doty, Marcus, & Lee, 1996), the Smell Diskettes Olfaction Test (Simmen, Briner, & Hess, 1999), and the T&T Olfactometer (Toyota et al., 1978).

Other common methods of odor assessment include discrimination and memory tests. To evaluate odor memory, the patient is required to smell an inspection odorant and to select the same odorant from a set of alternative odorants (Tourbier & Doty, 2007).

Several studies have used both sensory questionnaires and odor tests to assess olfactory function in ASDs. The purpose of the present work is to review the literature investigating olfactory function in ASDs with the aim of exploring whether olfactory testing can be used as part of the clinical assessment of the condition along with behavioral assessment and/or be used as a biomarker in a subgroup of people with ASDs.

METHODS

A systematic literature review, covering the period January 1, 2003 through March 15, 2015, was conducted in PubMed, ScienceDirect, MedLine, PsycARTICLES, LILACS and Google Scholar database, according to the PRISMA guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). Articles published before 2003 were not taken into account in order to comply with the most recent definitions of ASDs, thus excluding potential biases arising from past, non-actual guidelines in the clinical diagnosis of autism.

The search strategy was as follows: "olfaction or smell or olfactory function or odor perception AND autism or autism spectrum disorder or ASD". Methods for study selection and inclusion criteria were documented in PROSPERO protocol #CRD42014013939.

The search was limited to articles published in peer-reviewed journals. After having discarded multiple hits, the obtained results were sorted by relevance and the studies directly focusing on ASDs and olfactory function were selected. Case reports are not presented in the results section but, where appropriate, are cited in the discussion section. The results from the literature review are first presented and then the possible associations between olfactory function and ASDs in the light of the most recent findings are critically discussed.

RESULTS

The systematic review of existing literature, detailed in Figure 2, led to twenty-five articles directly focusing on autism and olfactory function (see Table 1).

The articles included in the review have been further classified depending on the type of sensory assessment. Among the twenty-five studies taken into account, thirteen employed olfactory assessment through psychophysiological testing (olfactory test). In particular, seven studies used an odor identification test (with five studies finding significant group differences between people with ASDs and controls), four studies employed an olfactory sensitivity test (with one study reporting a between-groups difference), three studies evaluated odor pleasantness (with two studies obtaining different trends in ASDs and healthy people), and finally one study used an odor discrimination test. Two out of thirteen articles failed to find any difference concerning olfactory function between the ASDs and control group. Overall, most of the thirteen articles cited used a mix of the methodologies mentioned above.

Furthermore, a sensory questionnaire was administered in ten studies (all of which found an overall sensory impairment, and eight of which reported a combined taste/smell impairment). Two studies reported genetic/epigenetic findings and, finally, autonomic responses to olfactory stimuli were evaluated in two studies. A more detailed description of the above-listed findings is presented in Table 2.

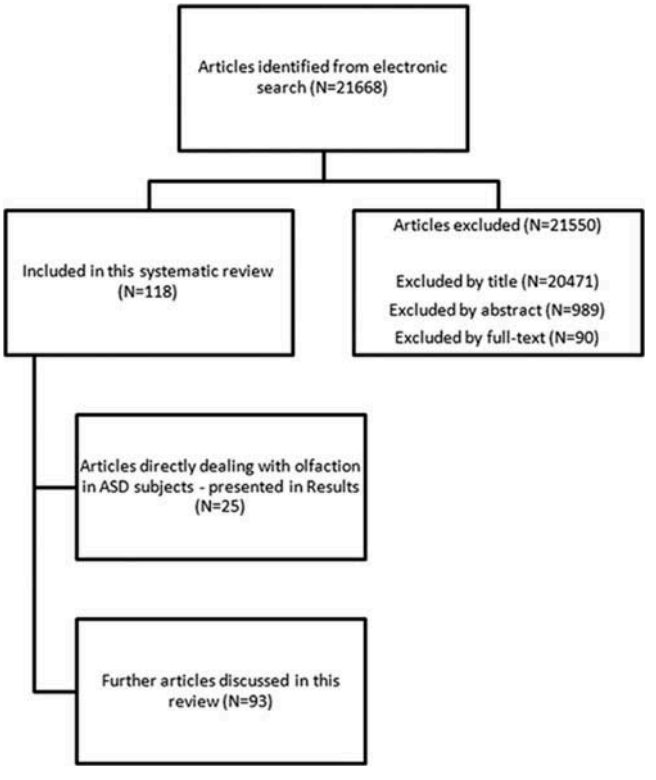

Figure 2 Study selection.

Studies Related to Olfactory Testing in ASDs

Olfactory testing is one of the most frequently used sensory assessment in studies related to ASDs. In most cases, an olfactory identification test has been employed. Odor identification impairment was found in 71.4% of the studies in people with Asperger syndrome (AS; Suzuki et al., 2003), high-functioning autism (HFA; Bennetto, Kuschner, & Hyman, 2007), pervasive developmental disorders (PDDs; De Assumpção & Adamo, 2007), and ASDs (Galle, Courchesne, Mottron, & Frasnelli, 2013). Other studies reported a difference in odor identification ability between children with HFA (or general ASDs) and with AS (Legiša, Messinger, Kermol, & Marlier, 2013; May et al., 2011), with children with HFA having a more severe impairment on this task. No difference in odor identification was found in two other studies (Brewer, Brereton, & Tonge, 2008; Dudova et al., 2011).

In four articles published, an odor threshold evaluation was performed (Ashwin et al., 2014; Dudova et al., 2011; Suzuki et al., 2003; Tavassoli & Baron-Cohen, 2012). In three studies, n-butanol—a compound stimulating not only the classical olfactory pathway but also the trigeminal system—was used as a reference odor, with a different method for test administration, based on the modified version of the two-bottle Cain test (Cain, Gent, Catalanotto, & Goodspeed, 1983). In the fourth study (Ashwin et al., 2014), isopropyl alcohol (70% vol) was employed. In another study (Galle et al., 2013), birhinal phenyethylalcohol sensitivity was also assessed by a three-alternative, forced-choice, staircase method (Ehrenstein & Ehrenstein, 1999).

Table 1 Studies dealing with olfactory evaluation in ASDs or ASD-like syndromes.

Study	*n* (case/control)	Age, IQ	Design	Findings
Suzuki et al. (2003) UK	24 (12 AS/12 TD)	Age 33 ± 8 vs 31 ± 5 y, FSIQ 107 ± 15 vs 112 ± 8	Cross-sectional study; 1-butanol olfactory sensitivity, UPSIT odor identification test	Impaired identification ability in people with AS, no difference in sensitivity
Rogers et al. (2003) USA	102 (26 ASD/20 fragile X syndrome/32 mixed DD/24 TD)	Age: Autism 33.67 ± 3.6 m, fragile X syndrome 36.11 ± 8.1 m, DD 33.23 ± 6.7 m, TD 19.50 ± 4.8 m. Mental age: Autism 20.74 ± 6.3 m, fragile X syndrome 20.14 ± 6.8 m, DD 23.13 ± 6.9 m, TD 23.38 ± 6.3 m	Cross-sectional study; Short Sensory Profile	Significant differences in taste/smell sensitivity. Children with ASDs and fragile X syndrome had more sensory symptoms than the two other groups
Leekam et al. (2007) UK	82 (33 ASDs/19 DD/15 language impairment/15 TD) 200 (200 ASDs)	Age 34–140 m; non-verbal IQ: LFA 49.38 ± 20.69, DD 45.89 ± 22.34, HFA 102.12 ± 20.17; language impairment: 90.21 ± 17.85, TD 108.60 ± 15.71 Age 32 m–38 y; LFA IQ < 70, HFA IQ > 70	Cross-sectional study; DISCO questionnaire Cross-sectional study; DISCO questionnaire	Higher frequency of sensory symptoms in children with autism; 90% of children with autism had sensory symptoms
Bennetto et al. (2007) USA	48 (21 HFA/27 TD)	Age 10–18 y	Cross-sectional study; taste identification and threshold, Sniffin' Sticks screening odor identification	Slight impairment in taste identification in children with ASDs; no impaired taste detection, deficit in olfactory identification

(*Continued*)

Table 1 (Continued).

Study	*n* (case/control)	Age, IQ	Design	Findings
De Assumpção and Adamo (2007) Brazil	42 (21 PDD/21 TD)	Age 11–18 y	12-odor smell identification test; testing at baseline with and without a "linguistic stimulus" concerning possible alternative odors helpful for identification response, and after a period of 25 days	Children with PDD had olfactory impairment at baseline with and without linguistic stimuli, and after 25 days
Brewer et al. (2008) Australia	30 (15 HFA/15 TD)	Age 5–9 y; IQ > 70	Olfactory identification test by a visual analog of UPSIT	No difference in olfactory identification between children with HFA and controls
Wiggins et al. (2009) USA	34 (17 ASDs/17 TD)	Age 17–45 m; mental age 15–45 m	SSP	Children with ASDs reported abnormal SSP profiles, especially in auditory filtering, tactile and taste/smell sensitivity
Lane et al. (2010) USA	54 (54 ASDs)	Age 33–115 m (mean 79.02 ± 19.22 m)	SSP	High prevalence of sensory abnormalities among children with ASDs
Hilton et al. (2010) USA	62 (36 ASDs/26 TD)	Age 6–10 y; IQ > 70	SP	Sensory impairment in all domains in children with ASDs
Lane et al. (2011) USA	30 (30 ASDs+PDD-NOS)	Age 41–113 m	SSP	Sensory impairment in several domains including taste/smell sensitivity, especially for some clusters
Hrdlicka et al. (2011) Czech Republic	70 (35 ASDs/35 TD)	ASDs: Age 6–18 y (mean 10.8 ± 3.6 y); TD: mean 10.4 ± 2.4 y; IQ ≥ 70	Sniffin' Sticks Identification Test for olfactory evaluation, pleasantness of the odors rated on a 1–5 scale	Difference in pleasantness perception of some odors for subjects with autism and controls

(*Continued*)

Table 1 (Continued).

Study	*n* (case/control)	Age, IQ	Design	Findings
May et al. (2011) Australia	18 (9 ASDs/9 TD) 36 (12 HFA/12 AS/12 TD)	ASDs: Age 6.28 ± 0.48 y, FSIQ 95.0 ± 20.8; TD: Age 7.10 ± 1.40 y, FSIQ 102.4 ± 18.8. ASDs: Age 10.6 ± 2.1 y, IQ 84.5 ± 13.7; AS: Age 10.8 ± 2.0 y, IQ 102.8 ± 11.7; TD: Age 9.7 ± 2.0 y, IQ 111.0 ± 12.1	UPSIT for odor identification ability at baseline and at 5-year follow-up Unilateral UPSIT	Different OI-age relationship in subjects with autism compared with controls; subjects with autism had impaired olfactory identification relative to controls with similar deficit in both nostrils
Dudova et al. (2011) Czech Republic	70 (35 ASDs/35 TD)	ASDs: Age 6–18 y (mean 10.8 ± 3.6 y); TD: mean 10.4 ± 2.4 y; IQ ≥ 70	Cross-sectional study; Sniffin' Sticks Threshold Test (n-butanol version) and Identification Test	Impairment in olfactory threshold for subjects with ASDs, no difference in odor identification
Nadon et al. (2011) Canada	95 (95 Autism+AS+PDD-NOS)	Age 3–10 y (mean 7.3 ± 2.5 y)	Eating Profile and SSP questionnaires	Children with sensory problems (especially tactile, taste/smell and visual/auditory altered sensitivities) have more eating disturbances than children with typical performances
Kumar et al. (2011) USA	N/A	N/A	Study exploiting the genetic heterogeneity of ASDs to derive a predictive map of candidate genes by an integrated bioinformatics approach	Four critical brain regions of ASD pathogenesis discovered, among which olfactory bulb, responsible for smell information transmission
Dudova and Hrdlicka (2012, 2013) Czech Republic	35 (35 ASDs)	Age 6–18 y (mean 10.8 ± 3.6 y); IQ ≥ 70	CARS Scale for autism psychopathology; Sniffin' Sticks for smell evaluation	No correlations between olfactory function and CARS Scale nor with its subsection

(*Continued*)

Table 1 (Continued).

Study	*n* (case/control)	Age, IQ	Design	Findings
Tavassoli and Baron-Cohen (2012) UK	80 (38 ASD/42 TD)	ASDs: Age 35.9 ± 10.9 y, FSIQ 112.6 ± 15.3; TD: Age 28.8 ± 6.5 y, FSIQ 115.7 ± 10.8	Autistic Spectrum Quotient (AQ) questionnaire; Sniffin' Sticks Threshold Test (n-butanol version) for smell assessment, olfactory adaptation test performed with highest concentration of n-butanol	No significant between-group difference in olfactory threshold;, normal olfactory adaptation in adults with ASDs
Woodard et al. (2012) USA	16 (8 ASDs/8 TD)	Age 24–38 m	M-CHAT questionnaire, evaluation of responses to sensory stimuli by autonomic and behavioral rating scales	Children with ASDs were more hyper-sensitive and less hypo-sensitive to a number of sensory stimuli
Legiša et al. (2013) Italy/France	16 (8 HFA/8 TD)	Age 8–14 y; CARS Score > 30, FSIQ Range 75–89	Cross-sectional, case-control study; eight odors presented, with different levels of pleasantness; evaluation of autonomic response, facial expression and self-reported odor rating	Small differences in facial expression responses to the odors and in autonomic response; children with ASDs rated as less unpleasant odors such as sweat, chlorine and feces than controls
Galle et al. (2013) Canada	30 (10 ASDs/9 AS/11 TD) 15 (5 ASDs/5 AS/5 TD)	Age: ASDs 25.5 ± 5.8 y, AS 25.44 ± 6.8 y, TD 22 ± 3.32 y; FSIQ: ASDs 111.6 ± 12.5, AS 109.44 ± 18.84, TD 109.73 ± 13.19; Age: ASDs 24.8 ± 7.16 y, AS 22.2 ± 4.44 y, TD 21.4 ± 2.19 y; FSIQ: ASD 112.8 ± 14.1, AS 119.4 ± 15.85, TD 110 ± 7.25	UPSIT for odor identification evaluation Odor threshold to n-butanol and phenylethanol, odor discrimination, subjective ratings of pleasantness, intensity, and familiarity, self-rated chemosensory sensitivity	Odor identification impaired in subjects with ASDs but not in subjects with AS. No significant difference in odor threshold, discrimination, subjectivity, and self-rated chemosensory sensitivity

(*Continued*)

Table 1 (Continued).

Study	*n* (case/control)	Age, IQ	Design	Findings
Tavassoli et al. (2014) UK/USA	402 (221 ASDs/181 TD)	Age: ASDs 38.7 ± 12.0 y, TD 37.1 ± 12.9 y; Raven Score: ASDs 50.1 ± 10.3, TD 51.0 ± 9.0	Cross-sectional study to evaluate sensory over-response in adults with ASDs. AQ used for detecting autistic traits, SP for sensory profiling, Raven progressive Matrices Test for intellectual screening measure	Adults with ASDs had higher self-reported sensory over-responsivity than controls; sensory over-responsivity positively correlated with autistic traits in both groups
Ausderau et al. (2014) USA	1307 (1307 ASDs)	Age 2–12 y	National survey on sensory features in children with ASDs; Sensory Experience Questionnaire administration	Strong associations between hyper-responsiveness and enhanced perception as well as between hypo-responsiveness and sensory interests, repetitions and seeking behaviors in children with ASDs
Berko et al. (2014) USA	95 (47 ASDs/48 TD)	Mothers > 35 years of age	Genetic study; testing of ectodermal cell type by a quantitative genome-wide DNA methylation assay in children with ASDs and TD children	OR2L13G-protein coupled olfactory receptor involved in initializing neuronal response to odorants, labile in ASDs in terms of DNA methylation and expression
Ashwin et al. (2014) UK	34 (17 ASDs/17 TD)	Adult males with HFA/AS	Cross-sectional study on olfactory sensitivity with Alcohol Sniff Test	Hypersensitivity in people with ASDs, correlation between hypersensitivity and autism severity score

Note. AS = Asperger syndrome; ASDs = autism spectrum disorders; DD = Developmental Disability; FSIQ = Full-Scale Intelligence Quotient; HFA = high-functioning autism; IQ = Intelligence Quotient; LFA = low-functioning autism; m = months; PDD = pervasive developmental disorder; PDD-NOS = PDD – not otherwise specified; SP = Sensory Profile; SSP = Short Sensory Profile; TD = typical development; y = years.

Table 2 Main findings of the current literature on ASDs and olfaction.

Type of sensory assessment	No. of studies	Findings
Olfactory testing/ psychophysiological evaluation	13	Olfaction impairment in ASDs: Odor identification: 71.4% (5/7) (Bennetto et al., 2007; De Assumpção & Adamo, 2007; Galle et al., 2013; May et al., 2011; Suzuki et al., 2003) Olfactory sensitivity: 50.0% (2/4) (Ashwin et al., 2014*; Dudova et al., 2011) Odor discrimination: 0% (0/1) Odor pleasantness: 66.7% (2/3) (Hrdlicka et al., 2011; Legiša et al., 2013) No olfaction impairment in ASDs: 15.4% (2/13) (Brewer et al., 2008; Tavassoli & Baron-Cohen, 2012)
Sensory questionnaire/ sensory profile administration	10	Sensory impairment in ASDs: Overall sensory response: 100% (10/10 articles) (Ausderau et al., 2014; Hilton et al., 2010; Lane et al., 2010, 2011; Leekam et al., 2007; Nadon et al., 2011; Rogers et al., 2003; Tavassoli et al., 2014*; Wiggins et al., 2009; Woodard et al., 2012) Taste/smell sensitivity: 80% (8/10) (Hilton et al., 2010; Lane et al., 2010, 2011; Leekam et al., 2007; Nadon et al., 2011; Rogers et al., 2003; Tavassoli et al., 2014*; Wiggins et al., 2009) No olfactory impairment: 0% (0/8)
Genetic/epigenetic approach	2	Olfactory bulb discovered as critical area for ASD pathogenesis (Kumar et al., 2011); OR2L13 olfactory GPCR labile in ASDs in terms of DNA methylation and expression (Berko et al., 2014)
Autonomic response to olfactory stimuli	2	Small differences in autonomic and facial responses to odors in ASDs and TD (Legiša et al., 2013; Woodard et al., 2012)

Note. *Over-responsivity. ASD = austistic spectrum disorders; GPCR = G-protein coupled receptor.

Odor threshold appeared to be impaired in one study (Dudova et al., 2011), probably suggesting a different pathway of dysfunction in ASDs more central than peripheral, justifying the deficits found in odor identification. In the study by Tavassoli and Baron-Cohen (2012) in particular, no difference was found between people with ASDs and healthy control individuals, clustered by the Autism Spectrum Quotient (AQ) questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001). Ashwin et al. (2014) found a trend towards hypersensitivity in persons with ASDs, correlated with autism severity, assessed by the AQ. Galle et al. (2013) conduected a study on odor discrimination using a modified version of the odor discrimination test (Tanabe et al., 1975), and no difference between individuals with ASDs and healthy controls was found. Odor pleasantness was assessed in three studies, and a difference in subjective odor perception was found in two of them (Hrdlicka et al., 2011; Legiša et al., 2013), These findings suggest a possible deficit in defined areas of olfactory processing in ASDs. In the third study, no difference in the Chemical Sensitivity Scale (CSS; Nordin, Millquist, Löwhagen, & Bende, 2002) was found (Galle et al., 2013). Finally, no correlation between olfactory function and the Childhood Autism Rating Scale (CARS) was found in two Czech studies (Dudova & Hrdlicka, 2012, 2013).

Taste evaluation was also employed in one study (Bennetto et al., 2007), with taste identification and electrogustometry for taste threshold (Levitt, 1971; Loucks &

Doty, 2004), revealing no particular deficits in ASDs, except for a slight difference in citric acid and quinine identification.

Studies Based on Sensory Questionnaires

Self and/or parent report questionnaires are largely employed to evaluate sensory responses in ASDs, especially in the assessment of very young children or toddlers.

Ten studies have been included in this literature review (Ausderau et al., 2014; Hilton et al., 2010; Lane, Dennis, & Geraghty, 2011; Lane, Young, Baker, & Angley, 2010; Leekam et al., 2007; Nadon, Ehrmann Feldman, Dunn, & Gisel, 2011; Rogers, Hepburn, & Wehner, 2003; Tavassoli, Miller, Schoen, Nielsen, & Baron-Cohen, 2014; Wiggins, Robins, Bakeman, & Adamson, 2009; Woodard et al., 2012).

The presence of sensory impairment, and possible correlations with ASD severity and with intellectual disability were assessed and all the studies reported sensory abnormalities in the overall sensory evaluation, in most cases assessed by the Short Sensory Profile (SSP; Dunn, 1999; Miller et al., 1999). Significant differences in taste/olfactory sensitivity were found in a group of children aged 2–4 years with ASDs and Fragile X syndrome. Sensory impairment—especially concerning olfaction and taste subdomains—was reported in children with ASDs, both high and low functioning, with respect to other neurodevelopmental disorders such as developmental delay (Hilton et al., 2010; Leekam et al., 2007), known to share common cortical pathways like the insular cortex.

In another study, Hilton et al. (2010) found that the oral/olfactory domains at the Sensory Profile questionnaire were correlated with the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005) in both persons with ASDs and healthy controls. Other studies found significant differences in other subdomains, such as tactile sensitivity and auditory filtering, in some cases with a clear deficit also in taste and olfaction (Lane et al., 2010), probably suggesting an overall dysfunction in sensory integration circuitry.

In a large cohort of children with ASDs, significant correlations between sensory reactivity and enhanced perception, as well as between hypo-responsiveness and sensory interests, repetitions and seeking behaviors in the ASDs group, were found (Ausderau et al., 2014; Baranek, 2009).

In another study, Woodbury-Smith, Robinson, and Baron-Cohen (2005) reported sensory over-responsivity in a group of adults with ASDs, with a positive correlation with AQ scores (Tavassoli et al., 2014).

Furthermore, according to Galle et al. (2013), scores on the Eating Profile (Nadon et al., 2011), a questionnaire developed to identify eating behavior profiles, were correlated with olfactory sensory deficits in persons with ASDs, demonstrating a probable link between these two conditions that is often associated with ASDs.

Studies Related to Genetics/Epigenetics

A genetic/epigenetic approach in relation to olfaction in people with ASDs was used in two studies (Berko et al., 2014; Kumar et al., 2011). In Kumar et al. (2011), the expression profile derived from a bioinformatics research suggested four critical brain regions related to ASD pathogenesis: the olfactory bulb (involved in both olfactory signal transmission and social behavior, at least in mouse models; Crawley, 2007), the occipital lobe, the prefrontal cortex and the pituitary. Berko et al. (2014) found that the

OR2L13G-protein coupled olfactory receptor, known to be involved in initializing neuronal response to odorants, was extremely labile in ASDs in terms of DNA methylation and expression, suggesting a possible rationale for olfactory dysfunction in ASDs.

Autonomic Response to Olfactory Stimuli

Autonomic response to olfactory stimuli was evaluated in two studies (Legiša et al., 2013; Woodard et al., 2012). In Woodard et al. (2012), people with ASDs were found to be more physiologically sensory reactive in terms of heart rate (HR) compared to neurotypicals across all sensitivity stimuli presented. In Legiša et al. (2013), very subtle differences between children with HFA and typically developing children in autonomic responses, obtained by HR and skin conductance, and facial expression matching were found, and a clear impairment to self-report emotional reactions to odor presentation was observed in the ASD group.

DISCUSSION

Limitations and Methodological Issues

The link between ASDs and olfactory dysfunction is still largely debated. ASD is an extremely complex condition, largely unresolved, from different points of view, including genetics/epigenetics, behavioral and neurophysiological features (D'Cruz et al., 2013; Hollander et al., 2003). Furthermore, several methodological limitations of the reviewed studies, such as small sample sizes, different age ranges and/or the employment of trigeminal stimulants for olfactory sensitivity should be considered. Indeed, the effect of age should be specifically taken into account due to a different timeline for olfactory function development, with olfactory sensitivity developing earlier in childhood, and olfactory identification ability developing later during adolescence. This timeline could be more heterogeneous and/or shifted in those with ASDs compared to those who develop typically (Dudova et al., 2011).

Summary of the Main Results

Studies on olfactory testing in ASDs have generally demonstrated a decrease in the ability to identify odors in people with ASDs when compared to healthy controls (Bennetto et al., 2007; De Assumpção & Adamo, 2007; Galle et al., 2013; May et al., 2011; Suzuki et al., 2003), with very rare cases in which odor identification did not appear to be impaired (Brewer et al., 2008; Dudova et al., 2011).

This evidence confirms a deficit in the higher-level processing of sensory stimuli in ASDs, possibly linked to poorer verbal labeling and semantic memory (Hedner, Larsson, Arnold, Zucco, & Hummel, 2010; Oberg, Larsson, & Backman, 2002).

Other studies, focused on olfactory sensitivity (threshold) and discrimination, as well as pleasantness/familiarity, have reported contradictory results, with some evidence of decreased olfactory abilities in ASDs (Dudova et al., 2011; Hrdlicka et al., 2011; Legiša et al., 2013), and some other studies reporting preserved (Galle et al., 2013; Suzuki et al., 2003; Tavassoli & Baron-Cohen, 2012) or increased (Ashwin et al., 2014) olfactory abilities.

Interestingly, some odors stimulating the trigeminal nerve such as mint and chlorine have been reported to be differently perceived in children with ASD compared to typically developing children and have been associated to differences in heart rate and skin conductance responses (Legiša et al., 2013). Since the trigeminal pathway is also stimulated by painful stimuli (Hummel, Iannilli, Frasnelli, Boyle, & Gerber, 2009; Smeets & Dalton, 2005), a lowered reactivity may be related to decreased pain sensitivity in ASDs (Kalat, 1978; Kaplan, Sadock, & Grebb, 1994). Furthermore, recent evidence demonstrated a different attitude in children with ASDs with respect to typically developing children in the act of sniffing, with children with ASDs less able to modulate their sniffs according to odor pleasantness (taking vigorous sniffs of unpleasant odors), possibly suggesting a sensory-motor coordination impairment related to this function in ASDs (Rozenkrantz et al., 2015).

Modulators

One of the main modulators of olfactory function in ASDs is age. Indeed, the ability to detect odors (olfactory sensitivity tasks) develops earlier in life, while odor identification capabilities are acquired later in adolescence (Dudova et al., 2011), and in a more heterogeneous way in children with ASDs than in neurotypicals.

The presence of specific genetic conditions could also affect the sense of smell in autism. For example, in patients with fragile X syndrome, the prevalence of olfactory impairment is higher, and also related to the severity of the condition (Rogers et al., 2003).

Finally, the severity of ASD symptoms could be related to smell impairment. Indeed, Ashwin et al. (2014) found a clear correlation between autism severity and olfactory hyper-sensitivity in an olfactory threshold task, while patients with HFA appear to have a more marked impairment than delayed subjects with a similar IQ with respect to children with low-functioning autism (LFA; Leekam, Libby, Wing, Gould, & Taylor, 2002).

Clinical Implications

Olfactory assessment in ASDs could have several clinical implications. Firstly, a standardized olfactory assessment could assist clinical evaluation and potentially improve diagnostic accuracy in ASDs.

Indeed, despite a growing interest in sensory assessment (Grandin & Panek, 2013) demonstrated by the inclusion of sensory features in the DSM-5 criteria and recent experimental research, it still remains a relatively unexplored area. Moreover, actual clinical practice still evaluates touch, sight and auditory profile as custom sensory assessment, mainly due to the absence of standardized tools for olfactory and gustatory evaluation. Secondly, specific and appropriate olfactory environments may potentially be used to modulate and influence the emotional state and social, behavioral functioning in people with ASDs, possibly improving their neurophysiological status.

Environmental sensory stimuli can indeed strongly impact the quality of life in children and adults with ASDs, generating either sensory-seeking behaviors or sensory overloading, with substantial interference in their affective, cognitive and social functions, arousal and emotion regulation.

Furthermore, especially in childhood and low-functioning conditions, individuals with ASDs are often unable to explain their distress, meaning that parents and caregivers cannot organize the sensory environment around their needs in order to minimize the chances of that distress occurring.

Specific psychoeducational strategies such as storytelling, comic strip conversations, themes of normalizing, and describing responses can be used and developed to help people with ASDs share and process their sensory experiences (Kirby, Dickie, & Baranek, 2015).

Olfaction may be also used as a reinforcer in ASD. When exposed to pleasant smells (like orange; Hrdlicka et al., 2011), people with ASDs seem to better perform at sorting tasks (Wilder et al., 2008); interestingly, there is a correlation, at least with extreme values, between a better identification of more pleasant odors and a worse performance on more unpleasant ones (Dudova et al., 2011).

Related to this finding, customized olfactory training tools for people with ASDs could be developed (Ashwin et al., 2014).

Finally, another clinical implication to be considered relates to the link between a different perception of odors, tastes and food selectivity reported in many people with autism.

Development of food preferences clearly begins in early childhood, and depends on a complex interaction between biological predisposition, tendencies toward food neophobia, the ability to learn associations between foods and contexts, and the eating environment itself (Bennetto et al., 2007; Birch, 1999; Field, Garland, & Williams, 2003; Hrdlicka et al., 2011; Martins, Young, & Robson, 2008; Schreck & Williams, 2006).

On top of this, in individuals with ASDs atypical sensory processing of taste and food odors should be considered (Cermak, Curtin, & Bandini, 2010; Hubbard, Anderson, Curtin, Must, & Bandini, 2014; Nadon et al., 2011; Smith, Roux, Naidoo, & Venter, 2005).

Implications for ASD Pathophysiology

Systematic research on olfaction in ASD could also help to better understand the complex ASD pathophysiology.

The olfactory pathway involves a number of brain regions, including the olfactory, orbitofrontal and insular cortex, the limbic system and the hypothalamus. Furthermore the different tasks developed for smell evaluation rely on different brain regions and networks—from the more peripheral, such as in sensitivity tasks, to the more central, such as in odor identification tasks—allowing for a quite precise recognition of a possibly defective area within such brain networks.

Anatomically, one of the most important brain structures in olfactory function, the orbitofrontal cortex—primarily involved in higher-level odor processing—is also related to social control and behavioral flexibility (Eslinger & Damasio, 1985), core characteristics of ASDs and the latter being in turn associated with repetitive behaviors (D'Cruz et al., 2013).

Furthermore, the orbitofrontal cortex is functionally connected to the medial temporal lobe areas, including the amygdala, whose activation is strongly predicted by olfactory and gustatory stimuli (Costafreda, Brammer, David, & Fu, 2008). People with ASDs have been repeatedly reported as having amygdala dysfunction genetically

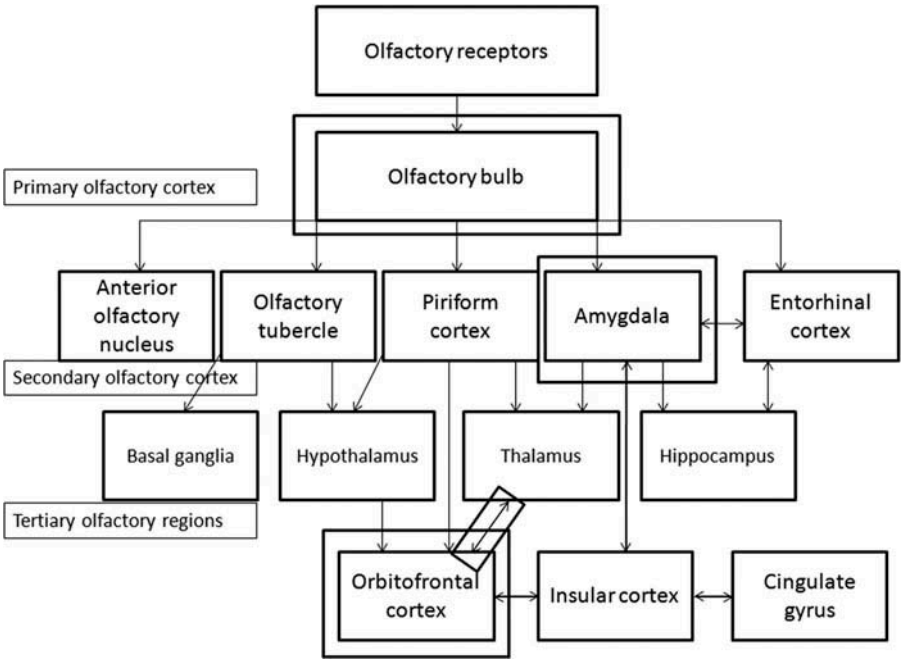

Figure 3 Olfactory pathway (domains evidenced in black rectangles are differently functioning areas in ASDs, modified from Albrecht & Wiesmann, 2009).

(Sokolowski & Corbin, 2012), anatomically and functionally (Baron-Cohen et al., 2000; Pierce, Muller, Ambrose, Allen, & Courchesne, 2001; Stanfield et al., 2008).

In functional imaging studies of emotional processing (Critchley et al., 2000), amygdala dysfunction has been related to orbitofrontal dysfunction and/or frontotemporal connectivity, implying the olfactory processing involvement (May et al., 2011; Suzuki et al., 2003; see Figure 3).

Furthermore, the olfactory bulb mainly involved in olfactory transmission has been also associated with social behavior (Crawley, 2007), and the occipital lobe, involved in both olfactory and visual processing, have been implicated in ASDs probably due to electrical abnormalities in this area (Boucher & Lewis, 1992; Nass, Gross, & Devinsky, 1998). The prefrontal cortex seems to be less activated in persons with autism during cognitive tasks (Silk et al., 2006), with its role known to be critical for executive function skills. Finally, the pituitary secretion of hormones such as oxytocin and vasopressin—well known to underlie social behaviors (Crawley et al., 2007; Insel, 2010)—has been reported to be impaired in ASDs, contributing to the condition (Chamberlain & Herman, 1990).

Interestingly, vasopressin and oxytocin, known as affiliation hormones, present receptors within the olfactory bulb (Brang & Ramachandran, 2010) and their levels have been correlated with the good functioning of olfactory function (Strauss et al., 2015; Woolley et al., 2015). As mentioned, such molecules (in particular oxytocin) have been found to be reduced in people with ASDs (Green et al., 2001; Modahl et al., 1998) and have been proposed as potential mechanisms for autism treatment (Hollander et al., 2003, 2007).

ASDs have also been associated with hyperserotonemia (Lam, Aman, & Arnold, 2006), i.e., an excess in plasma-based serotonin, and this is thought to reduce the

functioning of serotonin terminals at brain level due to negative feedback and desensitization. Social behaviors based on olfactory cues were reduced by the administration of a serotonin agonist, suggesting that hyperserotonemia during development could impair the functioning of the olfactory bulbs in rats (McNamara, Borella, Bialowas, & Whitaker-Azmitia, 2008).

In conclusion, evidence for a different sensory reactivity in people with ASDs is present in the current literature. In this field, the olfactory function, known as an early biomarker for neurodegeneration and 5-year mortality in elderly people, could be considered a neglected area, especially when compared to sight and hearing, thus representing an important addition to current research. In some cases, people with ASDs seem to have a decreased olfactory function, especially in more complex tasks (such as odor identification), involving cortical components such as—but not limited to—the orbitofrontal cortex, but overall, the results are still contradictory. Although we are far from fully understanding the mechanisms underlying autism, a standardized sensory assessment of ASDs should be developed for both clinical and research reasons and could provide some insights into different aspects of ASD pathogenesis (Martin & Daniel, 2014; Schecklmann et al., 2013). Indeed, an olfactory evaluation could be a simple, non-invasive tool with which to assess cortical functioning in ASDs with good reliability (Haehner et al., 2009), as well as providing clinical information to families and affected individuals. Thus, we suggest the employment of sensory and in particular olfactory evaluation in the initial assessment of ASDs in young children, possibly in addition to traditional diagnostic methods, even to cluster individuals with ASDs into subgroups. Meanwhile, it is recommended that new tests are developed for more reliable olfactory assessment in toddlers, where classic olfactory testing may be not appropriate, thus representing an important drawback in the field given the high diagnostic value of ASD assessment in very early childhood.

Original manuscript received 9 April 2015
Revised manuscript accepted 6 August 2015
First published online 4 September 2015

ORCID

Giovanni Pioggia http://orcid.org/0000-0002-8089-7449

REFERENCES

Albrecht, J., & Wiesmann, M. (2006). The human olfactory system. *Anatomy and Physiology. Nervenarzt*, *77*(8), 931–939. doi:10.1007/s00115-006-2121-z

Albrecht, J., & Wiesmann, M. (2009). Olfactory pathways. In M. D. Binder, N. Hirokawa, & U. Windhorst (Eds.), *Encyclopedia of neuroscience* (pp. 3003–3006). Berlin: Springer.

Amaral, D. G., Schumann, C. M., & Nordahl, C. W. (2008). Neuroanatomy of autism. *Trends in Neurosciences*, *31*(3), 137–145. doi:10.1016/j.tins.2007.12.005

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: American Psychiatric Press.

Ashwin, C., Chapman, E., Howells, J., Rhydderch, D., Walker, I., & Baron-Cohen, S. (2014). Enhanced olfactory sensitivity in autism spectrum conditions. *Molecular Autism*, *5*, 53. doi:10.1186/2040-2392-5-53

Ausderau, K., Sideris, J., Furlong, M., Little, L. M., Bulluck, J., & Baranek, G. T. (2014). National survey of sensory features in children with ASD: Factor structure of the sensory experience

questionnaire (3.0). *Journal of Autism and Developmental Disorders*, *44*, 915–925. doi:10.1007/s10803-013-1945-1

Baranek, G. T. (2009). *Sensory experiences questionnaire version 3.0*. Unpublished manuscript.

Baranek, G. T., Boyd, B. A., Poe, M. D., David, F. J., & Watson, L. R. (2007). Hyperresponsive sensory patterns in young children with autism, developmental delay and typical development. *American Journal of Mental Retardation*, *112*, 233–245. doi:10.1352/0895-8017(2007)112[233:HSPIYC]2.0.CO;2

Baron-Cohen, S., Ring, H. A., Bullmore, E. T., Wheelwright, S., Ashwin, C., & Williams, S. C. R. (2000). The amygdala theory of autism. *Neuroscience & Biobehavioral Reviews*, *24*, 355–364. doi:10.1016/S0149-7634(00)00011-7

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism spectrum quotient (AQ): Evidence from Asperger syndrome/high functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, *31*, 5–17. doi:10.1023/A:1005653411471

Bennetto, L., Kuschner, E. S., & Hyman, S. L. (2007). Olfaction and taste processing in autism. *Biological Psychiatry*, *62*(9), 1015–1021. doi:10.1016/j.biopsych.2007.04.019

Berko, E. R., Suzuki, M., Beren, F., Lemetre, C., Alaimo, C. M., Calder, R. B., … Greally, J. M. (2014). Mosaic epigenetic dysregulation of ectodermal cells in autism spectrum disorder. *PLoS Genetics*, *10*(5), e1004402. doi:10.1371/journal.pgen.1004402

Birch, L. L. (1999). Development of food preferences. *Annual Review of Nutrition*, *19*, 41–62. doi:10.1146/annurev.nutr.19.1.41

Boucher, J., & Lewis, V. (1992). Unfamiliar face recognition in relatively able autistic children. *Journal of Child Psychology and Psychiatry*, *33*, 843–859. doi:10.1111/j.1469-7610.1992.tb01960.x

Boyd, B. A., Baranek, G. T., Sideris, J., Poe, M. D., Watson, L. R., Patten, E., & Miller, H. (2010). Sensory features and repetitive behaviors in children with autism and developmental delays. *Autism Research*, *3*, 78–87.

Brang, D., & Ramachandran, V. S. (2010). Olfactory bulb dysgenesis, mirror neuron system dysfunction, and autonomic dysregulation as the neural basis for autism. *Medical Hypotheses*, *74*, 919–921. doi:10.1016/j.mehy.2008.11.048

Brewer, W. J., Brereton, A., & Tonge, B. J. (2008). Dissociation of age and ability on a visual analogue of the University of Pennsylvania smell identification test in children with autism. *Research in Autism Spectrum Disorders*, *2*, 612–620. doi:10.1016/j.rasd.2008.01.003

Buschhüter, D., Smitka, M., Puschmann, S., Gerber, J. C., Witt, M., Abolmaali, N. D., & Hummel, T. (2008). Correlation between olfactory bulb volume and olfactory function. *Neuroimage*, *42*(2), 498–502. doi:10.1016/j.neuroimage.2008.05.004

Cain, W. S., Gent, J., Catalanotto, F. A., & Goodspeed, R. B. (1983). Clinical evaluation of olfaction. *American Journal of Otolaryngology*, *4*, 252–256. doi:10.1016/S0196-0709(83)80068-4

Cermak, S. A., Curtin, C., & Bandini, L. G. (2010). Food selectivity and sensory sensitivity in children with autism spectrum disorders. *Journal of the American Dietetic Association*, *110*, 238–246. doi:10.1016/j.jada.2009.10.032

Chamberlain, R. S., & Herman, B. H. (1990). A novel biochemical model linking dysfunctions in brain melatonin, proopiomelanocortin peptides, and serotonin in autism. *Biological Psychiatry*, *28*, 773–793. doi:10.1016/0006-3223(90)90513-2

Constantino, J. N., & Gruber, C. P. (2005). *Social responsiveness scale*. Los Angeles, CA: Western Psychological Services.

Costafreda, S. G., Brammer, M. J., David, A. S., & Fu, C. H. Y. (2008). Predictors of amygdala activation during the processing of emotional stimuli: A meta-analysis of 385 PET and fMRI studies. *Brain Research Reviews*, *58*, 57–70. doi:10.1016/j.brainresrev.2007.10.012

Crawley, J. N. (2007). Mouse behavioral assays relevant to the symptoms of autism. *Brain Condition*, *17*, 448–459.

Crawley, J. N., Chen, T., Puri, A., Washburn, R., Sullivan, T. L., Hill, J. M., … Young, W. S. (2007). Social approach behaviors in oxytocin knockout mice: Comparison of two independent lines tested in different laboratory environments. *Neuropeptides*, *41*, 145–163. doi:10.1016/j.npep.2007.02.002

Critchley, H. D., Daly, E. M., Bullmore, E. T., Williams, S. C., Van Amelsvoort, T., Robertson, D. M., … Murphy, D. G. (2000). The functional neuroanatomy of social behaviour: Changes in cerebral blood flow when people with autistic disorder process facial expressions. *Brain*, *123*, 2203–2212. doi:10.1093/brain/123.11.2203

D'Cruz, A. M., Ragozzino, M. E., Mosconi, M. W., Shrestha, S., Cook, E. H., & Sweeney, J. A. (2013). Reduced behavioral flexibility in autism spectrum disorders. *Neuropsychology*, *27*(2), 152–160. doi:10.1037/a0031721

De Assumpção, F. B., Jr., & Adamo, S. (2007). Smell recognition in pervasive developmental disorders. *Arquivos De Neuro-Psiquiatria*, *65*(4b), 1200–1205.

Deems, D. A., & Doty, R. L. (1987). Age-related changes in the phenyl ethyl alcohol odor detection threshold. *Transactions – Pennsylvania Academy of Ophthalmology and Otolaryngology*, *39*(1), 646–650.

Doty, R. L. (2000). *The odor threshold test administration manual*. Haddon Hts., NJ: Sensonics, Inc.

Doty, R. L., Marcus, A., & Lee, W. W. (1996). Development of the 12-item cross-cultural smell identification test (CC-SIT). *Laryngoscope*, *106*, 353–356. doi:10.1097/00005537-199603000-00021

Doty, R. L., Shaman, P., & Dann, M. (1984). Development of the University of Pennsylvania smell identification test: A standardized microencapsulated test of olfactory function. *Physiology & Behavior*, *32*, 489–502. doi:10.1016/0031-9384(84)90269-5

Dudova, I., & Hrdlicka, M. (2012). Relationship of olfactory functions and psychocondition in patients with autism spectrum disorders. *Child and Adolescent Disorders and Treatment − Disorders (Clinical)*, *S416*.

Dudova, I., & Hrdlicka, M. (2013). Olfactory functions are not associated with autism severity in autism spectrum disorders. *Neuropsychiatric Disorder and Treatment*, *9*, 1847–1851.

Dudova, I., Vodicka, J., Havlovicova, M., Sedlacek, Z., Urbanek, T., & Hrdlicka, M. (2011). Odor detection threshold, but not odor identification, is impaired in children with autism. *European Child & Adolescent Psychiatry*, *20*, 333–340. doi:10.1007/s00787-011-0177-1

Dunn, W. (1999). Development and validation of the short sensory profile. In W. Dunn (Ed.), *The sensory profile examiner's manual*. San Antonio, TX: The Psychological Corporation.

Ehrenstein, W., & Ehrenstein, A. (1999). Psychophysical methods. In U. Windhorst & H. Johansson (Eds.), *Modern techniques in neuroscience research* (pp. 1211–1214). New York, NY: Springer.

Eslinger, P. J., & Damasio, A. R. (1985). Severe disturbance of higher cognition after bilateral frontal lobe ablation: Patient E.V.R. *Neurology*, *35*, 1731–1741. doi:10.1212/WNL.35.12.1731

Field, D., Garland, M., & Williams, K. (2003). Correlates of specific childhood feeding problems. *Journal of Paediatrics and Child Health*, *39*, 299–304. doi:10.1046/j.1440-1754.2003.00151.x

Frijters, J. E. (1980). Three-stimulus procedures in olfactory psychophysics: An experimental comparison of Thurstone-Ura and three-alternative forced-choice models of signal detection theory. *Perception and Psychophysics*, *28*, 390–397. doi:10.3758/BF03204882

Galle, S. A., Courchesne, V., Mottron, L., & Frasnelli, J. (2013). Olfaction in the autism spectrum. *Perception*, *42*, 341–355. doi:10.1068/p7337

Grandin, T., & Panek, R. (2013). *The autistic brain: Thinking across the spectrum*. Boston, MA: Houghton Mifflin Harcourt.

Green, L., Fein, D., Modahl, C., Feinstein, C., Waterhouse, L., & Morris, M. (2001). Oxytocin and autistic disorder: Alterations in peptide forms. *Biological Psychiatry*, *50*, 609–613. doi:10.1016/S0006-3223(01)01139-8

Guarneros, M., Ortiz-Romo, N., Alcaraz-Zubeldia, M., Drucker-Colín, R., & Hudson, R. (2013). Nonoccupational environmental exposure to manganese is linked to deficits in peripheral and central olfactory function. *Chemical Senses*, *38*(9), 783–791. doi:10.1093/chemse/bjt045

Haehner, A., Mayer, A. M., Landis, B. N., Pournaras, I., Lill, K., Gudziol, V., & Hummel, T. (2009). High test-retest reliability of the extended version of the "Sniffin' sticks" test. *Chemical Senses*, *34*, 705–711. doi:10.1093/chemse/bjp057

Hawkes, C. H. (2003). Olfaction in neurodegenerative disorder. *Movement Disorders*, *18*(4), 364–372. doi:10.1002/mds.10379

Hedner, M., Larsson, M., Arnold, N., Zucco, G. M., & Hummel, T. (2010). Cognitive factors in odor detection, odor discrimination, and odor identification tasks. *Journal of Clinical and Experimental Neuropsychology*, *32*, 1062–1067. doi:10.1080/13803391003683070

Hilton, C. L., Harper, J. D., Kueker, R. H., Lang, A. R., Abbacchi, A. M., Todorov, A., & LaVesser, P. D. (2010). Sensory responsiveness as a predictor of social severity in children with high functioning autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *40*, 937–945. doi:10.1007/s10803-010-0944-8

Hollander, E., Bartz, J., Chaplin, W., Phillips, A., Sumner, J., Soorya, L., … Wasserman, S. (2007). Oxytocin increases retention of social cognition in autism. *Biological Psychiatry*, *61*(4), 498–503. doi:10.1016/j.biopsych.2006.05.030

Hollander, E., Novotny, S., Hanratty, M., Yaffe, R., DeCaria, C. M., Aronowitz, B. R., & Mosovich, S. (2003). Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders. *Neuropsychopharmacology*, *28*(1), 193–198. doi:10.1038/sj.npp.1300021

Hrdlicka, M., Vodicka, J., Havlovicova, M., Urbanek, T., Blatny, M., & Dudova, I. (2011). Brief report: Significant differences in perceived odor pleasantness found in children with ASD. *Journal of Autism and Developmental Disorders*, *41*, 524–527. doi:10.1007/s10803-010-1084-x

Hubbard, K. L., Anderson, S. E., Curtin, C., Must, A., & Bandini, L. G. (2014). A comparison of food refusal related to characteristics of food in children with autism spectrum disorder and typically developing children. *Journal of the Academy of Nutrition and Dietetics*, *114*(12), 1981–1987. doi:10.1016/j.jand.2014.04.017

Hummel, T., Iannilli, E., Frasnelli, J., Boyle, J., & Gerber, J. (2009). Central processing of trigeminal activation in humans. *Annals of the New York Academy of Sciences, International symposium on Olfaction and Taste*, *1170*, 190–195. doi:10.1111/j.1749-6632.2009.03910.x

Hummel, T., Sekinger, B., Wolf, S. R., Pauli, E., & Kobal, G. (1997). "Sniffin' sticks": Olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. *Chemical Senses*, *22*(1), 39–52. doi:10.1093/chemse/22.1.39

Insel, T. R. (2010). The challenge of translation in social neuroscience: A review of oxytocin, vasopressin, and affiliative behavior. *Neuron*, *65*, 768–779. doi:10.1016/j.neuron.2010.03.005

Jackman, A. H., & Doty, R. L. (2005). Utility of a three-item smell identification test in detecting olfactory dysfunction. *The Laryngoscope*, *115*, 2209–2212. doi:10.1097/01.mlg.0000183194.17484.bb

Kalat, J. W. (1978). Speculations on similarities between autism and opiate addiction. *Journal of Autism and Childhood Schizophrenia*, *8*, 477–479. doi:10.1007/BF01538051

Kaplan, H. I., Sadock, B. J., & Grebb, J. A. (1994). *Kaplan and Sadock's synopsis of psychiatry: Behavioral sciences, clinical psychiatry* (7th ed.). Baltimore, MD: Williams and Wilkins.

Kirby, A. V., Dickie, V. A., & Baranek, G. T. (2015). Sensory experiences of children with autism spectrum disorder: In their own words. *Autism*, *19*(3), 316–326. doi:10.1177/1362361314520756

Kobal, G., Hummel, T., Sekinger, B., Barz, S., Roscher, S., & Wolf, S. (1996). "Sniffin' sticks": Screening of olfactory performance. *Rhinology*, *34*, 222–226.

Kumar, A., Croft Swanwick, C., Johnson, N., Menashe, I., Basu, S. N., Bales, M. E., & Banerjee-Basu, S. (2011). A brain region-specific predictive gene map for autism derived by profiling a reference gene set. *PLoS One*, *6*(12), e28431. doi:10.1371/journal.pone.0028431

Lam, K. S., Aman, M. G., & Arnold, L. E. (2006). Neurochemical correlates of autistic disorder: A review of the literature. *Research in Developmental Disabilities*, *27*, 254–289. doi:10.1016/j.ridd.2005.03.003

Lane, A. E., Dennis, S. J., & Geraghty, M. E. (2011). Brief report: Further evidence of sensory subtypes in autism. *Journal of Autism and Developmental Disorders*, *41*, 826–831. doi:10.1007/s10803-010-1103-y

Lane, A. E., Young, R. L., Baker, A. E. Z., & Angley, M. T. (2010). Sensory processing subtypes in autism: Association with adaptive behavior. *Journal of Autism and Developmental Disorders*, *40*, 112–122. doi:10.1007/s10803-009-0840-2

Leekam, S. R., Libby, S. J., Wing, L., Gould, J., & Taylor, C. (2002). The diagnostic interview for social and communication disorders: Algorithms for ICD-10 childhood autism and Wing and Gould autistic spectrum disorder. *Journal of Child Psychology and Psychiatry*, *43*(3), 327–342. doi:10.1111/1469-7610.00024

Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. *Journal of Autism and Developmental Disorders*, *37*, 894–910. doi:10.1007/s10803-006-0218-7

Legiša, J., Messinger, D. S., Kermol, E., & Marlier, L. (2013). Emotional responses to odors in children with high-functioning autism: Autonomic arousal, facial behavior and self-report. *Journal of Autism and Developmental Disorders*, *43*, 869–879. doi:10.1007/s10803-012-1629-2

Levitt, H. (1971). Transformed up-down methods in psychoacoustics. *The Journal of the Acoustical Society of America*, *49*, 467–477. doi:10.1121/1.1912375

Loucks, C. A., & Doty, R. L. (2004). Effects of stimulation duration on electrogustometric thresholds. *Physiology & Behavior*, *81*, 1–4. doi:10.1016/j.physbeh.2003.12.014

Majak, K., Ronkko, S., Kemppainen, S., & Pitkanen, A. (2004). Projections from the amygdaloid complex to the piriform cortex: A PHA-L study in the rat. *Journal of Comparative Neurology*, *476*, 414–428. doi:10.1002/cne.20233

Marco, E. J., Hinkley, L. B., Hill, S. S., & Nagarajan, S. S. (2011). Sensory processing in autism: A review of neurophysiologic findings. *Pediatric Research*, *69*, 48R–54R. doi:10.1203/PDR.0b013e3182130c54

Martin, G., & Daniel, N. (2014). Autism spectrum disorders and chemoreception: Dead-end, or fruitful avenue of inquiry? *Frontiers in Psychology*, *5*, 42. doi:10.3389/fpsyg.2014.00042

Martins, Y., Young, R. L., & Robson, D. C. (2008). Feeding and eating behaviors in children with autism and typically developing children. *Journal of Autism and Developmental Disorders*, *38*, 1878–1887. doi:10.1007/s10803-008-0583-5

Martzke, J. S., Kopala, L. C., & Good, K. P. (1997). Olfactory dysfunction in neuropsychiatric disorders: Review and methodological considerations. *Biological Psychiatry*, *42*, 721–732. doi:10.1016/S0006-3223(96)00442-8

May, T., Brewer, W. J., Rinehart, N. J., Enticott, P. G., Brereton, A. V., & Tonge, B. J. (2011). Differential olfactory identification in children with autism and Asperger's disorder: A comparative and longitudinal study. *Journal of Autism and Developmental Disorders*, *41*, 837–847. doi:10.1007/s10803-010-1101-0

McIntosh, D. N., Miller, L. J., & Shyu, V. (1999). Development and validation of the short sensory profile. In W. Dunn (Ed.), *Sensory profile: Examiner's manual* (pp. 59–73). San Antonio, TX: The Psychological Corporation.

McNamara, I. M., Borella, A. W., Bialowas, L. A., & Whitaker-Azmitia, P. M. (2008). Further studies in the developmental hyperserotonemia model (DHS) of autism: Social, behavioral and peptide changes. *Brain Research*, *1189*, 203–214. doi:10.1016/j.brainres.2007.10.063

Miller, L. J., McIntosh, D. N., McGrath, J., Shyu, V., Lampe, M., Taylor, A. K., … Hagerman, R. J. (1999). Electrodermal responses to sensory stimuli in individuals with fragile X syndrome: A preliminary report. *American Journal of Medical Genetics*, *83*, 268–279. doi:10.1002/(SICI)1096-8628(19990402)83:4<268::AID-AJMG7>3.0.CO;2-K

Moberg, P. J., Kamath, V., Marchetto, D. M., Calkins, M. E., Doty, R. L., Hahn, C. G., … Turetsky, R. I. (2014). Meta-analysis of olfactory function in schizophrenia, first-degree family members, and youths at-risk for psychosis. *Schizophrenia Bulletin*, *40*(1), 50–59. doi:10.1093/schbul/sbt049

Modahl, C., Green, L. A., Fein, D., Morris, M., Waterhouse, L., Feinstein, C., & Levin, H. (1998). Plasma oxytocin levels in autistic children. *Biological Psychiatry*, *43*, 270–277. doi:10.1016/S0006-3223(97)00439-3

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G., The PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7), e1000097. doi:10.1371/journal.pmed.1000097

Nadon, G., Ehrmann Feldman, D., Dunn, W., & Gisel, E. (2011, September 22). Association of sensory processing and eating problems in children with autism spectrum disorders. *Autism Research and Treatment*, *2011*, 541926.

Nass, R., Gross, A., & Devinsky, O. (1998). Autism and autistic epileptiform regression with occipital spikes. *Developmental Medicine & Child Neurology*, *40*, 453–458. doi:10.1111/j.1469-8749.1998.tb15395.x

Nordin, S., Millquist, E., Löwhagen, O., & Bende, M. (2002). The chemical sensitivity scale: Psychometric properties and comparison with the noise sensitivity scale. *Journal of Environmental Psychology*, *23*, 359–367. doi:10.1016/S0272-4944(03)00002-1

Oberg, C., Larsson, M., & Backman, L. (2002). Differential sex effects in olfactory functioning: The role of verbal processing. *Journal of the International Neuropsychological Society*, *8*, 691–698. doi:10.1017/S1355617702801424

Owen, J. P., Ziv, E., Bukshpun, P., Pojman, N., Wakahiro, M., Berman, J. I., … Mukherjee, P. (2013). Test-retest reliability of computational network measurements derived from the structural connectome of the human brain. *Brain Connectivity*, *3*(2), 160–176.

Pierce, K., Muller, R. A., Ambrose, J., Allen, G., & Courchesne, E. (2001). Face processing occurs outside the fusiform "face area" in autism: Evidence from functional MRI. *Brain*, *124*, 2059–2073.

Pinto, J. M., Wroblewski, K. E., Kern, D. W., Schumm, L. P., & McClintock, M. K. (2014). Olfactory dysfunction predicts 5-year mortality in older adults. *PLoS One*, *9*(10), e107541.

Price, J. L., Slotnick, B. M., & Revial, M. F. (1991). Olfactory projections to the hypothalamus. *Journal of Comparative Neurology*, *306*, 447–461.

Rogers, S. J., Hepburn, S., & Wehner, E. (2003). Parent reports of sensory symptoms in toddlers with autism and those with other developmental disorders. *Journal of Autism and Developmental Disorders*, *33*(6), 631–642.

Rozenkrantz, L., Zachor, D., Heller, I., Plotkin, A., Weissbrod, A., Snitz, K., … Sobel, N. (2015). A mechanistic link between olfaction and autism spectrum disorder. *Current Biology*. doi:10.1016/j.cub.2015.05.048

Schecklmann, M., Schwenck, C., Taurines, R., Freitag, C., Warnke, A., Gerlach, M., & Romanos, M. (2013). A systematic review on olfaction in child and adolescent psychiatric disorders. *Journal of Neural Transmission*, *120*, 121–130.

Schreck, K. A., & Williams, K. (2006). Food preferences and factors influencing food selectivity for children with autism spectrum disorders. *Research in Developmental Disabilities*, *27*, 353–363.

Shipley, M. T., & Ennis, M. (1996). Functional organization of olfactory system. *Journal of Neurobiology*, *30*, 123–176.

Silk, T. J., Rinehart, N., Bradshaw, J. L., Tonge, B., Egan, G., O'Boyle, M. W., & Cunnington, R. (2006). Visuospatial processing and the function of prefrontal-parietal networks in autism spectrum disorders: A functional MRI study. *American Journal of Psychiatry*, *163*, 1440–1443.

Simmen, D., Briner, H. R., & Hess, K. (1999). Screening of olfaction with smell diskettes. *Laryngorhinootologie*, *78*(3), 125–130.

Smeets, M. A., & Dalton, P. (2005). Evaluating the human response to chemicals: Odor, irritation and non-sensory factors. *Environmental Toxicology and Pharmacology*, *19*(3), 581–588.

Smith, A. M., Roux, S., Naidoo, N. T., & Venter, D. J. L. (2005). Food choices of tactile defensive children. *Nutrition*, *21*, 14–19.

Sokolowski, K., & Corbin, J. G. (2012). Wired for behaviors: From development to function of innate limbic system circuitry. *Frontiers in Molecular Neuroscience*, *5*, 55.

Stanfield, A. C., McIntosh, A. M., Spencer, M. D., Philip, R., Gaur, S., & Lawrie, S. M. (2008). Towards a neuroanatomy of autism: A systematic review and meta-analysis of structural magnetic resonance imaging studies. *European Psychiatry*, *23*, 289–299.

Strauss, G. P., Keller, W. R., Koenig, J. I., Gold, J. M., Ossenfort, K. L., & Buchanan, R. W. (2015). Plasma oxytocin levels predict olfactory identification and negative symptoms in individuals with schizophrenia. *Schizophrenia Research*, *162*(1–3), 57–61.

Suzuki, Y., Critchley, H. D., Rowe, A., Howlin, P., & Murphy, D. G. M. (2003). Impaired olfactory identification in Asperger's syndrome. *The Journal of Neuropsychiatry & Clinical Neurosciences*, *15*(1), 105–107.

Tabert, M. H., Steffener, J., Albers, M. W., Kern, D. W., Michael, M., Tang, H., … Devanand, D. P. (2007). Validation and optimization of statistical approaches for modelling odorant-induced fMRI signal changes in olfactory-related brain areas. *Neuroimage*, *34*, 1375–1390.

Tanabe, T., Iino, M., & Takagi, S. F. (1975). Discrimination of odors in olfactory bulb, pyriform-amygdaloid areas and orbitofrontal cortex of the monkey. *Journal of Neurophysiology*, *38*, 1284–1296.

Tavassoli, T., & Baron-Cohen, S. (2012). Olfactory detection thresholds and adaptation in adults with autism spectrum condition. *Journal of Autism and Developmental Disorders*, *42*, 905–909.

Tavassoli, T., Miller, L. J., Schoen, S. A., Nielsen, D. M., & Baron-Cohen, S. (2014). Sensory over-responsivity in adults with autism spectrum conditions. *Autism*, *18*, 428.

Toledano, A., Borromeo, S., Luna, G., Molina, E., Solana, A. B., García-Polo, P., … Álvarez-linera, J. (2012). Objective assessment of olfactory function using functional magnetic resonance imaging. *Acta Otorrinolaringológica Española*, *63*(4), 280–285.

Tourbier, I. A., & Doty, R. L. (2007). Sniff magnitude test: Relationship to odor identification, detection, and memory tests in a clinic population. *Chemical Senses*, *32*(6), 515–523.

Toyota, B., Kitamura, T., & Takagi, S. F. (1978). *Olfactory disorders – Olfactometry and therapy.* Tokyo, Japan: Igaku-Shoin.

Turetsky, B. I., Moberg, P. J., Yousem, D. M., Doty, R. L., Arnold, S. E., & Gur, R. E. (2000). Reduced olfactory bulb volume in patients with schizophrenia. *American Journal of Psychiatry*, *157*, 828–830.

Wang, J., Eslinger, P. J., Smith, M. B., & Yang, Q. X. (2005). Functional magnetic resonance imaging study of human olfaction and normal aging. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *60*(4), 510–514.

Watson, L. R., Patten, E., Baranek, G. T., Poe, M., Boyd, B., Freuler, A., & Lorenzi, J. (2011). Differential associations between sensory response patterns and language, social, and communication measures in children with autism or other developmental disabilities. *Journal of Speech Language and Hearing Research*, *54*, 1562–1576.

Wiggins, L. D., Robins, D. L., Bakeman, R., & Adamson, L. B. (2009). Breif report: Sensory abnormalities as distinguishing symptoms of autism spectrum disorders in young children. *Journal of Autism and Developmental Disorders*, *39*, 1087–1091.

Wilder, D. A., Schadler, J., Higbee, T. S., Haymes, L. K., Bajagic, V., & Register, M. (2008). Identification of olfactory stimulus as reinforcers in individuals with autism: A preliminary investigation. *Behavioral Interventions*, *23*, 97–103.

Woodard, C. R., Goodwin, M. S., Zelazo, P. R., Aube, D., Scrimgeour, M., Ostholthoff, T., & Brickley, M. (2012). A comparison of autonomic, behavioral, and parent-report measures of sensory sensitivity in young children with autism. *Research in Autism Spectrum Disorders*, *6*, 1234–1246.

Woodbury-Smith, M., Robinson, J., & Baron-Cohen, S. (2005). Screening adults for Asperger syndrome using the AQ: Diagnostic validity in clinical practice. *Journal of Autism and Developmental Disorders*, *35*, 331–335.

Woolley, J. D., Lam, O., Chuang, B., Ford, J. M., Mathalon, D. H., & Vinogradov, S. (2015). Oxytocin administration selectively improves olfactory detection thresholds for lyral in patients with schizophrenia. *Psychoneuroendocrinology*, *53*, 217–222.

Zatorre, R. J., & Jones-Gotman, M. (1991). Human olfactory discrimination after unilateral frontal or temporal lobectomy. *Brain*, *114*, 71–84.