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ORIGINAL PAPER

Behavioral Phenotype of ASD Preschoolers with Gastrointestinal Symptoms or Food Selectivity

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Abstract This study investigated the prevalence and type of gastrointestinal (GI) and food selectivity (FS) symptoms in 163 preschoolers with ASD, and their possible links with core ASD features and emotional/behavioural problems. 40.5% of children with ASD had at least one severe GI symptom or FS. Preschoolers with and without GI symptoms and with and without FS were significantly different on several emotional/behavioural problems and restrictive/repetitive behaviours, whereas they did not differ significantly on performance IQ and autistic severity. The GI plus FS group presented with Sleep Problems, Self-injurious Behaviors and Anxiety Problems. Results indicated the need for early identification of GI disturbances and FS in order to design tailored intervention for these symptoms frequently associated to challenging behaviours in ASD.

Keywords Young Children · Child Behavior Checklist 1½–5 · Restrictive and repetitive behaviours · Externalizing Problems · Anxiety Problems · Sleep Problems

Introduction

Autism Spectrum Disorders (ASD) are neurodevelopmental disorders characterized by persistent social communication difficulties as well as restricted interests, repetitive activities and sensory abnormalities (APA 2013). The clinical presentation of ASD may vary widely in terms of severity of core features as well as psychiatric and medical comorbidities (Kohane et al. 2012; Matson and Williams 2013). Among these latter, food selectivity (FS) and functional gastrointestinal (GI) symptoms

Results from this study will be presented as a poster at the upcoming IMFAR 2017—International Meeting for Autism Research, San Francisco (USA).

Margherita Prosperi and Elisa Santocchi have contributed equally to this work.

This paper is based on an earlier study (Fulceri et al. 2016a): a new cohort of patients with ASD was evaluated in the current study.

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have been reported in ASD individuals with prevalence rates of 46–89% (Johnson et al. 2014), and of 9–91% (Matson and Fodstad 2009) respectively.

The wide variability in these symptoms could be ascribed to several reasons. Specifically, it could depend on the different types of methods used to gather and assess symptoms, or on the type of study's design, or on the different characteristics of the study sample (e.g., age, gender, core ASD symptoms, IQ). It is not surprising that studies relating to a limited number of more strictly defined FS/GI symptoms, in which the medical records were used as a data source or where the time period considered was more limited, have revealed a lower prevalence of FS/GI symptoms (Black et al. 2002; Molloy and Manning-Courtney 2003; Nikolov et al. 2009). Conversely, studies including less strictly defined FS/GI symptoms, collecting data only from parental reports and for longer time period (Goodwin et al. 1971; Horvath and Perman 2002a; Parracho et al. 2005; Valicenti-McDermott et al. 2006) usually reported a significantly higher prevalence than in former types of investigation.

In particular, studies exploring the type of GI symptoms in pediatric ASD samples (birth to 18 years of age) reported that the most common are: chronic constipation (from 8.9%—Taylor et al. 2002—to 44.8%—Parracho et al. 2005), chronic diarrhea (from 3.1%—Fombonne and Chakrabarti 2001—to 75.6%—Parracho et al. 2005), chronic abdominal pain (from 2%—Molloy and Manning-Courtney 2003—to 46.6%—Parracho et al. 2005), gastro-esophageal reflux (from 7%—Molloy and Manning-Courtney 2003—to 19%—Ming et al. 2008). The investigations that have tried to determine whether GI symptoms are associated to behavioral problems in ASD individuals have reported a greater severity of problematic behaviors as irritability (Bresnahan et al. 2015), anxiety and affective disorders (Valicenti-McDermott et al. 2006; Fulceri et al. 2016a), dysregulation and externalizing problems (Horvath and Perman 2002a), rigid/compulsive behaviors (Peters et al. 2014; Marler et al. 2017), increased sensory sensitivity (Mazurek et al. 2013), and sleep problems (Horvath and Perman 2002b; Maenner et al. 2012) in children with ASD and concurrent GI symptoms compared to ASD peers without GI symptoms. Abdominal pain, constipation or diarrhea are unpleasant and could be associated with impairment in attention and concentration, self-damaging acts, and agitation especially in children who are not able to communicate their discomfort (Horvath and Perman 2002b; Buie et al. 2010b; Adams et al. 2011; Kral et al. 2013; Fulceri et al. 2016a). According to this view, the consensus report for evaluation, diagnosis and treatment of GI disorders in individuals with ASD (Buie et al. 2010a) recommends to investigate all behaviors (verbal or motor) that might indicate the presence of a GI symptomatology, especially in those ASD individuals who are unable to communicate effectively their discomfort. For example, symptoms and signs such as sobbing 'for no reason at all', delayed echolalia that includes reference to pain or stomach, facial grimacing, unusual posturing, unexplained increase in repetitive behaviors, self-injuring behaviors, aggression, sleep disturbances, increased irritability and oppositional behaviors are all cited as behaviors that may be markers of abdominal pain (Buie et al. 2010a). In keeping with these data, two studies (Nikolov et al. 2009; Chaidez et al. 2014) that used the 'Aberrant Behavior Checklist' (Aman et al. 1985) to evaluate the severity of a range of problem behaviors found significantly more maladaptive symptoms (especially irritability and social withdrawal) in children with ASD and GI symptoms compared to ASD children without GI symptoms.

As far as the association between GI symptoms and autism severity, some of the studies have shown a positive correlation (Adams et al. 2011; Wang et al. 2011; Gorrindo et al. 2012; Chaidez et al. 2014; Tomova et al. 2015), whereas others did not confirm it (Molloy and Manning-Courtney 2003; Chandler et al. 2013). For example, in a recent study on 8–18 year-olds high-functioning ASD individuals (Mazefsky et al. 2014), subjects who were suffering from GI symptoms did not significantly differ from those without GI symptoms as far as severity of autistic symptoms. This study is in line with results of a large population-based sample of 8 year-olds children with ASD where no association between the severity of repetitive behaviors (as an index of autism severity) and GI problems was detected (Maenner et al. 2012).

Feeding problems are approximately five times more frequent in children with ASD compared to typically developing (TD) peers (Sharp et al. 2013), and FS (i.e. only eating a narrow variety of foods) is frequently reported as a common component of feeding problems in this population (Field et al. 2003; Bandini et al. 2010; Ledford and Gast 2006). There is evidence that low dietary diversity in ASD may increase the risk of nutritional issues, including vitamin and mineral deficiencies (Bandini et al. 2010; Zimmer et al. 2012), and poor bone growth (Hediger et al. 2008). Furthermore, it has been demonstrated a correlation between feeding/mealtime difficulties and problematic behaviors in children with ASD (e.g. repetitive behaviors, sensory difficulties, externalizing and internalizing behavioral problems, sleep problems) (Johnson et al. 2014; Allen et al. 2015), as well as significantly higher rates of emotional and behavioral problems in ASD children with FS as compared to ASD children without FS (Postorino et al. 2015). In addition, the negative impact of FS on family stress (Curtin et al. 2015)

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and its persistence over time in about half of the children with ASD (Bandini et al. 2017) have been recently reported. Despite this, in a study where autistic symptoms in children with ASD were evaluated with ADOS-G (Lord et al. 2000) and ADI-R (Le Couteur et al. 2003), no significant differences were registered between groups with or without feeding problems (Postorino et al. 2015).

Moreover, some investigations on the possible relationship between FS and GI symptoms have observed that FS may contribute to GI problems at least in a proportion of individuals with ASD (Gorrindo et al. 2012; Chaidez et al. 2014; Mazefsky et al. 2014; Postorino et al. 2015; Sharp et al. 2013): in particular, selective eating patterns may explain increased rates of constipation among children with ASD (Ibrahim et al. 2009).

Some previous investigations on ASD and FS/GI problems assume a diagnosis of ASD based on record review or data review (Bresnahan et al. 2015; Horvath and Perman 2002a; Kang et al. 2014; Maenner et al. 2012; Valicenti-McDermott et al. 2006). Thus, studies applying the reference standard for evaluation and diagnosis (i.e. Autism Diagnostic Observation Schedule—ADOS) are warranted.

In the current study, we aim to investigate the following issues: first, the prevalence and type of GI and FS problems in rigorously evaluated preschoolers with ASD (using the ADOS); second, the possible links between the presence of these symptoms and ASD severity, cognitive development, repetitive/stereotyped behaviors, internalizing and externalizing behavioral problems. Finally, we explore the existence of specific ASD clinical phenotypes for children with isolated GI symptoms, FS or both.

Methods

Participants

A total of 163 preschoolers with ASD (see Table 1 for a complete description of the sample) were included in the study, comprising 137 males and 26 females (mean age [SD] = 43.16 [13.85] months; range 20–71 months). Children were recruited from November 2009 to June 2016 at a tertiary care university hospital. The inclusion criteria for the patients were as follows: (1) a clinical diagnosis of Autistic Disorder, Asperger's Disorder, or Pervasive Developmental Disorder-Not Otherwise Specified based on DSM-IV-TR criteria or of Autism Spectrum Disorders based on the DSM-5 criteria. The diagnosis was performed by a multidisciplinary team including a senior child psychiatrist and an experienced clinically trained research child psychologist during a 5–8 days of extensive evaluation and it was confirmed by the ADOS administered by research reliable evaluators (E.S., A.N., F.A., R.I.) for $n = 155$ children; (2) age-range: 18–72 months. The exclusion criteria were: (1) secondary causes of ASD or conditions to consider in the differential diagnosis of ASD (e.g. deafness). These disorders were ruled-out through paediatric and neurological examinations, audiometry, high-resolution karyotyping or array comparative genomic hybridization (aCGH), DNA analysis of FRA-X and screening tests for inborn errors of metabolism; (2) thyroid hormone disorders—implicated in intellectual disability (Bunevicius 2009) and ASD (Frye et al. 2017)—through the evaluation of TSH, FT4 and FT3 in a blood sample; (3) Coeliac Disease (CD). This was ruled-out with serological screening (determination of the titres of Anti-Gliadin—AGA—IgA and IgG, Anti-Transglutaminase—anti tTG—IgA, and Anti-Endomysium—EMA—IgA antibodies) in order to exclude a possible organic cause of GI symptoms, given also the recent evidence of an increased prevalence of CD in subjects with ASD as compared to children with typical development (Calderoni et al. 2016); (4) gluten-free diet; (5) therapy with drugs for GI symptoms; (6) psychotropic medication.

The current study was carried out according to the standards for good ethical practice of the university hospital, and in accordance with the guidelines of the Declaration of Helsinki. Written informed consent from a parent/guardian of each participant was obtained.

Table 1 Demographic and clinical characteristics of participants with ASD

Characteristic	ASD ($n = 163$)
Male, *n* (%)	137 (84.05%)
Female, *n* (%)	26 (15.95%)
Mean age in months (*SD*)	43.16 (±13.85)
Age range (months)	20–71
GI+ (at least one out of the 6 GI symptoms scored as 2)	42 (25.8%)
FS+ (item 24 of CBCL "doesn't eat well" scored as 2)	44 (27.0%)
GI+ plus FS+ (at least one out of the 6 GI and/or item 24 of CBCL scored as 2)	66 (40.5%)
GI mean score	1.26
FS mean score	0.87
Item 12 of CBCL: Constipated, doesn't move bowels	36 (22.1%)
Item 19 of CBCL: Diarrhea or loose bowels	4 (2.5%)
Item 45 of CBCL: Nausea, feel sick	1 (0.6%)
Item 52 of CBCL: Painful bowel movements	12 (7.4%)
Item 78 of CBCL: Stomachaches or cramps	2 (1.2%)
Item 93 of CBCL: Vomiting, throwing up	1 (0.6%)

ASD autism spectrum disorders, *n* number of subjects, *SD* standard deviation, *GI* gastrointestinal, *FS* food selectivity, *CBCL* Child Behaviour Checklist

Procedure

The following instruments were administered as part of a comprehensive multidisciplinary assessment.

Child Behavior Checklist 1½–5

The Italian version of the Child Behavior Checklist (CBCL 1½–5; Achenbach and Rescorla 2000) is one of the most widely used checklist consisting of 100 statements about the child's behaviors filled by parents and rated on a three-point Likert scale (0, not true; 1, somewhat or sometimes true; 2, very true or often true). The CBCL provides seven syndrome scales scores (i.e., Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Aggressive Behavior, Attention Problems and Sleep Problems), three summary scales scores (i.e., Internalizing, Externalizing and Total Problems), five DSM-oriented scales [i.e., Affective Problems, Anxiety Problems, Pervasive Developmental Disorder Problems (PDP), Attention Deficit Hyperactivity Disorder (ADHD) Problems, and Oppositional Defiant Problems (ODP)]. A T-score of 63 and above for summary scales, and a T-score of 70 and above for syndrome and DSM-oriented scales, are generally considered clinically significant. We also used an additional CBCL profile called 'dysregulation profile' (Althoff et al. 2010), that is the summary of the scores of three syndromic scales (Anxious/Depressed, Attention Problems, and Aggressive Behavior).

In order to explore GI symptoms, we used, among the 100 statements, six specific items that explore the GI function and one item regarding FS: they are all part of the CBCL 1½–5 'Somatic Complaints' syndrome scale. The six GI items are: item 12: Constipated, doesn't move bowels; item 19: Diarrhea or loose bowels; item 45: Nausea, feels sick; item 52: Painful bowel movements; item 78: Stomachaches or cramps; item 93: Vomiting, throwing up. For all these items it is specified that they occur without any medical cause or during any other medical illness. A total GI score ranging from 0 to 12 can be obtained. Children were defined as suffering from GI symptoms when at least one out of the six items was scored as '2', i.e., 'very or often true'. Thus, the following two groups were identified: ASD GI+: composed of ASD children with at least one GI symptom rated as '2'; ASD GI−: composed of ASD children without any GI symptom rated as '2'.

Food selectivity is considered in the item 24 ('Doesn't eat well') in which parents are invited to write a specification of the selective behavior. Children were defined as suffering from food selectivity only when this item was scored as '2', i.e., 'very or often true' and parents specified the type of food selectivity.

Since these seven items contribute to the scores of other syndrome, summary and DSM-oriented scales, we calculated the scores of all the CBCL 1½–5 scales after zeroing the scores of the seven items to obtain CBCL scores that are not corrupted by the presence of these symptoms.

Autism Diagnostic Observation Schedule (ADOS) is the reference standard semi-structured examiner rated measure for child observation and assessment of skills in communication, social interaction, quality of play and imagination. It consists of standardised activities that allow the examiner to observe the occurrence of behaviors that have been identified as being important to the diagnosis of ASD. In this study, the ADOS-G (Lord et al. 2000) in the 2009–2014 period and the ADOS-2 (Lord et al. 2012a, b) in the 2015–2016 period were used. According to a recently published algorithm (Gotham et al. 2009), the Calibrated Severity Score (CSS) was obtained for each participant based on ADOS raw scores. The ADOS CSS ranges 1–10 and allows comparing different versions and modules of ADOS. Moreover, the ADOS CSS provides a measure of autism symptoms that is independent of age and language ability and thus is better suited, than the usual ADOS scores, for assessing the severity of ASD (Shumway et al. 2012). Eight children were not able to complete the ADOS evaluation for a total lack of collaboration.

Repetitive Behavior Scale-Revised (RBS-R; Lam and Aman 2007) is a questionnaire that provides a detailed assessment of restricted repetitive and stereotyped patterns of behavior, interests, and activities. It was recently applied in Italian preschoolers with ASD (Fulceri et al. 2016b). Items are rated on a four-point Likert scale (ranging from 0 = behavior does not occur to 3 = behavior occurs often and is a severe problem) and grouped into six subscales: (1) Stereotyped Behavior; (2) Self-Injurious Behavior; (3) Compulsive Behavior; (4) Ritualistic Behavior; (5) Sameness Behavior; and (6) Restricted Interests Behaviors. Two raw scores can be calculated for each subscale: one based on the summed item scores within each subscale, named 'Score', and one based on the number of items endorsed (i.e. number of items with non-zero score), named 'Endorsement'. Total Score (the sum of all Subscales-Scores), Total Number-Endorsed Score (the sum of all Number-Endorsed–Subscale-Scores), Global Rating Score (the judgment of the parents as to how the RRB affect the child's life summarized in a score that ranges from 1 to 100) were calculated. A two-factor solution scoring of RBS-R was also adopted for this study (Georgiades et al. 2010; Mirenda et al. 2010). Specifically, in this kind of solution scoring, a Low-Level Index (composed of items pertaining to Stereotyped, and Self-Injurious subscales) and a High-Level Index (composed of items related to Compulsive, Ritualistic, Sameness and Restricted Interests Behaviors subscales) were evaluated.

Cognitive Assessment

A number of standardised tests were used to assess intellectual abilities due to differences in the verbal skills and functioning level of children. These included: the Leiter International Performance Scale-Revised (LIPS-R; Roid and Miller 1997), the Griffiths Mental Developmental Scales-Extended-Revised (GMDS-ER; Luiz and Knoesen 2006), and the Italian version of Wechsler Preschool and Primary Scale of Intelligence (WPPSI; Wechsler 1989). When the tool provides a mental age (MA), IQ was estimated dividing MA by the child's chronological age (CA): ([MA/CA] × 100). For this study, we consider the non-verbal IQ scores (performance IQ). A total of 105 ASD children were able to complete the cognitive evaluation.

Data Analysis

We used Student's *t*-test to compare children with and without GI symptoms, constipation, or FS on the score obtained on ADOS, Performance IQ, RBS-R, and CBCL. In case of statistically significant differences ($p < 0.05$), Cohen's d was computed, as an estimate of effect size (Cohen 1988) and it was evaluated as negligible ($d < 0.20$), small ($0.20 \leq d < 0.50$), medium ($0.50 \leq d < 0.80$), or large ($d \geq 0.80$). To strengthen results only differences with a medium or large effect size were considered. We used the Kruskal Wallis test to identify the clinical profiles of three groups identified on the basis of the presence of isolated or combined constipation and FS (followed by Mann–Whitney test to compare the couple of groups). Cohen's r was computed as effect size and it was evaluated as negligible ($r < .10$), small ($0.10 \leq r < .30$), medium ($0.30 \leq r < .50$), or large ($r \geq .50$). In this case, because the numerousness of samples was low, we considered all the differences with exact significance < 0.05 and with a medium or large effect size as relevant.

We used Pearson correlation analyses to investigate in the total sample the mutual influence between the GI and FS scores and the scores obtained on ADOS, standardized performance IQ tests, CBCL scales, and RBS-R. Effect size (two-tailed significance) was evaluated as trivial (<0.10), small (0.10–0.29), medium (0.30–0.49), large (0.50–0.69), and very large (≥0.70) in accordance with a recent study (Cicchetti et al. 2011).

SPSS19 software was used for data analyses.

Preliminary Analyses

Out of the total sample of 163 patients, 58 subjects could not be assessed with psychometric scales; these patients were significantly younger (36.48 ± 11.27 vs 46.84 ± 13.81 months; $p < 0.0001$; Cohen's $d = 0.80$), with a higher score at both ADOS CSS (7.49 ± 1.77 vs 6.13 ± 1.61; $p < 0.0001$; Cohen's $d = 0.82$) and at CBCL Pervasive Developmental Problems (71.34 ± 8.53 vs 66.33 ± 9.24; $p = 0.001$; Cohen's $d = 0.56$)—compared to children who could be assessed with psychometric scales. All differences were large except for PDP scale, which had a medium-sized effect.

We have verified if the aforementioned not evaluable children were different from the evaluable children also for GI and/or FS symptoms. Results indicated that the two groups did not significantly differ from each other as far as the number of subjects with GI symptoms ($p = 0.16$), food selectivity ($p = 0.07$), and the mean score of six GI symptoms ($p = 0.85$) are concerned. Thus, since a possible bias derived from a different distribution of children suffering from GI and FS in evaluable and not evaluable children has been ruled out, we have performed all the analyses considering the sample of 163 children as a whole.

Results

Prevalence and Type of GI and FS Symptoms in the Total Sample

25.8% of children with ASD had at least one severe GI symptom. The GI mean score was 1.26. The most scored GI symptoms were 'Constipated' (22.1%) and 'Painful Bowel Movement' (7.4%). FS was rated in the 27.0% of our participants. The mean score for food selectivity was 0.87. The 40.5% of children with ASD had at least one severe GI symptom or FS, and in many cases (12.27%) they are associated (see Table 1).

Behavioral Differences Between Children With and Without GI Symptoms

No significant differences were found as for as age, gender, performance IQ, and ADOS calibrated severity score (CSS). The two groups were significantly different for some CBCL scales. In particular, scores on Total Problems (63.60 ± 10.43 vs 56.21 ± 9.84; $p < 0.0001$; Cohen's $d = 0.74$), Externalizing Problems (57.69 ± 8.64 vs 53.43 ± 8.46; $p = 0.006$; Cohen's $d = 0.50$), Affective Problems (60.00 ± 9.66 vs 55.40 ± 6.93; $p = 0.001$; Cohen's $d = 0.60$), Sleep Problems (59.14 ± 10.50 vs 54.65 ± 5.86; $p = 0.001$; Cohen's $d = 0.62$) and on Dysregulation Profile (179.88 ± 18.17 vs 171.52 ± 16.23; $p = 0.006$; Cohen's $d = 0.50$) were significantly higher in ASD children with GI symptoms than in ASD children without GI symptoms; a medium effect size was found for all these scales.

On the RBS-R, a significant difference with a medium effect size was found on Stereotyped Behaviors (Endorsement $p = 0.005$ Cohen's $d = 0.52$). Other differences on

Table 2 ASD children GI+ versus ASD children GI−: clinical differences

Variables	ASD GI+ ($n=42$) Mean ± *SD*	ASD GI− ($n=121$) Mean ± *SD*	Student *t* test (*t* value)	Cohen's *d*
ADOS CSS	7.12 ± 1.71	6.39 ± 1.77	2.30*	0.42
CBCL syndrome scales				
Emotionally Reactive	59.86 ± 10.56	56.56 ± 8.15	2.08*	0.38
Anxious/Depressed	58.41 ± 7.87	55.90 ± 6.74	1.98*	0.36
Somatic Complaints	51.33 ± 2.49	50.81 ± 2.53	1.16	
Withdrawn	71.74 ± 10.03	68.83 ± 10.02	1.62	
Sleep Problems	59.14 ± 10.50	54.65 ± 5.86	3.43***	0.62
Attention Problems	64.69 ± 7.61	61.58 ± 8.19	2.16*	0.39
Aggressive Problems	56.79 ± 6.31	54.04 ± 5.50	2.68**	0.48
CBCL Summary Scales				
Internalizing Problems	60.98 ± 8.92	57.01 ± 8.97	2.47*	0.45
Externalizing Problems	57.69 ± 8.64	53.43 ± 8.46	2.80**	0.50
Total Problems	63.60 ± 10.43	56.21 ± 9.84	4.13***	0.74
CBCL DSM-IV Oriented Scales				
Affective Problems	60.00 ± 9.66	55.40 ± 6.93	3.33***	0.60
Anxiety Problems	58.71 ± 9.26	55.45 ± 6.88	2.42*	0.43
PDP	69.86 ± 8.68	67.51 ± 9.44	1.41	
ADHD	59.57 ± 7.83	57.25 ± 6.75	1.84	
ODP	55.95 ± 6.14	53.84 ± 5.55	2.07*	0.37
CBCL Dysregulation Profile	179.88 ± 18.17	171.52 ± 16.23	2.79**	0.50
Repetitive Behaviour Scale-Revised				
Stereotyped behaviors				
Score	7.50 ± 4.68	5.88 ± 4.91	1.86	
Endorsement	4.91 ± 2.23	3.69 ± 2.43	2.84**	0.52
Self-injurious behaviors				
Score	1.93 ± 2.91	1.37 ± 2.49	1.19	
Endorsement	1.52 ± 1.88	0.97 ± 1.38	2.05*	0.36
Compulsive behaviors				
Score	2.33 ± 2.70	2.21 ± 2.93	0.25	
Endorsement	1.69 ± 1.60	1.39 ± 1.55	1.08	
Ritualistic/sameness behaviors				
Score	5.76 ± 6.56	4.3 ± 5.21	1.46	
Endorsement	3.71 ± 3.16	2.92 ± 2.82	1.53	
Restricted interest behaviors				
Score	2.76 ± 2.74	1.95 ± 2.01	2.04*	0.37
Endorsement	1.52 ± 1.11	1.19 ± 1.02	1.79	
Total behaviors				
Score	20.29 ± 15.61	15.72 ± 13.41	1.82	
Endorsement	13.36 ± 7.47	10.16 ± 6.90	2.54*	0.46
High level	10.88 ± 10.51	8.46 ± 8.66	1.49	
Low level	9.43 ± 6.64	7.26 ± 6.55	1.85	
Parents' Global Impression	43.32 ± 26.58	37.05 ± 28.59	1.08	

GI+: ASD subjects with at least one out of the six GI symptoms scored at the CBCL as '2-very true'

GI−: ASD subjects without GI symptoms scored as '2'

n number of subjects, *SD* standard deviation, *ASD* autism spectrum disorders, *GI* gastrointestinal, *CBCL* Child Behaviour Checklist, *DSM-IV* Diagnostic and statistical manual of mental disorders Fourth Edition, *ADOS CSS* Autism Diagnostic Observation Schedule calibrated severity score, *DSM-IV* Diagnostic and statistical manual of mental disorders Fourth Edition, *PDP* Pervasive Developmental Problems scale, *ADHD* Attention Deficit and Hyperactivity Disorders scale, *ODP* Oppositional Defiant Problems scale, *ns* not significant

*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001

ADOS CSS, on CBCL and on RBS-R at a $p < 0.05$ with a small effect size are listed in Table 2.

Behavioral Differences Between Children With and Without FS

No significant differences were found as for as age, gender, performance IQ, and ADOS severity score between children with or without FS. ASD children with FS showed significantly higher scores with a medium effect size on Emotionally Reactive ($p = 0.001$ Cohen's $d = 0.60$), Sleep Problems ($p = 0.002$ Cohen's $d = 0.57$), Attention Problems ($p = 0.002$ Cohen's $d = 0.57$), Aggressive Problems ($p < 0.001$ Cohen's $d = 0.66$), Externalizing Problems ($p < 0.001$ Cohen's $d = 0.64$), Total Problems ($p < 0.001$ Cohen's $d = 0.81$), Anxiety Problems ($p < 0.001$ Cohen's $d = 0.65$), Attention Deficit Hyperactivity Disorder Problems ($p = 0.001$ Cohen's $d = 0.59$), Oppositional Defiant Problems ($p < 0.001$ Cohen's $d = 0.72$), and Dysregulation Profile ($p = 0.001$ Cohen's $d = 0.67$). The difference in Total Problems scale had a large effect size ($p < 0.001$ Cohen's $d = 0.81$). At the RBS-R, FS children showed significantly more Stereotyped Behaviors (score: $p = 0.003$ Cohen's $d = 0.54$), Ritualistic/Sameness Behaviors (score: $p = 0.002$ Cohen's $d = 0.55$), Restricted Interest Behaviors (score: $p = 0.003$ Cohen's $d = 0.53$) and Total Behaviors (score: $p = 0.001$ Cohen's $d = 0.58$), all differences with a medium effect size (see Table 3).

Correlations Between GI Items or FS Item and Clinical Variables

No correlation between GI items or FS item and ADOS CSS or performance IQ was detected.

GI and FS scores were positively correlated with the scores in various domains of the CBCL. In particular, as far as GI score is concerned, we observed a medium effect size in Emotionally Reactive (Pearson's r = .32), Sleep Problems (Pearson's r = .38), Aggressive Problems (Pearson's r = .36), Internalizing Problems (Pearson's r = .35), Externalizing Problems (Pearson's r = .33), Total Problems (Pearson's r = .48), Affective Problems (Pearson's r = .47), Anxiety Problems (Pearson's r = .33), ODP (Pearson's r = .30), Dysregulation Profile (Pearson's r = .35). As far as FS score is concerned, we observed a medium effect size only for some CBCL scales: Aggressive Problems (Pearson's $r = .30$), Externalizing Problems (Pearson's $r = .31$), Total Problems (Pearson's $r = .38$), Anxiety Problems (Pearson's $r = .30$), ADHD (Pearson's $r = .30$), ODP (Pearson's $r = .31$), Dysregulation Profile (Pearson's $r = .31$).

GI score was correlated with some RBS-R scores and precisely Stereotyped behaviors score (Pearson's r = .30), Stereotyped behaviors endorsement (Pearson's r = .36), Total behaviors endorsement (Pearson's r = .32), and Low Level (Pearson's r = .30) (see Table 4).

Behavioral Differences in Children with Constipation and/or FS

First, we have analyzed constipated (n = 36) versus non-constipated (n = 127) children. Significant differences are maintained between children with and without Constipation as far as higher scores on Total Problems ($p < 0.01$) and Aggressive Problems ($p < 0.05$) with a medium effect size (Cohen's $d = 0.59$ and 0.55 respectively). Other differences at a $p < 0.05$ with a small effect size are reported on Table 5.

Then, we analyzed behavioral and clinical differences in children with isolated or combined constipation and food selectivity. Three subgroups were formed:

1. 'Constipated': 11 children with significant constipation in absence of other relevant GI symptoms or FS. Mean age: 37.4 ± 8.37 months.
2. 'Food selectivity': 24 children with significant FS in absence of constipation and other relevant GI symptoms. Mean age: 46.6 ± 17.08 months.
3. 'Food selectivity + Constipation': 12 children with constipation and significant FS in absence of other relevant GI symptoms. Mean age: 43.7 ± 10.89 months.

Due to the small sample size of these subgroups, we accepted differences at a $p < 0.05$ and with a medium effect size as relevant. No significant differences were found as for as age, gender, performance IQ, and the ADOS-CSS among these three groups. In general, the 'FS plus GI' group reached higher mean scores on many CBCL scales with respect to the other two groups. Significant results are reported in Table 6. Scores on 'Sleep Problems' (CBCL) and 'Self-injurious Behaviors' (RBS-R) were significantly different in the comparison among the three groups. In particular, the 'Food selectivity + Constipation' group had significantly higher mean score on 'Sleep Problems' than 'Constipated' group ($p = 0.04$; $r = .43$) and on 'Self-injurious Behaviors' than 'Food selectivity' group ($p = 0.02$; $r = .41$; $p = 0.01$; $r = .45$). 'Food selectivity + Constipation' group also showed significantly higher scores in 'Anxiety Problems' scale than 'Constipated' group ($p = 0.04$; $r = .44$) (see Table 6 and Fig. 1).

Discussion

The present study used a cross-sectional design to examine the prevalence and the type of GI symptoms and FS in a carefully evaluated sample of preschoolers with ASD.

Table 3 Clinical differences between ASD individuals with and without FS

Variables	FS+ ($n=44$) Mean ± *SD*	FS− ($n=119$) Mean ± *SD*	Student *t* test (*t* value)	Cohen's *d*
ADOS CSS	6.55 ± 1.78	6.59 ± 1.79	−0.15	
CBCL syndrome scales				
Emotionally Reactive	61.20 ± 11.10	56.01 ± 7.54	3.41***	0.60
Anxious/Depressed	58.70 ± 8.25	55.75 ± 6.50	2.39*	0.42
Sleep Problems	58.84 ± 9.35	54.68 ± 6.48	3.20**	0.57
Attention Problems	65.66 ± 8.15	61.17 ± 7.82	3.22**	0.57
Aggressive Problems	57.43 ± 6.13	53.76 ± 5.41	3.71***	0.66
CBCL Summary Scales				
Internalizing Problems	61.11 ± 9.79	56.89 ± 8.59	2.68**	0.48
Externalizing Problems	58.41 ± 8.71	53.09 ± 8.25	3.60***	0.64
Total Problems	63.95 ± 10.93	55.95 ± 9.47	4.59***	0.81
CBCL DSM-IV Oriented Scales				
Affective Problems	59.30 ± 9.73	55.58 ± 6.97	2.70**	0.48
Anxiety Problems	59.77 ± 9.04	55.00 ± 6.69	3.66***	0.65
PDP	70.77 ± 9.50	67.13 ± 9.05	2.25*	0.40
ADHD	60.77 ± 7.91	56.76 ± 6.48	3.30***	0.59
ODP	57.25 ± 6.50	53.33 ± 5.10	4.04***	0.72
CBCL Dysregulation Profile	181.80 ± 19.20	170.83 ± 15.27	3.40***	0.67
Repetitive Behaviour Scale-Revised				
Stereotyped behaviors				
Score	8.18 ± 5.91	5.61 ± 4.27	3.06**	0.54
Endorsement	4.70 ± 2.64	3.75 ± 2.31	2.26*	0.40
Ritualistic/sameness behaviors				
Score	6.84 ± 7.06	3.87 ± 4.76	3.08**	0.55
Endorsement	4.07 ± 3.23	2.77 ± 2.73	2.56*	0.46
Restricted interest behaviors				
Score	3.00 ± 2.56	1.85 ± 2.03	2.98**	0.53
Endorsement	1.57 ± 1.04	1.17 ± 1.04	2.18*	0.39
Total behaviors				
Score	22.64 ± 16.84	14.77 ± 12.37	3.25***	0.58
Endorsement	13.41 ± 7.82	10.08 ± 6.72	2.68**	0.48
High level	12.48 ± 11.21	7.82 ± 8.03	2.93**	0.52
Low level	10.16 ± 8.02	6.95 ± 5.83	2.80**	0.50

FS+: ASD subjects with item 24 of CBCL (doesn't eat well) scored as '2-very true'

FS−: ASD subjects without item 24 of CBCL (doesn't eat well) scored as '2-very true'

FS food selectivity, *n* number of subjects, *SD* standard deviation, *ADOS CSS* Autism Diagnostic Observation Schedule calibrated severity score, *DSM-IV* Diagnostic and statistical manual of mental disorders Fourth Edition, *PDP* Pervasive Developmental Problems scale, *ADHD* Attention Deficit and Hyperactivity Disorders scale, *ODP* Oppositional Defiant Problems scale, *ns* not significant

*p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001

In addition, we explored whether GI symptoms and FS are related to certain clinical variables of the ASD sample (i.e. core ASD features and emotional/behavioral problems).

Prevalence of GI Symptoms and FS in ASD Children

The percentage of ASD children with GI symptoms and/or FS was high (40.5%). In particular, the rate of children with strictly defined GI symptoms was 25.8% and, among these subjects, we confirmed the higher prevalence of 'constipation' and of 'abdominal pain' already reported in literature (Horvath and Perman 2002b; Valicenti-McDermott et al. 2006; Buie et al. 2010b; Adams et al. 2011; Fulceri et al. 2016a). We also found a consistent percentage of children with FS (27.0%): this symptom was frequently associated to GI problems, suggesting a link between these

Table 4 Pearson's correlation coefficients between the GI an FS scores and clinical variables in the total sample

	Mean ± SD	GI score	FS score
ADOS CSS	6.56 ± 1.79	0.16	−0.03
Performance IQ	91.84 ± 21.71	−0.10	−0.04
CBCL syndrome scales			
Emotionally Reactive	57.41 ± 8.92	0.32*	0.25
Anxious/Depressed	56.55 ± 7.11	0.24	0.20
Somatic Complaints	50.94 ± 2.53	0.22	0.14
Withdrawn	69.58 ± 10.07	0.27*	0.18
Sleep Problems	55.80 ± 7.57	0.38*	0.26
Attention Problems	62.38 ± 8.14	0.27	0.27
Aggressive Problems	54.75 ± 5.83	0.36*	0.30*
CBCL Summary Scales			
Internalizing Problems	58.03 ± 9.10	0.35*	0.22
Externalizing Problems	54.53 ± 8.68	0.33*	0.31*
Total Problems	58.11 ± 10.48	0.48*	0.38*
CBCL DSM-IV Oriented Scales			
Affective Problems	56.58 ± 7.96	0.47*	0.25
Anxiety Problems	56.29 ± 7.67	0.33*	0.30*
PDP	68.12 ± 9.29	0.26	0.21
ADHD	57.85 ± 7.10	0.23	0.30*
ODP	54.39 ± 5.76	0.30*	0.31*
CBCL Dysregulation Profile	173.67 ± 17.09	0.35*	0.31*
Repetitive Behaviour Scale-Revised			
Stereotyped behaviors			
Score	6.30 ± 4.89	0.30*	0.25
Endorsement	4.01 ± 2.43	0.36*	0.22
Self-injurious behaviors			
Score	1.52 ± 2.61	0.20	0.17
Endorsement	1.11 ± 1.54	0.25	0.21
Compulsive behaviors			
Score	2.24 ± 2.86	0.07	0.17
Endorsement	1.47 ± 1.56	0.16	0.16
Ritualistic/sameness behaviors			
Score	4.67 ± 5.61	0.18	0.22
Endorsement	3.12 ± 2.92	0.22	0.19
Restricted interest behaviors			
Score	2.16 ± 2.24	0.17	0.16
Endorsement	1.28 ± 1.05	0.15	0.09
Total behaviors			
Score	16.90 ± 14.10	0.26	0.26
Endorsement	10.98 ± 7.17	0.32*	0.24
High level	9.08 ± 9.20	0.18	0.23
Low Level	7.82 ± 6.62	0.30*	0.25
Parents' Global Impression	38.56 ± 28.14	0.20	0.09

GI score: sum of the scores at 6 GI items of CBCL

FS score: score at item 24 of CBCL (doesn't eat well)

SD standard deviation, *GI* gastrointestinal, *FS* food selectivity, *CBCL* Child Behaviour Checklist, *DSM-IV* Diagnostic and statistical manual of mental disorders Fourth Edition, *ADOS CSS* Autism Diagnostic Observation Schedule calibrated severity score, *DSM-IV* Diagnostic and statistical manual of mental disorders Fourth Edition, *PDP* Pervasive Developmental Problems scale, *ADHD* Attention Deficit and Hyperactivity Disorders scale, *ODP* Oppositional Defiant Problems scale

*$p \leq 0.001$

two features. It was proposed that in some cases FS could represent a consequence of a GI problem (Maenner et al. 2012; Mazurek et al. 2013; McElhanon et al. 2014): for example, delayed gastric emptying and hyporexia secondary to constipation could cause it (Williams et al. 2005). Otherwise, constipation may facilitate the onset of episodes of gastro-esophageal reflux with subsequent rejection of food (Buie et al. 2010b). Consequently, a sort of vicious circle is established between GI problems and FS (Vissoker et al. 2015). The large overlap between FS and GI symptoms in our sample pointed out the importance to gather information about FS when clinicians are confronted with the presence of GI symptoms and vice-versa (Ibrahim et al. 2009; Nikolov et al. 2009; Whitehouse et al. 2011). For example, an insufficient intake of fiber due to a child who eats almost only 'pasta' may cause the occurrence of constipation (Cooke et al. 2003; Dovey et al. 2008). In other cases, FS may be related to sensory problems (i.e. sensory sensitivity) independently from GI abnormalities (Cermak et al. 2010; Mazurek et al. 2013; Suarez et al. 2014). Eating is one of the daily life activities that may be negatively affected by sensory symptoms (Dunn 1997; Nadon et al. 2011; Sharp et al. 2013), a complex set of behavioral reactions to the sensory environment that represents a diagnostic criterion for ASD in the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association 2013). Thus, when a child has FS it is also necessary to gather information about his/her sensory symptoms; our data do not allow to deepen this association, but in future the link between FS and sensory sensitivity needs to be investigated using specific instruments such as the Sensory Profile (Dunn 1999, 2014).

Behavioral Problems, Autism Severity and Repetitive Behaviors

Findings from current study along with previously published reports (Maenner et al. 2012; Mazefsky et al. 2014; Fulceri et al. 2016a) provided evidence that ASD subjects with GI and/or FS symptoms had higher level of behavioral problems, in particular externalizing (Horvath and Perman 2002b; Maenner et al. 2012; Bresnahan et al. 2015) and affective problems (Valicenti-McDermott et al. 2006; Nikolov et al. 2009). Moreover, higher CBCL dysregulation profile score was associated with GI/FS dysfunctions. Thus, an accurate investigation of GI and FS symptoms is necessary, especially for ASD children with internalizing and/or externalizing problems in order to plan ad hoc treatment for these comorbid conditions, in addition to evidence-based early interventions.

Literature suggests that ASD children with GI symptoms, and in particular those with constipation, display a higher prevalence of sleep disturbances (Horvath and Perman

Table 5 Clinical differences between ASD individuals with and without constipation

Variables	Constipated+ ($n=36$) Mean ± *SD*	Constipated− ($n=127$) Mean ± *SD*	Student *t* test (*t* value)	Cohen's *d*
ADOS CSS	7.20 ± 1.81	6.40 ± 1.74	2.37*	0.46
CBCL syndrome scales				
Sleep Problems	58.47 ± 10.35	55.05 ± 6.42	2.43*	0.46
Aggressive Problems	57.36 ± 6.40	54.20 ± 5.55	2.30*	0.55
CBCL Summary Scales				
Externalizing Problems	57.11 ± 8.94	53.80 ± 8.50	2.04*	0.39
Total Problems	62.75 ± 10.36	56.80 ± 10.17	3.09**	0.59
CBCL DSM-IV Oriented Scales				
Affective Problems	59.19 ± 9.68	55.84 ± 7.27	2.26*	0.43
ODP	56.06 ± 6.33	53.91 ± 5.52	1.99*	0.38
Repetitive Behaviour Scale-Revised				
Stereotyped behaviors (endorsement)	4.78 ± 2.26	3.79 ± 2.44	2.18*	0.41
Self-injurious behaviors (endorsement)	1.58 ± 1.96	0.98 ± 1.37	2.12*	0.40

Constipated+: ASD subjects with item 12 of CBCL (constipated, doesn't move bowels) scored as '2-very true'

Constipated−: ASD subjects without item 12 of CBCL (constipated, doesn't move bowels) scored as '2-very true'

ASD autism spectrum disorders, *n* number of subjects, *SD* standard deviation, *ADOS CSS* Autism Diagnostic Observation Schedule calibrated severity score, *CBCL* Child Behaviour Checklist, *ODP* Oppositional Defiant Problems scale, *DSM-IV* Diagnostic and statistical manual of mental disorders Fourth Edition

*p ≤ 0.05, **p ≤ 0.01

Table 6 Significant differences among three ASD subgroups: subjects with only constipation; subjects with only FS; subjects with both constipation and FS

Variables	FS *plus* Constipation ($n=12$) Mean ± *SD*	Constipated ($n=11$) Mean ± *SD*	FS ($n=24$) Mean ± *SD*	Kruskal Wallis test χ^2	Kruskal Wallis test Asymp. Sig.	Mann–Whitney test Mann–Whitney *U*	Mann–Whitney test *Z* score	Mann–Whitney test Exact Sig.	Mann–Whitney test *r*
						FS *plus* Constipation vs. Constipated			
ADOS CSS	6.16 ± 1.26	7.81 ± 2.18	6.33 ± 1.92	4.57	0.10	34.50	−1.97	0.05	-
CBCL syndrome scales									
Sleep Problems	61.08 ± 10.70	52.82 ± 5.08	55.71 ± 5.16	6.20	0.05	33.00	−2.07	0.04	0.43
CBCL DSM-IV Oriented Scales									
Anxiety Problems	62.00 ± 12.31	53.36 ± 3.98	57.92 ± 6.74	5.29	0.07	32.00	−2.13	0.04	0.44
Variables	FS *plus* Constipation ($n=12$) Mean ± *SD*	Constipated ($n=11$) Mean ± *SD*	FS ($n=24$) Mean ± *SD*	Kruskal Wallis test χ^2	Kruskal Wallis test Asymp. Sig.	Mann–Whitney Test Mann–Whitney *U*	Mann–Whitney Test *Z* score	Mann–Whitney Test Exact Sig.	Mann–Whitney Test *r*
						FS *plus* Constipation vs. FS			
Repetitive Behaviour Scale-Revised									
Self-injurious behaviors									
Score	2.67 ± 2.74	1.45 ± 1.86	1.08 ± 1.77	5.72	0.06	74.00	−2.45	0.02	0.41
Endorsement	2.25 ± 1.86	1.36 ± 1.75	0.79 ± 1.10	6.99	0.03	66.50	−2.73	0.01	0.45

ASD autism spectrum disorders, *FS* food selectivity, *n* number of subjects, *SD* standard deviation, *ADOS CSS* Autism Diagnostic Observation Schedule Calibrated Severity Score, *CBCL* Child Behaviour Checklist, *DSM-IV* Diagnostic and statistical manual of mental disorders Fourth Edition

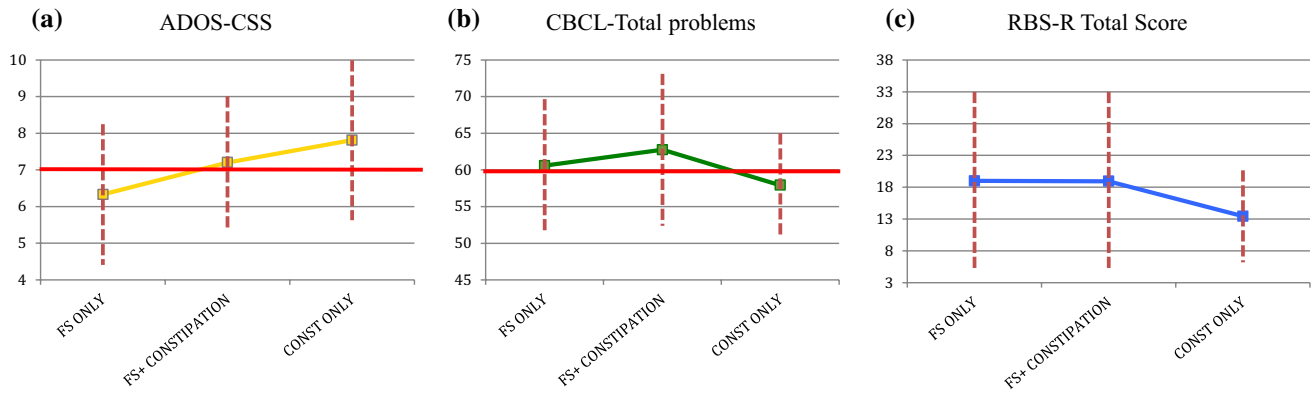

Fig. 1 Different trends on ADOS-CSS, Total Problems (CBCL) and Total Repetitive Behaviours Scale-Revised (RBS-R) scores in the three subgroups. Children with only FS show lower autism severity, but more behavioural and repetitive problems. The profile of children with only constipation is the opposite. *FS* food selectivity, *ADOS-CSS* Autism Diagnostic Observation Schedule Calibrated Severity Score, *CBCL* Child Behaviour Checklist, *GI+* at least one out of the six GI symptoms was scored at the CBCL as '2-very true', *RBS-R* Repetitive Behaviour Scale-Revised. The *red horizontal bar* in **a** and **b** shows the cut-off score for ADOS-CSS and CBCL-Total problems, respectively. No cut-off score for (**c**) is established. (Color figure online)

2002a; Maenner et al. 2012; Klukowski et al. 2015). Our results pointed out that also ASD preschoolers with FS had more sleep problems and that these problems reach the highest level when constipation and food selectivity are associated. According to this finding, we can suggest pediatricians to consider the vicious circle between GI problems and FS as a possible factor contributing to sleep difficulties in children with ASD. In fact, GI symptoms could interfere with sleep quality and/or sleep quantity (Kang et al. 2014): therefore, it is not surprising to find an association between the two (Hollway et al. 2013; Williams et al. 2012). Sleep problems are very common in children with ASD (Sikora et al. 2012) and it may be appropriate to take into account their association with constipation and FS in the treatment of sleep disorders: for example, in these cases promising results have been reported using non-drug therapies like probiotics (Critchfield et al. 2011). This option could reduce the use of drugs for sleep problems in children with ASD.

As far as autism symptoms, in general we do not confirm significant difference in severity of autism in ASD preschoolers who suffer from concomitant GI and/or FS symptoms and we can only report a tendency to a higher severity (measured by the ADOS-CSS) in ASD GI+ children (which is supported also by the correlation analysis) and in constipated children. This result is in contrast to some previous findings (Nikolov et al. 2009; Adams et al. 2011; Wang et al. 2011; Gorrindo et al. 2012; Chaidez et al. 2014) in which an association between GI symptoms and ASD severity was detected. However, some consideration can be proposed if we take into account not only the CSS, but also the second diagnostic area associated with ASD in the DSM-5 (i.e. restricted and repetitive behaviors). In fact, ASD preschoolers with GI symptoms and with FS showed higher scores on stereotyped behaviors; moreover, the GI score was correlated with stereotyped behaviors. This result indicated a relationship between repetitive behaviors and GI symptoms, and is compatible with recent literature (Marler et al. 2017; Tomova et al. 2015) reporting an increase in RRB as a possible marker of abdominal discomfort (Buie et al. 2010b). Therefore, the presence of GI symptoms should be thoroughly investigated, especially when children with ASD show an apparently not explained increase of repetitive behaviors (Peters et al. 2014). Suarez et al. (2014) have suggested that the increase of RRB could have a different mechanism for ASD children with FS. These authors, in a longitudinal study on FS in preschoolers, proposed a relationship between RRB and sensory over-responsivity (SOR). According to their hypothesis, SOR leads to discomfort with many sensory experiences, including eating, that in turn may increase the RRB in an attempt to alleviate anxiety due to the disturbing sensations associated to SOR. However, the causal nature of these relationships can be questioned. Further studies are warranted to clarify the pathophysiology and the brain mechanisms underlying the RRB domain since, beyond involvement of the cortico–striato–thalamo-cortical circuitry (Calderoni et al. 2014), the contribution of the corpus callosum and the cerebellum has also been recently reported (D'Mello et al. 2015; Wolff et al. 2015).

Identification of Specific Subgroups: Children with Constipation and Food Selectivity

To explore the specific role of constipation and FS in the behavioral phenotype of children with ASD we have considered only children with constipation and/or FS as their unique symptom. Even if this strict inclusion criterion implies that the final subgroups are small, some considerations may be proposed. First, ASD children in the three subgroups (constipation, FS, and constipation plus FS) did not significantly differ from each other with regard to age, performance IQ, or ADOS-CSS. Second, ASD children with constipation plus FS displayed higher behavioral and RRB problems without an increasing of autism severity. In particular, the combined group had significantly higher score on sleep problems, anxiety and self-injurious behaviors. This behavioral triad, independent from CSS scores, could describe a specific clinical phenotype resulting from the cumulative effect of constipation and FS. This finding could support the idea that the GI *plus* FS group is composed of specific ASD subjects (Ibrahim et al. 2009; Nikolov et al. 2009; Whitehouse et al. 2011), in which high rates of behavioral problems (in particular anxiety, sleep problems and self-injurious behaviors) are associated to GI/FS symptoms, and not to autism per se.

Third, our findings described a different behavioral and autism profile for children with constipation or with FS. In fact, constipated children have more severe autism, but less behavioral and RRB problems. This trend could suggest that constipation and autism severity are linked, paving the way for further investigations on the potential mechanisms involved in their relationship (Li and Zhou 2016). Conversely, FS represents a true medical comorbidity frequently associated to behavioral problems but without a direct impact on autism severity measured with ADOS CSS.

Our study has the limit that GI and FS data have been gathered using parent questionnaire CBCL 1½–5 without a subsequent verification by a medical specialist. This weakness is partly mitigated by a previous investigation that has shown greater than 90% agreement between a parental report questionnaire that assesses GI symptoms and the paediatric gastroenterologist direct evaluation (Gorrindo et al. 2012). In addition, since ASD patients were recruited in a tertiary care center, a selection bias toward more severe cases cannot rule out: therefore, caution should be exercised in the generalization of our findings to ASD children treated in a general neuropsychiatric practice.

GI and FS symptoms represent frequent, important and challenging problems for family with a child with ASD; therefore, mealtime and toilet difficulties in ASD individuals require a specific investigation during the anamnesis and the assessment of these children. According to current findings, when GI or FS symptoms are present, preschoolers with ASD show a higher comorbidity of both internalizing and externalizing problems, a more frequent dysregulated profile and more stereotyped and self-injurious behaviors. All these symptoms are more frequent in children with both constipation and food selectivity, and a more severe picture emerges when they are combined. ASD individuals with constipation and reduced feeding due to FS had a behavioral functioning that appears to be worse than expected considering that IQ and severity of autism is similar to children who do not have these symptoms. Our results emphasize the importance of further investigating the possible mechanisms underlying the association between GI/FS problems and clinical challenging behaviors, such as sleep disorders, internalizing/externalizing problems, and RRB. Furthermore, this raises the question as to whether treatment addressing GI and FS symptoms may be beneficial for ASD patients with behavioral and/or sleep problems. In this framework, the role of probiotic treatment in ameliorating core and associated symptoms of ASD is now under investigation in prospective randomized controlled trials (Navarro et al. 2016; Santocchi et al. 2016).

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Author Contributions MP and ES participated in the design of the work and wrote the first draft of the manuscript. GB and AN analyzed the data and participated in the design of the work. MB, FF, FA, RI, AC, RT evaluated the patients and collected the data. FM and SC participated in the design of the work, helped to evaluate, edit the manuscript and performed critical revision. Each Author has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Written informed consent was obtained from parents or legal guardians of all individual participants.

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