ORIGINAL ARTICLE

Gender Differences Among Children With Autism Spectrum Disorder: Differential Symptom Patterns

自闭症谱系障碍患儿的性别差异：症状模式的差异

Diferencias de género en niños con trastornos del espectro autista: patrones de síntomas diferenciales

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ABSTRACT

The gender ratio among children in the autism spectrum of more than four boys to every girl is widely recognized. The authors present an analysis of gender differences among 79 482 symptoms and strengths in 1495 boys and 336 girls aged 2 to 18 years from parent-identified autistic children reported to a structurally novel anonymous parent-entered online database, Autism360. The data reveal differences that provide previously undetected clues to gender differences in immune and central nervous system and gastrointestinal functional disturbances. Together with published observations of male/female differences in inflammation, oxidative stress, and detoxication, these findings open doors to research focusing on gender physiology as clues to etiologic factors in autism. This study exemplifies a research method based on a large, detailed, patient-entered, structured data set in which patterns of individual illness and healing may answer collective questions about prevention and treatment.

摘要

广泛认可的自闭症谱系患儿中的男女性别比例在四比一以上。通过一个名为 Autism360 的、由父母输入数据的新型结构型匿名在线数据库，获得父母认定的自闭症报告，作者们在 1495 名年龄在 2–18 岁之间的男孩和 336 名女孩中针对 79482 项症状和优势进行了性别差异的分析。数据显示，这些差异提供了之前未被发现的线索，使人们发现了免疫、中枢神经系统和胃肠功能紊乱等方面的性别差异。与已经公布的关于男女两性在炎症、氧化应激和解毒作用方面的差异相结合，这些发现打开了性别生理学研究的大门，而这项研究正好为自闭症病因学提供了线索。本研究举例证明了一种以大型、详细、患者录入的结构化数据集为基础的研究方法，在该数据集中，个体病症和治疗的模式有可能回答关于预防和治疗的综合性问题。

SINOPSIS

La proporción por sexos entre los niños del espectro autista, que es de más de cuatro niños por niña, es un dato ampliamente admitido. Los autores presentan un análisis de las diferencias por sexo en 79.482 síntomas y puntos fuertes en 1.495 niños y 336 niñas de edades comprendidas entre los 2 y los 18 años, datos procedentes de niños autistas identificados por el padre o la madre y comunicados a una base de datos anónima en línea, de estructura novedosa, en la que los padres son quienes introducen los datos, Autism360. Los datos revelan la existencia de diferencias que facilitan unas pistas que no habían sido detectadas anteriormente sobre las diferencias por sexo en los trastornos funcionales gastrointestinales, en el sistema inmunitario y en el sistema nervioso central. Junto con las observaciones publicadas sobre las diferencias niño/niña con respecto a la inflamación, el estrés oxidativo y la desintoxicación, estos hallazgos abren puertas a la investigación centrada en la fisiología de género para la búsqueda de pistas sobre los factores etiológicos del autismo. Este estudio ejemplifica un método de investigación que se basa en un amplio y detallado conjunto de datos estructurados, introducidos por los pacientes, en el que patrones individuales de enfermedad y curación pueden dar respuesta a preguntas colectivas sobre prevención y tratamiento.

INTRODUCTION

In an interview following the 2011 International Meeting for Autism Research (IMFAR), Marisela Huerta, PhD, referred to the gender difference in autism spectrum disorders (ASD) as the elephant in the room.[1] The scientific attention drawn to the preponderance of boys is small when contrasted with the large 4.2:1 gender ratio generally recognized[2] as exceeding all other common chronic illnesses. This male dominance has been studied from differing vantage points. As in the story of the blind elephant observers, the meaning of this severe gender disparity in ASD remains limited.[3]

The data reported here provide a novel means to document gender differences. The principles[4] on which this article is based are that the individual, not the disease, is the therapeutic target and that treatment may be guided by questions concerning individual unmet needs for beneficial factors and noxious substances to be avoided or eliminated. The patented[5] information technology[6] supporting this study captures 15 or more specific items (eg, symptoms, signs, life events, quirks, family history, laboratory data, and other elements of a medical narrative) and at least one description of a strength or special skill. The record is patient- or par-

ent-entered, password protected, and anonymous. It is intended to create a portrait of the person's individuality. The process is open-ended and free of charge; the online user at the interface (Autism360.org) is the immediate beneficiary of an organized medical database. Autism360 also presents treatment options based on the experience of cluster-mates based on proximity analysis. The semantics[7] underlying the database flow from the general acceptance of "spectrum" to refer to autism over the past decade at the same time as contrary efforts to make autism's definition precise. The dimensionality of "spectrum" is enlarged along two or more axes into which the granular data of Autism360's members are encoded. A three-dimensional portrait of all the data underlying this report is pictured in reference 7—showing 79482 symptoms of 1831 parent-identified autistic children aged 2 to 18 years.

METHODS

Autism360.org was established to serve individuals with ASD and their caregivers. The profile items of each individual are represented as intersections in space. The three dimensions of our everyday experience allow us to visualize three attributes (system [S], function [F], and location [W, for "where"] that carry the literal meanings of the patients' medical narratives. The website interface allows users to drill down to select any profile items they regard as serious, mysterious, vexing, or otherwise helpful to describe their individuality. If, for example, they select *constipation*, that selection is registered at the intersection between *digestive* (system-S), *decrease* (function-F), and *bowel* (location-W) and occupies a point in a conceptual space in which X, Y, and Z axes are S, F, and W. Severity, time descriptors, and other modifiers are encoded as intersections along 21 other dimensions of the system's hyperspace. The encoding is unseen by the user. The lexicon from which the user chooses narrative details was built over 2 decades in a single general medical practice in which SFW codes were recorded for every word of every patient. The intent of the encoding process was to capture the literal meaning of the words as freely as possible from implications. The aim was to follow the traditional medical imperative of listening to and recording the patient's own words and withholding judgment until the flow of information is complete. Judgment in this context refers to the diagnostic purpose of a conventional medical interview. Autism360's intent is to capture as complete a set of characteristics as patients choose to describe the ways they may differ from others—as contrasted with the usual diagnostic intent to categorize a patient based on standard medical diagnostic groupings. Details sufficient to satisfy diagnostic criteria within a larger data set are accessible but not the primary point of Autism360. This technology achieves an interchange among individual and collective data that lets users locate their place in a multidimensional spectrum.

Our hope is to form a system in which the patient's interest in an accurate, detailed portrait is joined to the collective interest in creating a data structure that reveals patterns. One pattern is based on the proximity of individual data determined by cluster analysis. Clusters permit users to find "others like me" and discover treatment options based on their collective experience. Other patterns are formed by the collective data viewed from various perspectives such as gender. Another kind of pattern may be revealed by associations of data elements in statistical analysis or queries that deliver the collective patterns, for example, of children with or without constipation.

The possibility of forming patterns allows the individual motive to provide good information that serves patient care to further benefit the collective interest in research. Our overriding interest in protecting the confidentiality of the data is preserved by ensuring that the data is anonymous from the start. Only birth year and month are collected, and an alias is substituted for name, freeing the patient (and the system) from any threat to confidentiality.

The current analysis of individual symptom patterns was undertaken based on a previously published analysis[6] of system-function patterns visualized within a selection of eight systems and six functions. The selection was based on three criteria: high data density among the 39 x 42 system-function intersections (Figure 1) and the inclusion of interesting and novel profile items. Abnormal *odors* exemplifies an interesting category, and *strengths* (mentioned in psychologists' reports) are novel in medical records and studies of disease. The 8 x 6 subset (Figure 2) of the more sparse 39 x 42 grid's totality reduced the total number of sampled profile items from 79482 to 52725. The previously published graphical data[6] revealed eye-catching differences within an overall appearance of similarity between boys and girls. To test the reliability of visual presentation and to be more precise about gender differences, we arranged the data in a table in which each row represents one of 713 profile items. A pair of columns itemize the count of each profile item for boys and girls (totals in the database were 1495 and 336, respectively). Thus, the table counts subjects who reported a particular profile item based on gender. As such, the count data lends itself to proportion analysis. A two-sample proportion test (Figure 3) was employed to determine whether or not a statistical difference existed in the proportion based on gender. A normal approximation was used to compute a z score (Figure 4) and a level of statistical significance. When the level of significance was equal or less than a P value of .05, it suggested that the difference between genders for a particular profile item was beyond random chance. In those cases where we suspected a violation in the use of a normal approximation based on a low n, a Fisher's exact test was employed to compute an exact P value.

We used statistical metrics as a means for sorting Profile Items by z value to rank prevalence of 693 Profile Items with valid P values at the extremes of their distribution (invalid items had no boys, and only one or two girls). In the previous report based on the same data research methodology,[7] we sought eye-catching gender

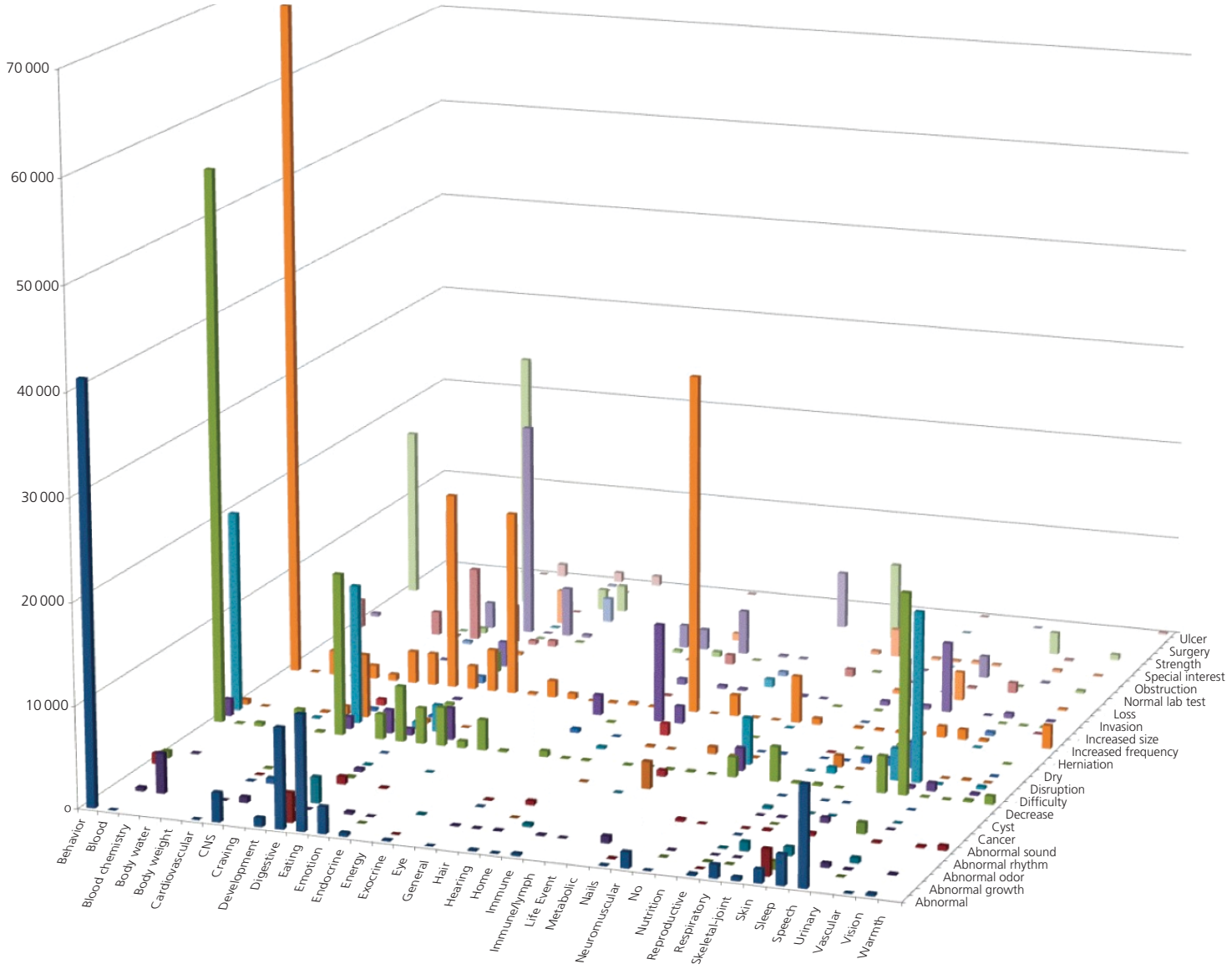


Figure 1 The 79 482 profile items encoded as intersections among 39 systems and 42 functions from 1831 individuals aged 2 to 18 years from Autism360.

Abbreviation: CNS, central nervous system.

differences without statistical measures. This approach embodied the data-intensive science dubbed *Fourth Paradigm* by Jim Gray[8] and provided patterns observed from "high altitude" but which may lack the precision required for practical assessments of the differences we seek to detect. Our calculation and reporting of *P* values in this article may err in the opposite direction. The very appearance of *P* values in a scientific publication gives the impression that something is being proved. The use of probability statistics to describe gender differences in this article, however, gives the reader a spectrum of male-to-female prevalence of profile items at the extremes of the distribution of their *z* values (Figure 5). Fisher's exact test is particularly helpful in many profile items with low prevalence where "eye-catching" differences are difficult to assess in data with asymmetrical numbers of subjects compared.

RESULTS

Table 1 presents strengths first and in detail because this is the first report in the medical literature to emphasize such attributes of individuality.

Table 2 displays profile items (PIs) with a higher than expected boy:girl (B:G) ratio among 1495 boys and 336 girls. The names of PIs are terms of self (or child) description used by patients over the years of the coding system. Their path to the current dataset consists of choice of text as shown from drop-down menus presented from Autism360's lexicon acquired from face-to-face narratives in a medical office setting over many years. The B:G ratio is given as a point of reference against 4.5:1 in the whole dataset. The *P* values are shown to indicate relative rank in the data and as a way to provide a sense of the significance—in the vernacular as well as statistical meaning—of B:G proportions

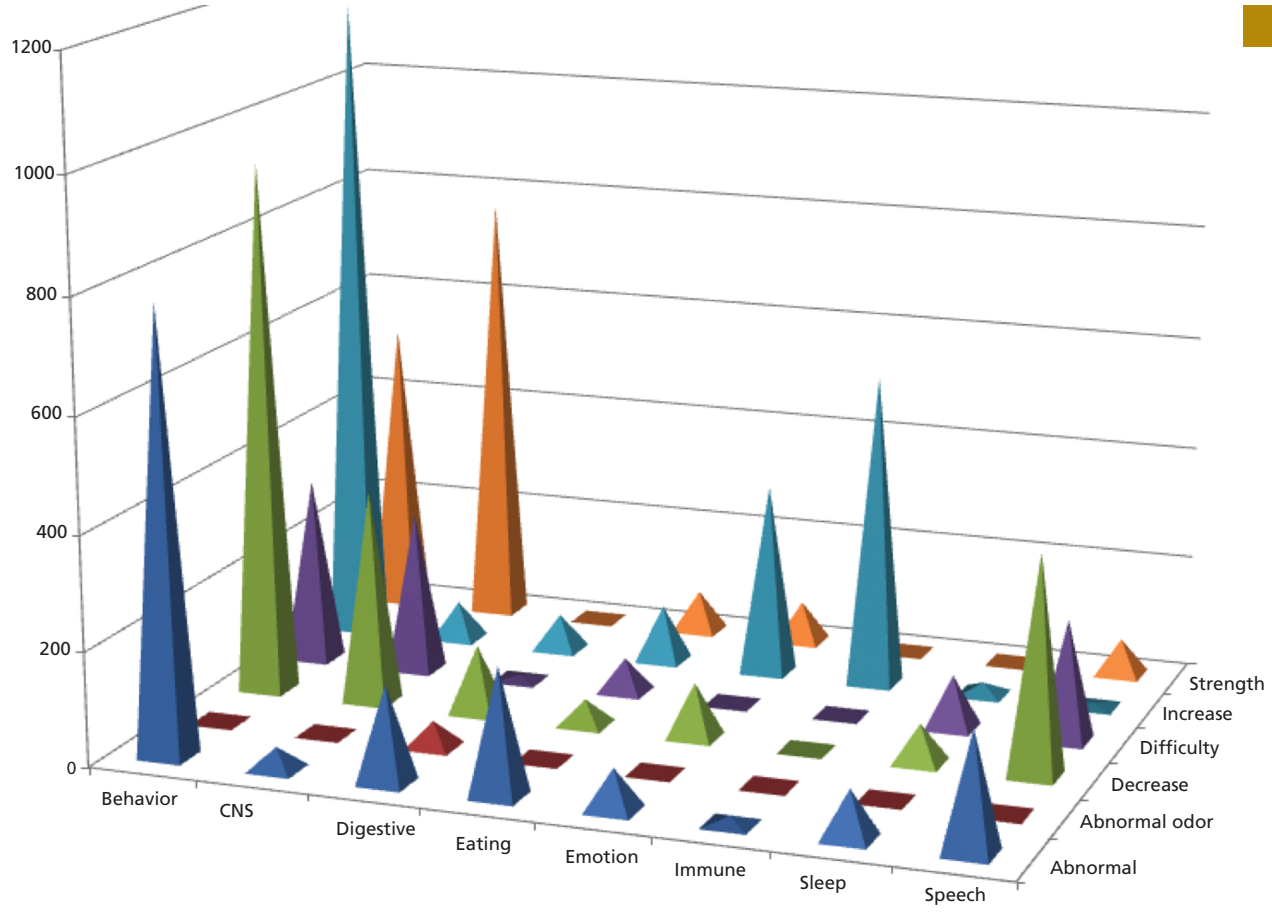


Figure 2 Subset of 52725 profile items encoded as intersections among 6 systems and 8 functions from 1525 boys and 336 girls from Autism360.
Abbreviation: CNS, central nervous system.

for items with low counts. In this table, "constipation" is the item in the data worth the harvest. A room full of clinicians and researchers experienced in the field of autism were asked, "Who among you believe that autistic boys and girls are very different?" All hands went up. Asked for specifics, "harder" and "weird" came up, but silence otherwise filled the air. Nor was the author (SMB) able to predict that "constipation"—so common in autistic children—should dominate the girls' data with such a high statistical probability. It matches a theoretical model based on the work of Derrick MacFabe, MD, and the synthesis by McGinnis cited previously, to wit: autonomic regulatory problems deriving from injury to midbrain structures by damage to centers that lie outside the blood brain barrier. The damage may lie in the realm of autoimmune inflammation; this speculation is reinforced by the remarkable pink dominance in symptoms suggesting loss of immune tolerance shown in Table 2. Blue zone data are more consistent with features found in Eliot's review[9] having to do with activity and restlessness. Rectal digging is one of the most troubling symptoms found in autistic children. It has the highest boy:girl ratio of all in the Autism360 data and begs for a theory of causation.

$$p = \frac{\binom{a+b}{a}\binom{c+d}{c}}{\binom{n}{a+c}} = \frac{(a+b)!\ (c+d)!\ (a+c)!\ (b+d)!}{a!\ \ b!\ \ c!\ \ d!\ \ n!}$$

Figure 3 A two-sample proportion test was employed to determine whether there was a statistical difference in the proportion based on gender for each of the 712 different profile items.

Table 3 lists PIs (other than strength) unique to the pink and blue zones sorted by system. The PI count is the total of unique system-function designations in each system category for the Girls' and Boys' data. The *P* values for each data item fall in a range from .05 to .63 and .052 to .71, respectively. The B:G ratios for each system category bear out the value of including data that are far from statistical significance to provide an overview of B:G differences.

Figure 6 shows all PIs in a comparison of the PI count data in Table 2 with strengths set aside. The graph summarizes findings that point to more central nervous system (CNS) and immune system problems among autistic girls and more behavioral abnormalities among autistic boys.

DISCUSSION

Cognitive difficulties and deficits, loss of immune tolerance, and gastrointestinal troubles are more preva-

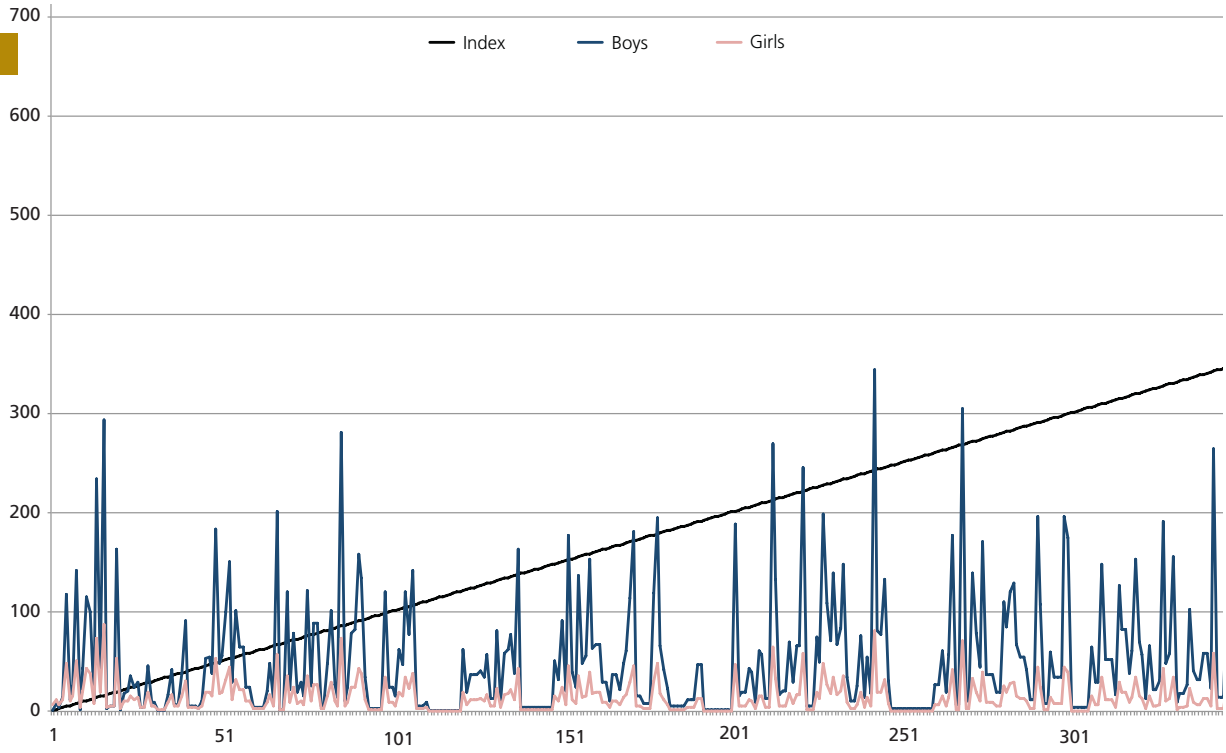
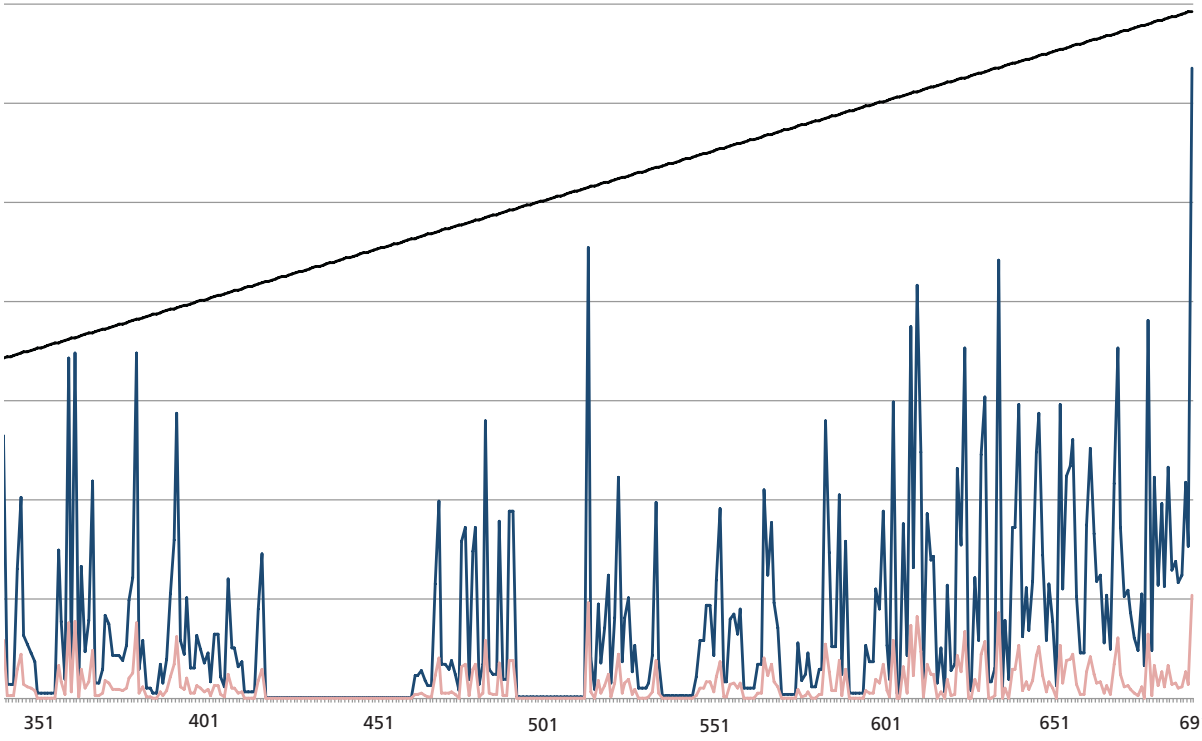


Figure 4 Profile items were sorted by *z* value to produce a table showing the extremes of *P* values among females (pink) and males (blue).

lent among autistic girls. Autistic boys show more behavioral abnormalities and increased activity. Words used in years of conversations with parents about their autistic children provide a way to begin to think about these findings. "Drunk" is a word that most often triggers a spark of recognition in parents grasping for a term to express how a once-bright child disappeared into a chaos of dysregulation, silly laughter, and erratic behavior. "Regulatory" helps us identify a theme that runs the entire lexicon of descriptions of autistic attributes. "Drunk" reflects a toxic state. "Regulatory" evokes a brainstem locale that McGinnis indicated was a principle target of toxicity in autism.[10] The principle etiologic factors[11] of autism are now generally acknowledged to be environmental toxins. Dr MacFabe in his 2012 Nobel Lecture[12] argued persuasively that toxins from gut microbial sources that provoke autistic behaviors in experimental animals injure fundamental biochemical and membrane functions that are gender dependent. Words describing the symptoms of autistic individuals can be combined with those from published literature. The latter offers additional clues to the question how gender differences may arise from exposing cells outside the blood-brain barrier in the brainstem to environmental and gut-derived toxins. Links are offered by the words *proclivity*, *unmasking*, and *starving* that appear in the titles of research findings[13-15] by a team led by Robert S.B. Clark, MD, and the Safar Center for Resuscitation Research at the University of Pittsburgh, Pennsylvania. Their studies submitted cultured male and female neuronal and lymphoid cells to various stressors, which unmasked different proclivities in cell death (apoptosis) mechanisms. Simply put, male cells underwent injury and rescue in domains of sulfation, glutathione, and oxidative stress featured in the research of Jill James, PhD,[16,17] and Richard Deth, PhD.[18] In that domain, a vicious cycle of oxidation of methylcobalamin engendered by heavy metals and other toxins cascades to impair N-acetylcysteine–dependent synthesis of glutathione, thus failure of glutathione's protection against oxidative stress. Male neurons studied by Clark's team underwent apoptosis via oxidative, nitrositive, and excitotoxic stress with rescue by N-acetylcysteine. The proclivity of female cells was toward protection from such stresses and apoptosis by an entirely different cytochrome c–dependent pathway. The key difference between male and female neuronal and lymphoid cells was the relative incapacity of male cells to maintain intracellular levels of reduced glutathione. The following review of gender differences reveals no comparable findings that implicate fundamental mechanisms. Girls with ASD may be more severely affected because of an increase in CNS apoptosis compared to neurotypical girls, and neurotypical girls may be protected from developing autism because of greater GSH reserve and decreased vulnerability to neuronal apoptosis.

Elise Eliot's scholarly and engaging book *Pink Brain, Blue Brain* invites the reader to understand that sex differences in cognition, emotions, and interpersonal behavior are quantitatively small.[9] Her thorough review of the literature documents that boys have higher math scores, spatial ability, and aptitude with maps. Girls have better social, verbal, and reading skills; penmanship; inhibitory control; and planning and organizational abilities. On the other side of the ledger, boys have more difficulty in school (especially in early years), irritability, sleep prob-



The distribution of profile items with low numbers revealed no overrepresentation planned within female- and male-dominant selections.

lems as newborns, stuttering and other speech impediments, attention problems and hyperactivity, aggression, and risk-taking, while girls have more depression and anxiety. Boys also have significantly higher infant mortality and morbidity:

> *Boys between two and five years old overwhelmingly select a toy truck, Hot Wheels car, ball, or other suitably male toy when given a choice between one of those and a doll. Three-year-old girls opt strongly for the baby doll, toy kitchen utensils, or toy beauty set (especially if any of the toys is pink).*[9(p105)]

Overall, however, Dr Eliot as a neurobiologist stresses caution in attributing gender differences to "genetics, hard wiring, and constitution" over environmental influences.[9] She points keenly to flaws in research that have given testosterone prominence as a major feature in gender differences and mechanisms in autism having to do with too much maleness. This is not to say that testosterone does not play the role implied in the studies reviewed below. Add a recent report that daughters of mothers affected by hyperandrogenic polycystic ovarian syndrome seem to have a higher risk for pervasive developmental disorders, probably due to unbalanced prenatal exposure to high levels of testosterone.[19]

Let's shift the literature review of gender differences to focus on biochemical and autism-related factors with a broad environmental view. The number of males born per 100 females (secondary sex ratio) is not stable over time. An increasing trend in Northern European populations in the 18th and early 20th centuries shifted to a markedly decreasing trend from the latter half of the 20th century until the present.[20,21] Sudden downward shifts seen in small populations associated with environmental and occupational chemical exposures are consistent with a male disadvantage in responding to toxic burdens.[22] A study of adults with Asperger's syndrome found 24 biomarkers distinguishing affected males from controls and 17 different analytes distinguishing females from controls. Neither gender-specific set of analytes provided separation in the opposite gender. The authors conclude that stratification by gender is essential to studies of autism spectrum conditions.[23] A novel autism candidate gene—retinoic acid-related (RAR) orphan receptor-alpha (RORA)—is associated with protecting neurons against oxidative stress, suppression of inflammation, and behaviors similar to those of ASD. One of RORA's transcriptional targets, CYP19A1 (aromatase), is responsible for converting testosterone to estrogen. The authors propose that in ASD, downregulation of RORA is involved in a self-reinforcing feedback cycle in which testosterone may suppress RORA expression.[24] Mitochondria from human females exhibit higher antioxidant gene expression and lower oxidative damage than mitochondria from males[25]; human preterm infants exhibit similar male disadvantage in GSH-dependent response to oxidative stress.[26] Human lymphocytes show similar gender-dependent levels of glutathione and glutathione S-transferases.[27] During moderate-intensity long-duration exercise, females demonstrate greater lipid utilization and less carbohydrate and protein metabolism than equally trained and nourished males,[28] and during strenuous exercise men

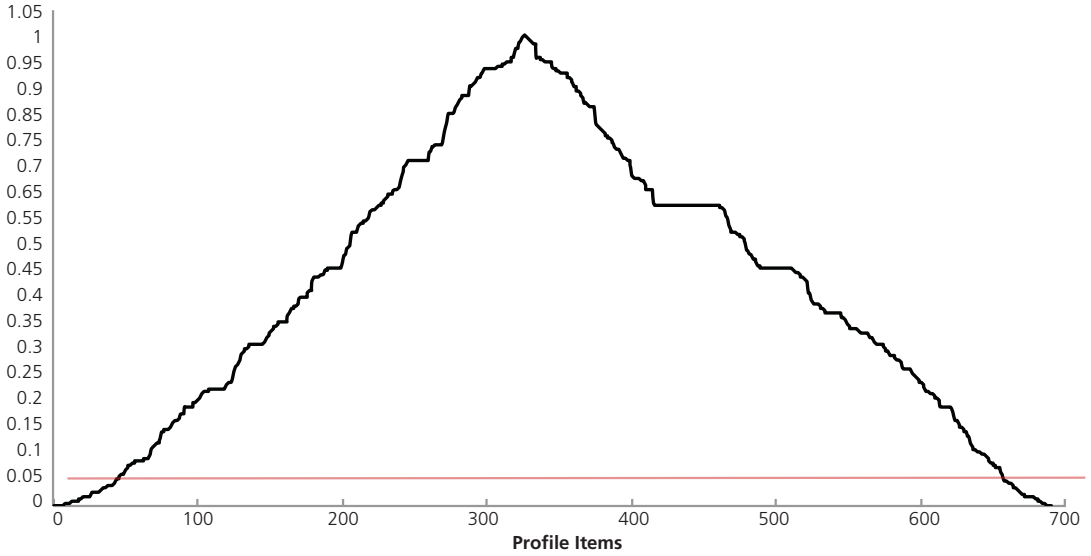


Figure 5 Thirty-one girl-dominant and 52 boy-dominant provile items from the extremes ($P < .05$, dark colors) were selected for detailed tabular presentation and graphic summarization. Two hundred profile items adjacent to each extreme (light pink and blue) were selected for categorization by system.

increase their need for amino acids, whereas women increase mobilization of fat to supplement increases in carbohydrate metabolism.[29]

Treatment with L-carnitine increased cellular respiration and improved survival in neurons from males, pointing to a reduced capacity or proclivity to utilize free fatty acid in males—demonstrated by reduction in the number of lipid droplets and concentration of triglycerides in the work of Du et al, who concluded, "Specifically, neurons from male mice and rats had an increased autophagic response to starvation associated with increased cell death, rather than increased mobilization and/or utilization of fat associated with increased cell survival as seen in females."[14] Cell survival is an attribute appropriate to long-lived neuronal and lymphoid cells that are agents of perception and guardians of memory in an organism. The molecular basis for perception—taking in stimuli from both internal and external environments—differs in those charged with conscious (CNS) vs unconscious (immune) recognition. The gist—decrease in perception and memory required for recognition—is the same. The female disadvantage in the pattern of PIs in this report indicates principal deficits in CNS and immune functions: cognition and immune tolerance, respectively. As such, they offer room for speculating that autistic girls may lack their gender's protection against oxidative stress associated with alternate mechanisms for apoptosis in neuronal and lymphoid development. That speculation is supported by studies showing gender-based differences in glutathione metabolism in humans[25,27] and the role of that protection in the face of environmental toxins.

Exposure to the insecticide chlorpyrifos had a greater adverse cognitive impact in boys, lowering working memory scores—a key component of IQ—by an average of 3 points more in boys than in girls. Parental nurturing, on the other hand, was associated with better working memory, particularly in boys. Horton, the author of the study, says, "There's something about boys that makes them a little more susceptible to both bad exposures and good exposures. One possible explanation for the greater sensitivity to chlorpyrifos is that the insecticide acts as an endocrine disruptor to suppress sex-specific hormones."[30] Studies of cerebellar structure and function in rats following gestational exposure to polychlorinated biphenyls (PCBs) revealed neurodevelopmental and behavioral changes greater in male than in female neonates.[31] Although body mass was not affected at birth, it was lower in PCB-exposed pups vs controls between birth and weaning and more so over time in females than males.[32] The cholinergic system of female mammals appears more responsive to stress than that of male mammals, where it is anatomically larger, higher in cell density, and more stable with age.[33] Male (but not female) rats respond to stress with decreased dopaminergic activity in the frontal cortex and amygdala. Females (but not males) showed that stress increased levels of 5-hydroxytryptamine and norepinephrine in CA3 of the hippocampus, where males (but not females) showed increased gamma-aminobutyric acid.[34] The maturity of newborn girls positively influences their cysteine uptake, which is responsible for 78% of the variation in their glutathione content. In newborn boys, however, gestational and postnatal ages did not influence cysteine uptake.[35] In vivo, intracellular total glutathione was higher in female-derived cells and in cells from more mature babies; postnatal age and gestational age had a positive effect on activity of glutathione reductase (GSSG-R). Oxygen (Fio2 ı 0.3) was associated with a lower activity of GSSG-R in boys early in life. In human newborn tissue (umbilical cord) subjected to

Table 1 Strengths

System	*P* ≤. 05 Pink Strengths	n Boys	n Girls	B:G	*P* value
Behavior	Ability to infer	21	11	1.91	.01815
CNS	Good play skills	46	19	2.42	.02103
Neuromuscular	Gymnastics	14	12	1.17	.00023
System	*P* ≥ .05 Pink Strengths	n Boys	n Girls	B:G	*P* value
Behavior	Responsible	19	8	2.375	.13
Behavior	Persistent	83	25	3.32	.18
Behavior	Strong will/desire to do things	135	38	3.552632	.20
Behavior	Good behavior at school	120	34	3.529412	.21
Behavior	Minimal distractibility	6	2	3	.63
CNS	Good awareness	38	15	2.533333	.06
CNS	Musical	184	54	3.407407	.06
CNS	Perfect musical pitch	56	20	2.8	.07
CNS	Good comprehension	58	17	3.411765	.32
CNS	Good communication	32	10	3.2	.36
CNS	Good social interaction	49	14	3.5	.42
CNS	Good visual memory	181	46	3.934783	.43
CNS	Art—sculpting, modeling	15	5	3	.44
CNS	Good imitation of gestures	66	18	3.666667	.46
CNS	Reading	133	33	4.030303	.59
CNS	Especially bright	148	36	4.111111	.65
CNS	Notices everything	133	32	4.15625	.72
Eating	Good appetite	270	65	4.153846	.58
Emotion	Ability to see other people's perspectives	44	12	3.666667	.55
Neuromuscular	Singing	151	45	3.355556	.08
Neuromuscular	Art—drawing	120	36	3.333333	.11
Neuromuscular	Skill: playing/small object	48	16	3	.16
Neuromuscular	Art—painting	34	11	3.090909	.28
Neuromuscular	Good handwriting	51	15	3.4	.35
Neuromuscular	Skill: doing fine work	20	6	3.333333	.53
Speech	Good expressive language	50	13	3.846154	.63
System	*P* ≤ .05 Blue Strengths	n Boys	n Girls	B:G	*P* value
Behavior	Mellow personality	117	11	10.64	.0031
Behavior	Affectionate	635	104	6.11	.0001
CNS	Mechanical disassembly (taking things apart)	118	16	7.38	.0464
CNS	Mechanical assembly (putting things together)	124	17	7.29	.0445
CNS	Problem-solving skills	56	5	11.20	.0372
CNS	Ability to memorize (photographic memory)	354	61	5.80	.0289
CNS	Good short-term memory	61	5	12.20	.0213
CNS	Knows numbers	381	65	5.86	.0178
CNS	Memory—numbers	113	12	9.42	.0088
CNS	Good at math	154	14	11.00	.0004
Neuromuscular	Balance	166	25	6.64	.0471
Neuromuscular	Good athlete	50	4	12.50	.0350
Neuromuscular	Physically strong	217	34	6.38	.0343
Neuromuscular	Physical ability (gross motor)	173	25	6.92	.0276
Neuromuscular	Skill: throw/catch ball	109	13	8.38	.0230
System	*P* ≥ .05 Blue Strengths	n Boys	n Girls	B:G	*P* value
Behavior	Behavior OK with parent	115	23	5.00	.60
Behavior	Pleasant/easy to care for	173	35	4.94	.55
Behavior	Likes to be held	223	45	4.96	.48
Behavior	Tidy	46	7	6.57	.33
Behavior	Answers parent	189	35	5.40	.26
Behavior	Reaches out to be held	176	32	5.50	.24
Behavior	Follows instructions	139	24	5.79	.21
Behavior	Ability to inhibit self	34	4	8.50	.21
Behavior	Cuddly	297	53	5.60	.08
CNS	Good long-term memory	172	35	4.91	.57
CNS	Good logic or judgment	30	5	6.00	.53
CNS	Memory—places	179	36	4.97	.52
CNS	Happy	455	96	4.74	.50
CNS	Problem-solving ability	81	15	5.40	.48
CNS	Good attention/focus	38	6	6.33	.41
CNS	Good self-help skills	80	14	5.71	.37
CNS	Knows colors	375	74	5.07	.24
CNS	Academics good	173	29	5.97	.12
CNS	Good with the computer	288	52	5.54	.11
CNS	Good sense of time	59	7	8.43	.10
CNS	Joint attention	46	4	11.50	.06
Emotion	Brave	34	5	6.80	.37
Neuromuscular	Physically coordinated	132	23	5.74	.24
Speech	Pronounces words well	102	19	5.37	.44

Abbreviations: B:G, boy:girl ratio; CNS, central nervous system.

Table 2 Profile Items With a Higher Than Expected Boy:Girl Ratio Among 1495 Boys and 336 Girls

System	*P* = <.05 Pink Profile Items	Boys	Girls	B:G	*P* value
Behavior	Dependent or clingy (independence problems)	4	7	0.57	9.9E-05
Behavior	Eats sand	44	20	2.20	.00665
CNS	Attention or focusing problem	142	51	2.78	.00219
CNS	Small head	2	4	0.50	.00219
CNS	Problems with spelling	43	21	2.05	.00235
CNS	Memory lapse	10	8	1.25	.00405
CNS	Developmental delay	294	88	3.34	.00782
CNS	Fainting spell (passed out)	1	2	0.50	.03048
CNS	Family history of ADD or ADHD	91	31	2.94	.03707
CNS	Loss of or poor balance	5	4	1.25	.04263
CNS	Sleepiness (somnolence)	5	4	1.25	.04263
CNS	Poor short-term memory	54	20	2.70	.04902
CNS	Learning disability or problem	163	53	3.08	.01238
CNS	Poor math skills	4	4	1.00	.02047
CNS	Dyslexia	17	9	1.89	.03093
Digestive	Oily bowel movements	4	4	1.00	.02047
Digestive	Constipation	235	74	3.18	.00530
Digestive	Obstipation (intractable constipation)	1	2	0.50	.03048
Digestive	Can't eat chewy food	3	4	0.75	.00789
Digestive	Bloating after eating	36	16	2.25	.01892
Digestive	Allergic stomach	12	11	1.09	.00024
Digestive	*Clostridium difficile* infection	5	5	1.00	.00952
Digestive	Reflux esophagitis	2	3	0.67	.01598
Digestive	Family history of diverticulitis	18	10	1.80	.01676
Digestive	Family history of gastritis	9	6	1.50	.02962
Eating	Excessive eating of sugar, candy, or sweet food	39	16	2.44	.03667
Eating	Eats lots of vegetables	26	16	1.63	.00082
Emotion	Always frightened or afraid	1	7	0.14	4.1E-07
Emotion	Hysteria or flipping out	24	12	2.00	.01900
Immune	Allergy, gluten	118	48	2.46	.00023
Immune	Family history of allergies	116	43	2.70	.00304
Immune	Allergy, egg	100	38	2.63	.00374
Immune	Allergy, strawberry	5	5	1.00	.00952
Immune	Sensitivity to bug bites (skin welts)	30	14	2.14	.01949
Immune	Allergy, rice	9	6	1.50	.02962
Immune	Sensitivity to latex	1	2	0.50	.03048
Immune	Allergy, cat	42	17	2.47	.03481
Immune	Allergy, ice cream	7	5	1.40	.03631
Immune	Allergy, infant formula	7	5	1.40	.03631
Immune	Allergy, shrimp	5	4	1.25	.04263
Immune	Cerebral allergies	3	3	1.00	.04485
Immune	Allergy, bug bite	10	6	1.67	.04686
Neuromuscular	Trouble walking	8	12	0.67	1.3E-06
System	***P* = <.05 Blue Profile Items**	**Boys**	**Girls**	**B:G**	***P* value**
Behavior	Behavior purposeless	49	3	16.33	.0174
Behavior	Destructive or mean behavior	86	9	9.56	.0217
Behavior	Does not try to communicate with words or gestures	125	12	10.42	.0026
Behavior	Excessively picks nose	105	12	8.75	.0194
Behavior	Inappropriate or repetitive play or behavior	252	42	6.00	.0494
Behavior	Limited interests	223	33	6.76	.0150
Behavior	Like fans or spinning objects	218	27	8.07	.0014
Behavior	Rectal digging	33	1	33.00	.0191
Behavior	Stimming—door closing	103	12	8.58	.0235
Behavior	Stimming—jumping	138	15	9.20	.0043
Behavior	Stimming—running back and forth	129	14	9.21	.0059
Behavior	Takes clothes off inappropriately	104	13	8.00	.0365
Behavior	Unresponsive to school activities	48	3	16.00	.0196
Eating	Picky or poor eater	233	33	7.06	.0067
Neuromuscular	Fidgeting, jumpy, or moving all the time	197	27	7.30	.0094
Speech	Receptive processing problem	114	13	8.77	.0143

Abbreviations: ADD, attention deficit disorder; ADHD, attention deficit/hyperactivity disorder; CNS, central nervous system.

oxidative stress (tert-butyl hydroperoxide), only male-derived tissue showed a sustained increase in glutathione. Responses of female-derived tissues were not variable and reversed proportional to the oxidative stress.[36] Considering that glutathione is a central element in the antioxidant defense, these results suggest that specific tissues derived from the baby girl are potentially better protected against an oxidative stress than those derived from the boy.[37]

Words such as *drunk* and *regulatory* arise from conversations with parents. "Antioxidant defense" and other references to biochemistry come from literature describing key aspects of gender differences in autism. Together, this vocabulary and perspectives from McGinnis and MacFabe allow us to compare and interpret the differences between boys and girls in the Autism360 data. "Strengths" come first, because clinical assessment benefits from their early mention (if not emphasis), especially in children treated by practitioners focused exclusively on pathology. Especially in nonverbal children (who practitioners may assume do not understand), the erosive repetition of their problems may be repaired by acknowledgement of their strengths. In autistic children, moreover, such talents leverage healing and form the basis for self-confidence and independence—the most valuable treasure that can be given to parents beyond a genetic legacy and life itself. Words spoken directly to a child—even one who shows no indication of attention—are heard and in retrospect may turn out to have mended a fragile spirit. Strengths in both upper and lower sections of Table 1 are elements such as handwriting for girls and math for boys found in neurotypical children. Beyond that, these data are offered to readers as a vocabulary to enrich conversations with parents and children.

Table 3 Profile Items (Other Than Strength) Unique to the Pink and Blue Zones Sorted by System

System	Pink PI Count	PIs Boys	PIs Girls	B:G
Behavior	38	3023	835	3.62036
CNS	24	1101	327	3.36697
Digestive	22	419	130	3.22308
Eating	11	342	105	3.25714
Emotion	15	442	140	3.15714
Immune	44	607	165	3.67879
Neuromuscular	12	772	208	3.71154
Speech	8	6706	1910	3.51099
Pink Systems Total	174	13412	3820	3.51099
System	Blue PI Count	PIs Boys	PIs Girls	B:G
Behavior	57	7659	1373	5.5783
CNS	12	212	30	7.06667
Digestive	26	631	90	7.01111
Eating	15	1016	173	5.87283
Emotion	15	835	141	5.92199
Immune	29	392	49	8
Neuromuscular	3	228	43	5.30233
Speech	15	1056	190	5.55789
Blue Systems Total	172	12029	2089	5.75826

Abbreviations: BG: boy:girl ratio; CNS, central nervous system; PI, profile item.

CONCLUSION

Reported here for the first time are detailed data on autistic symptoms gathered via a novel online system that permits patients and parents to benefit from an exchange between individual and collective data. Parents/patients and caregivers collaborate in creating, validating, and maintaining the medical record. The system guarantees ownership and confidentiality to par-

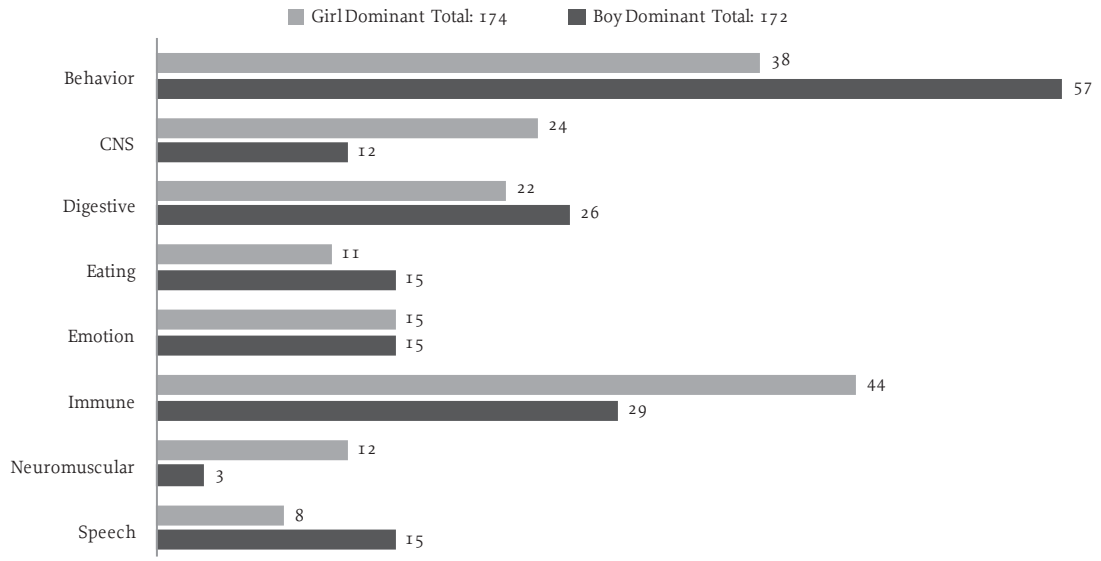


Figure 6 With strengths set aside, all profile items are shown in this comparison of the profile item count data in Table 2. The graph summarizes findings that point to more central nervous system and immune system problems among autistic girls and more behavioral abnormalities among autistic boys.

ticipants, who receive a well-organized medical record that includes their strengths with signs, symptoms, life events, and exposures that portray individuality. The invention of a multidimensional coding system for storing all medical data anticipated the use of the word *spectrum* that directs attention away from "name-it, blame-it, tame-it" medicine toward information and therapies based on special individual needs as contrasted with viewing the disease as the target of treatment. Users' contributions to a resource of value to others provides added incentive to participate.

Current efforts at computerizing medical records differ little in style from those begun half a century ago. Such past efforts to record, store, report, and analyze personal medical narratives have in the past tended to automate current paper systems rather than envisioning possibilities offered by advances in information technology that permit new ways of capturing, storing, analyzing, and representing personal and collective medical data. Autism360 provides an alternative path that may become necessary as information technology offers increasing access to tools to sort and preserve data. The data presented here reveal hitherto unrecognized clinical aspects of the unbalanced gender ratio in autism. Sorting is the key to finding clinically and scientifically relevant items in a large volume of data. Without a coding structure that permits logical sorting of the words we use to describe our strengths as well as our difficulties, we will not find efficient ways to use our keen human eyes to detect what is most significant. Use of the methods reported here reveal hitherto unseen gender differences in symptoms that reflect underlying mechanisms in oxidative stress and toxins. The use of *z* scores to sort symptoms by their relative male vs female proclivity gives a novel overview of the texture of clinical expression underlying the 4.5:1 gender ratio in the autism spectrum.

REFERENCES

1. Stone Health News. Autism in girls: are the right questions being asked? http://www.stonehearthnewsletters.com/autism-in-girls-are-the-right-questions-being-asked/autism/#sthash.1Hrddmfm.dpufhttp://www.stonehearthnewsletters.com/autism-in-girls-are-the-right-questions-being-asked/autism/. Accessed September 17, 2013.
2. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res. 2009;65(6):591-8.
3. Rivet TT, Matson JL. Review of gender differences in core symptomatology in autism spectrum disorders. Res Autism Spectrum Disorders 2011;5(3):957-76.
4. Baker SM. Principle-based medicine. Integr Med Clin J. 2011;10(5):22-32.
5. US Patent Office. US patent 7676384 filed Sept 15, 2000; issued March 9, 2010.
6. Baker SM. Autism 360: the development of an online database with patient-entered data. Integr Med Clin J. 2012;11(1):18-26.
7. Baker SM. Autism spectrum: new metaphor—new paradigm of illness. N A J Med Sci. 2012;5(3):193-7.
8. Hey T, Tansley S, Tolle K. Jim Gray on eScience: a transformed scientific method. Microsoft Research. http://research.microsoft.com/en-us/collaboration/fourthparadigm/4th_paradigm_book_jim_gray_transcript.pdf. Accessed September 24, 2013.
9. Eliot E. Pink brain, blue brain: how small differences grow into troublesome gaps—and what we can do about it. Boston, MA: Mariner Books; 2010.
10. McGinnis WR, Miller, VM, Audhya T, Edelson SM. Neurotoxic brainstem impairment as proposed threshold event in autistic regression. In: Autism: oxidative stress, inflammation, and immune abnormalities. Chauhan A, Chauhan V, Brown T, editors. Boca Raton, FL: CRC Press; 2019:153-76.
11. Landigren PJ, Lambertini L, Birnbaum LS. A research strategy to discover the environmental causes of autism and neurodevelopmental disabilities. Environ Health Perspect. 2012;120(7):a258-60.
12. MacFabe DF. Short-chain fatty acid fermentation products of the gut microbiome: implications in autism spectrum disorders Microb Ecol Health Dis. 2012 Aug 24;23. doi: 10.3402/mehd.v23i0.19260.
13. Du L, Bayir I, Lai Y, et al. Innate gender-based proclivity in response to cytotoxicity and programmed cell death pathway. J Biol Chem. 2004;279(37):38563-70.
14. Du L, Hickey RW, Bayir H, et al. Starving neurons show sex difference in autophagy. J Biol Chem. 2009;284(4):2383-96.
15. Manole MD, Tehranian-DePasquale R, Du L, Bayir H, Kochanek PM, Clark RS. Unmasking sex-based disparity in neuronal metabolism. Curr Pharm Des. 2011;17(35):3854-60.
16. James SJ, Melnyk S, Fuchs G. Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism. Am J Clin Nutr. 2009;89(1):425-30.
17. James SJ, Rose S, Melnyk S, et al. Cellular and mitochondrial glutathione redox imbalance in lymphoblastoid cells derived from children with autism. FASEB J. 2009 Aug;23(8):2374-83.
18. Deth RC. Molecular origins of human attention: the dopamine-folate connection. Berlin: Springer; 2003
19. Palomba S, Marotta R, Di Cello A, et al. Pervasive developmental disorders in children of hyperandrogenic women with polycystic ovary syndrome: a longitudinal case–control study. Clin Endocrinol (Oxf). Clin Endocrinol (Oxf). 2012 Dec;77(6):898-904
20. Fellman J, Eriksson AW. Temporal trends in the secondary sex ratio in Nordic countries. Biodemograph Soc Biol. 2011;57(2):143-54.
21. Grech V, Vassallo-Agius P, Savona-Ventura C. Secular trends in sex ratios at birth in North America and Europe over the second half of the 20th century. J Epidemiol Community Health. 2003;57(8):612-5.
22. Mackenzie CA, Lockridge A, Keith M. Declining sex ratio in a first nation community. Environ Health Perspect. 2005;113(10):1295-8
23. Schwarz E, Guest PC, Rahmoune H, et al. Sex-specific serum biomarker patterns in adults with Asperger's syndrome. Mol Psychiatry. 2011;16(12):1213-20.
24. Sarachana T, Xu M, Wu R-C, Hu VW. Sex hormones in autism: androgens and estrogens differentially and reciprocally regulate RORA, a novel candidate gene for autism. PLoS ONE. 2011;6(2):e17116. doi:10.1371/journal.pone.0017116
25. Borras C, Sastre J, Garcia-Sala D, Lloret A, Pallardo FV, Vina J. Mitochondria from females exhibit higher antioxidant gene expression and lower oxidative damage than males. Free Radic Biol Med. 2003;34(5):546-52.
26. Hamon I, Valdes V, Franck P, Buchweiller MC, Fresson J, Hascoet JM. Gender-dependent differences in glutathione (GSH) metabolism in very preterm infants. Arch Pediatr. 2011;18(3):247-52. French.
27. van Lieshout EM, Peters WH. Age and gender dependent levels of glutathione and glutathione S-transferases in human lymphocytes. Carcinogenesis. 1998;19(10):1873-5.
28. Tarnopolsky LJ, MacDougall J D, Atkinson SA, Tarnopolsky MA, Sutton JR. Gender differences in substrate for endurance exercise. J Appl Physiol. 1990;68(1):302-8.
29. Lamont LS, McCullough AJ, Kalhan SC. Gender differences in the regulation of amino acid metabolism. J Appl Physiol. 2003;95(3):1259-65.
30. Horton MK, Kahn LG, Perera F, Barr DB, Rauh V. Does the home environment and the sex of the child modify the adverse effects of prenatal exposure to chlorpyrifos on child working memory? Neurotoxicol Teratol. 2012;34(5):534-41.
31. Nguon K, Ladd B, Baxter MG, Sajelel-Sulkowska EM. Sexual dimorphism in cerebellar structure, function, and response to environmental perturbations. Prog Brain Res. 2005;148:341-51.
32. Nguon K, Baxter MG, Sajdel-Sulkowska EM. Perinatal exposure to polychlorinated biphenyls differentially affects cerebellar development and motor functions in male and female rat neonates. Cerebellum. 2005;4(2):112-22.
33. Rhodes ME, Rubin RT. Functional sex differences ('sexual diergism') of central nervous system cholinergic systems, vasopressin, and hypothalamic-pituitary-adrenal axis activity in mammals: a selective review. Brain Res Brain Res Rev. 1999;30(2):135-52
34. Luine V. Sex differences in chronic stress effects on memory in rats. Stress. 2002;5(3):205-16.
35. Lavoie JC, Rouleau T, Truttmann AC, Chessex P. Postnatal gender-dependent maturation of cellular cysteine uptake. Free Radic Res. 2002;36(8):811-7.
36. Lavoie JC, Chessex P. Gender-related response to a tert-butyl hydroperoxide-induced oxidation in human neonatal tissue. Free Radic Biol Med. 1994;16(3):307-13.
37. Lavoie JC, Chessex P. Gender and maturation affect glutathione status in human neonatal tissues. Free Radic Biol Med. 1997;23(4):648-57.