Original Article

# Autism as a biomedical platform for sex differences research

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**Abstract** Autism has become a 'biomedical platform' for sex differences research in fields such as genetics, endocrinology and neuroscience. Increasingly, researchers in these fields pose the male prevalence of autism as a model for investigating sex differences in the brain, and offer basic research on sex differences in the brain as a resource for understanding the etiology of autism. The use of autism as a biomedical platform for sex differences research obscures empirical and interpretive contestations surrounding claims about the male prevalence of autism. We argue that the uncritical use of this research platform across many fields stands to distort scientific research on autism and contribute to harmful gender stereotypes.
*BioSocieties* advance online publication 7 July 2014; doi:10.1057/biosoc.2014.17

**Keywords:** autism; Asperger's Syndrome; biomedical platform; gender; sex differences; translational research



In March 2010, the United States Institute of Medicine (IOM) hosted "Sex Differences and Implications for Translational Neuroscience Research", a workshop attended by a diverse group of 62 participants including university professors, graduate students, science writers, biomedical consultants and representatives of the National Institutes of Health (NIH), the United States Food and Drug Administration, the advocacy organization Autism Speaks and various pharmaceutical companies (Pankevich *et al*, 2011). The 110-page workshop report emphasizes sex as an important component of human neurological and psychiatric health and urges investigators to treat sex as a significant variable in basic neuroscience research. Autism serves as a prime example of an area ripe for translation between basic sex differences research and the clinic:

> Autism is a common neurodevelopmental disorder with a significant sex difference; males are four times more likely to be affected than females. One theory for this disparity is the "extreme male brain theory of autism" by Simon Baron-Cohen. This theory posits that males generally have less empathy than females, and autism is an

> extreme form of that sex distribution that occurs in the general population. […] This area should be fertile ground for hypothesis-driven translational neuroscience research that investigates sex differences.
>
> (Pankevich *et al*, 2011, p. 63)

Following Keating and Cambrosio (2003), we define a biomedical platform as a dynamic infrastructure – including tools, assays, conventions, protocols and definitions – upon which scientific claims relevant to human medicine can be built. The IOM report shows how a wide audience of scientists and funding organizations has come to accept the notion of autism as a biomedical platform for sex differences research – and how this platform is explicitly linked to the 'extreme male brain' (EMB) theory of autism.

Male prevalence is a common characteristic of all autism spectrum disorders (ASDs), although the degree of male-to-female bias varies from 14:1 among average-IQ and high-IQ individuals with high-functioning autism (HFA) and Asperger's to 2:1 for individuals with intellectual impairment (Wing, 1981b; Fombonne, 1999; Fombonne, 2005; Nicholas *et al*, 2008; Whiteley *et al*, 2010; Centers for Disease Control and Prevention (CDC), 2012). Among the majority of those with ASDs, who have mild to severe intellectual impairments, males outnumber females by approximately 2:1. This is consistent with the long-documented 2:1 male bias in all cognitive developmental disorders leading to intellectual impairment (Handen, 2007) and significantly less than the reported 10:1 male prevalence of attention deficit hyperactivity disorder (Seeman, 2010). Despite this, researchers single out autism as an especially revealing platform for neurological sex differences research.

In this article, we document a rising tide of sex differences research in genetics, neuroscience and endocrinology that advances the claim that autism's male prevalence is a unifying and striking hallmark of the disorder. Examining the language of grant proposals and peer-reviewed publications that link autism and sex difference, we find that autism's dramatic male prevalence has become an article of faith in autism and sex differences research. Yet while there are sex differences in the prevalence of the cluster of signs and symptoms currently described as autism, several compelling lines of evidence suggest that sex differences are not as dramatic and homogenous as imputed by this growing research platform.

We argue that the widely prevalent understanding of autism as a disorder of gender is, in part, a product of the sociohistorical conditions of the development of autism over the past half-century. Typing autism as a male disorder has facilitated the advancement of autism along several dimensions: as a diagnostic category; as an object of biomedical research; as a worthy matter of public concern, advocacy and investment; as a biological explanation for male dominance in the science professions; and as a pop culture archetype associated with male genius. All of these elements help to gird the use of autism as a biomedical platform for sex differences research today and repel critical examination of its implications for scientific research on autism and for broader understandings of gender difference.

## The EMB Theory

According to the EMB theory of autism, the cognitive and personality traits associated with autism are on a continuum with neurotypical male traits. The EMB model of autism

poses the clinical phenotype and neurobiology of autism as a resource for exploring the biological origins of gender stratification in activity preferences and career choices. University of Cambridge developmental psychologist Simon Baron-Cohen promotes a version of this theory that describes the cognitive style of HFA as an exaggerated version of the typical male cognitive style – strong at systemizing, weak at empathizing. Chief among the 'systemizing' traits of interest are those thought to be associated with male excellence in or preference for the science, technology, engineering and mathematics (STEM) professions. As Baron-Cohen (2009) has written:

> Males, maths and autism. On the face of it, these three things don't appear to be linked. And yet they are. Males are much more likely to apply to university to study maths, for example. In 2007, three quarters of applicants to read maths at Cambridge were male, as were 90 per cent of applicants for the computer sciences degree. Cambridge is not unique in this way. So why are males so attracted to studying maths? And why, in over 100 years of the existence of the Fields Medal, maths' Nobel Prize, have none of the winners have [sic] ever been a woman? Similarly, people with autism are much more likely to be male.

As Baron-Cohen (2003a) further reasons in the 2003 book *The Essential Difference*, "All the sciences utilize systemizing as their basis, and all are dominated by men […] only three of the 170 living Nobel Prize winners in science are women" (p. 71). Baron-Cohen claims that those who score high on systemizing also excel in STEM and that this explains the dominance of males in these professions: "On tests of intuitive physics, males score higher than females, and people with AS [Asperger's Syndrome] score higher than males. In addition, males are over-represented in departments of mathematics, and math is frequently chosen by people with AS as their favorite subject at school" (Baron-Cohen, 2003a, p. 152).

In the past decade, the EMB theory has influenced neurobiology and the behavioral sciences.[1] It has also entered into public discussions of male and female stereotypical behaviors and the question of women in science.[2] The EMB theory is frequently sourced by both experts and the popular media to support a view of stereotypical sex differences as fixed, innate and lodged in the brain. "They Just Can't Help It: There Really Are Big Differences Between the Male and Female Brain. And They Could Help Explain Conditions such as Autism" reads the headline of a 2003 story by Baron-Cohen (2003b) in *The Guardian*. The cover of *Newsweek* announced, "Girls, Boys and Autism: Why 4 of 5 Autistic Children Are Male, What New Science Tells Us About How Our Brains Work" (Cowley, 2003). Following the publication of Baron-Cohen's (2003a) *The Essential Difference* and *Science* article "Sex differences in the brain: Implications for explaining autism" (Baron-Cohen *et al*,

1 Along with Baron-Cohen, Rockefeller University neurobiologist Pfaff (Pfaff *et al*, 2011), Simon Fraser University evolutionary biologist Crespi and London School of Economics sociologist Badcock (Crespi and Badcock, 2008; Badcock and Crespi, 2008) and neuroscientist Keller of the Università Campus Bio-Medico di Roma (Keller and Ruta, 2010) are among the leading proponents of the EMB theory.

2 Empirical critiques of the EMB theory have been articulated within the autism research community (Ellis, 2005; Barbeau *et al*, 2009; Morsanyi *et al*, 2012) and by gender scholars in the social sciences (Nash and Grossi, 2007; Jordan-Young, 2010; Grossi and Fine, 2012; Sample, 2012). However, these critiques are not acknowledged in the expanding field of basic sex differences research that takes the male prevalence of autism as its starting point.

2005), articles and interviews in many major publications trumpeted the message that autism tells us something fundamental about the biological essence of masculinity and femininity: *New Scientist*, "Sugar and Spice" (Baron-Cohen, 2003c); *Wall Street Journal*, "Is the Autistic Brain Too Masculine?" (McGough, 2003); *Salon.com*, "Of Math and Makeup Tips" (Reiter, 2003); and *The Sunday Times*, "Hah! You Know He's Not a Girl" (Baxter, 2005).

## Male Prevalence of Autism: A History

Observations of the male prevalence of autism have played a role in the history of the autism diagnosis from its inception. In 1958, American psychologist Leo Kanner reported a sex ratio of 4 boys to 1 girl in a clinical sample of 100 autistic children (Kanner and Lesser, 1958). At the time, the term 'autistic' was used to describe symptoms of "schizophrenia, childhood type". Kanner sought to establish "early infantile autism" – a severely disabling, early presenting condition leading to profound communication and social deficits – as its own diagnostic category. Debate over the distinctions between childhood schizophrenia and autism in the 1970s eventually led to the inclusion of "infantile autism" as its own diagnosis in the 1980 Diagnostic and Statistical Manual of Mental Disorders (DSM)-III (Eyal *et al*, 2010). Sex difference was part of this debate, with the male prevalence of autism cited as evidence for two discrete disorders. For example, a 1979 publication in *Psychological Bulletin* noted, "With regard to autism, there seems to be universal agreement that males outnumber females in ratios ranging from 2:1 to 4:1. This ratio differs from that of adult schizophrenia, in which the sex ratio is the same and is one of the facts adduced to advance the contention that autism and adult schizophrenia are different nosological entities" (Eme, 1979, p. 589).

Independently of Kanner, in 1944, German psychiatrist Asperger (1944) described a condition he called "autistic psychopathy": a disturbance of behavior that leaves a child socially inept but with "a high level of original thought and experience" (p. 37). Although Asperger's "autistic psychopathy" was distinct from Kanner's "early infantile autism", both were described as male prevalent. Autistic psychopathy remained a little-known condition until 1981, when English psychiatrist Lorna Wing revived it in "Asperger's Syndrome: A Clinical Account". Wing emphasized similarities between the condition Asperger had described and infantile autism, despite large differences in IQ and speaking ability. Wing helped transform Asperger's from a little-known disorder or personality type into a much-discussed condition, seen as a potential gateway into the mystery of autism. The number of publications on Asperger's increased from 2 before 1981 to 900 by 2004 (Wing, 2005), and "Asperger's disorder" was added to the DSM-IV in 1994. Although "Asperger's disorder" was grouped together with "autistic disorder" in the pervasive developmental disorders category, the DSM-IV specified that an Asperger's diagnosis should exclude those with language and cognitive delays. Thus, Asperger's became part of the so-called "autism spectrum", characterizing the higher end of the IQ, speaking ability and functionality spectrum. In 2013, the DSM-V removed the Asperger's and autistic disorder diagnoses altogether, replacing them with the umbrella diagnosis "ASDs". This change reflects the view that Asperger's and autism share a common set of behaviors, differing primarily by the severity of symptoms.

The integration of Asperger's into the autism spectrum in the 1980s and 1990s helped facilitate the rise of the EMB theory of sex differences in the human brain, which links autism,

males and STEM talent. Male prevalence and skills in math and science became much more strongly associated with autism once Asperger's was placed on the same spectrum. In 1981, Wing published "Sex Ratios in Early Childhood Autism and Related Conditions". Wing's study of 158 children with autistic symptoms found that male prevalence varied with IQ. Wing found an overall sex ratio of 2.6 boys to 1 girl, but there was a significantly higher male prevalence (14.2 boys to 1 girl) in the group of children with IQs above 50. Recent epidemiological studies have reported similar findings, with a greater male prevalence in average-IQ and high-IQ autism populations (Fombonne, 1999, 2005). In this way, the inclusion of Asperger's on the autism spectrum raised the overall male prevalence of ASDs.

The association of Asperger's with math and science ability was also present in early characterizations of the disorder. In 1944, Asperger suggested that "autistic psychopaths" had exceptional skill in the fields of mathematics and science. He reported among his study subjects "a large number of people whose mathematical ability determines their professions; mathematicians, technologists, industrial chemists and high-ranking civil servants" (Asperger, 1944, p. 89). Asperger's description of autistic psychopathy noted similarities between male cognition and autistic personality, and connected this to the greater male prevalence of the condition. Asperger (1944) wrote,

> The autistic personality is an extreme variant of male intelligence. Even within the normal variation, we find typical sex differences in intelligence […] In general, girls are the better learners. They are more gifted for the concrete and the practical, and for tidy, methodical work. Boys, on the other hand, tend to have a gift for logical ability, abstraction, precise thinking and formulating, and for independent scientific investigation. […] In general, abstraction is congenial to the male thought processes, while female thought processes draw more strongly on feelings and instincts. In the autistic person abstraction is so highly developed that the relationship to the concrete, to objects and to people has largely been lost.
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> (pp. 84–85)

When Wing (1981a, b) revived Asperger's Syndrome in 1981, she extended his ideas. "It is interesting to note that Asperger described his syndrome, which some regard as a variety of autism associated with comparatively high levels of ability, as 'an extreme variant of male intelligence and male character' " (Wing, 1981b, pp. 134–135). Wing suggested that "studies of sex differences in the normal population may shed further light" on the male prevalence of autism (1981b, p. 135). She cited "reasonably well-established evidence for female superiority in at least some aspects of language, and the male superiority in visuo-spatial and mathematical skills", though she noted that "it is not yet established whether these differences are environmental or constitutional" (1981b, p. 135).

Since the 1980s, two popular archetypes – the autistic mathematical savant and the scientist–mathematician–tech wizard with Asperger's – have helped to cement the idea that autism and outstanding science-related abilities are inseparable (Figure 1). The rise of these archetypes is linked to sociological changes around autism diagnosis, treatment and research. In *The Autism Matrix*, Eyal *et al* (2010) persuasively argue that after the deinstitutionalization of intellectually disabled individuals living in state institutions in the 1960s, parents increasingly found autism to be an attractive diagnosis for their children with developmental disabilities, and that this in large part explains the increase in autism diagnoses over the past 40 years. As Eyal *et al* (2010) argue, the autism diagnosis was particularly attractive to parents


**Figure 1:** The mathematical savant autism archetype. Screen shot from a 2010 *ABC News* feature on mathematical genius that profiled Daniel Tammet, a man with Asperger's and synesthesia, who has memorized 22 514 digits of $\pi$ and can multiply 3-digit numbers in seconds. Tammet is described as an "autistic savant" and "mathematical genius".*Source*: Anon (2010).



because it opened avenues to therapy, offered an extensive parent support network and reduced stigma surrounding their child's condition (see also Silverman, 2012). The more children diagnosed with autism, the greater the motivation for parents to make autism an even less stigmatizing condition.

These pressures contributed to a growing focus of autism advocacy on the minority of autistics with high IQ or unusual talents. In the 1960s, autism parent-advocate Rimland (1964) argued that high parental intelligence is associated with autism and explained the above average IQ of some autistic children. In the early 1970s, American and British parent organizations collaborated on an effort to publicize "the near-normal autistic adolescent" (Dewey and Everard, 1974, p. 348). Today, many autism advocates and self-advocates emphasize savantism, in which individuals with developmental disabilities nonetheless possess prodigious abilities. Self-advocate Daniel Tammet's books *Born On A Blue Day: Inside the Extraordinary Mind of an Autistic Savant* (Tammet, 2007) and *Islands of Genius: The Bountiful Mind of the Autistic, Acquired, and Sudden Savant* (Treffert and Tammet, 2010) have been bestsellers. The Autism Research Institute Website includes a page on savantism (Edelson, 2011), and Autism Speaks regularly posts links to news stories on autistic savants, recently spotlighting a Good Morning America feature titled "Musical Savant, Derek Paravacini, Stuns Audiences" (Anon, 2011).

Asperger's has also produced culturally resonant archetypes that strengthen the associations between the male prevalence of autism and success in the STEM professions. Temple Grandin, a well-known autism self-advocate, devotes a chapter of her best-selling book *Thinking in Pictures* (1995) to the link between autism and genius. Grandin (1995) claims that Einstein had many traits of an adult with mild autism and suggests that Vincent van Gogh, Ludwig Wittgenstein and Bill Gates all exhibited autistic traits (Chapter 10). Fitzgerald, professor of child and adolescent psychiatry at Trinity College, Dublin, has similarly published extensive speculations on the autistic traits of famous men of genius. These include "Is the cognitive style of the persons with the Asperger's Syndrome also a 'mathematical style'?" (Fitzgerald, 2000) and "Asperger's disorder and mathematicians of genius" (Fitzgerald, 2002). Together, the popular and scientific

literature on autistic savants and high-IQ autism-identified scientists and engineers, mostly male, has helped to gender autism as a disorder and to create a perception of a natural and indelible link between the male prevalence of autism and male STEM ability.

## Interpreting the Male Prevalence of Autism

The autism spectrum is a fuzzy and controversial diagnostic construct. In this discussion, we use the terms 'HFA', 'Asperger's' and 'IQ' to describe aspects of the autism spectrum relevant to interpreting claims about the male prevalence of autism, while recognizing that these concepts, like claims about the male prevalence of autism, are also at least partially culturally, historically and socially produced. The conventional division of ASD individuals into 'high functioning' and 'low functioning' and the use of standard IQ measures to assess cognitive ability among those on the autism spectrum are particular matters of contention. Autism self-advocates and disability studies scholars argue that disability is often "a function of environment, rather than a feature intrinsic to the individual" (Broderick and Ne'eman, 2008, p. 465). The concept of 'high functioning', for example, implicitly suggests a normative conception of "what constitutes human social functioning" (Grinker, 2010, p. 175; see also Davidson, 2010 and Straus, 2013). Similarly, IQ is a measure developed for assessing neurotypical cognitive ability. Alternative IQ measures that do not involve verbal ability reveal higher performance than do standard assessments, challenging claims about the prevalence and nature of mental impairment among ASD individuals (Dawson *et al,* 2007, Barbeau *et al,* 2012, Soulières *et al*, 2012). The notion of a spectrum of severity in social functioning and cognitive ability in ASD, however, is broadly accepted in both clinical practice and the scientific research we analyze in this article. The terms HFA and Asperger's "describe individuals with average to above average intelligence, highly developed language skills, but significant social and behavioral concerns" (Bagatell, 2010, p. 35). Typically, "the experiences and needs of these individuals are very different from those considered low functioning" (ibid., p. 46).

As we have shown, the historical inclusion of Asperger's on the autism spectrum is partially responsible for the often-cited dramatic male prevalence of ASDs and the association of autism with STEM talent. However, even if the inclusion of Asperger's on the autism spectrum is regarded as uncontroversial, HFA and Asperger's individuals with average-to-high IQ do not represent the majority of people with autism. A meta-analysis of 23 epidemiological surveys of autism found that only 20 per cent of subjects with autism are without intellectual impairment (Fombonne, 1999). A 2005 review of autism epidemiology reported that "In 13 studies (865 subjects) where the sex ratio was available within the normal band of intellectual functioning, the median sex ratio was 5.5:1. Conversely, in 12 studies (813 subjects), the median sex ratio was 1.95:1 in the group with autism and moderate to severe intellectual disability" (Fombonne, 2005). A 2008 study of 8-year-old children in South Carolina reported that of 295 children diagnosed with ASDs, "In the IQ>70 range, the male:female prevalence ratio was 4.9:1, whereas in the IQ<70 range, the male:female prevalence ratio was 2.4:1 […]. Among individuals with the most severe cognitive impairments (IQ<34), boys and girls were equally affected" (Nicholas *et al*, 2008). In short, male prevalence is significantly less pronounced in autistic individuals with intellectual disability, showing a sex ratio typical of all developmental disorders with mental impairment (CDC, 2009; Whiteley *et al*, 2010).

The possibility that females may be underdiagnosed, and males overdiagnosed, further complicates claims of the male prevalence of autism. Referral and diagnostic gender bias is a long-documented phenomenon in the psychometric testing, special education and learning disability fields (Badian, 1999; Coutinho and Oswald, 2005; Reynolds and Fletcher-Janzen, 2007). Gender bias in autism diagnosis is understudied, but some evidence suggests that males are more likely to be diagnosed with autism and that women are underdiagnosed, in part due to stereotypes of the condition as a male disorder characterized by lack of verbal ability (Kopp *et al*, 2010; Cheslack-Postova and Jordan-Young, 2012). As Judith Gould, director of the British National Autistic Society's Lorna Wing Centre for Autism, argues, girls in Western cultures tend to be developmentally precocious in their verbal abilities, and thus their autistic symptoms may be less likely to draw diagnostic attention: "It might be that due to misconceptions and stereotypes, many girls and women with autism are never referred for diagnosis, and so are missing from statistics. […] Characteristics such as shyness and oversensitivity, common to people affected by autism, are sometimes deemed to be typically female traits" (quoted in Anon, 2008). A recent study suggests that females diagnosed with anorexia nervosa, a classically female-biased disorder, exhibit high levels of systemizing behavior that meets the diagnostic criteria for autism (Oldershaw *et al*, 2011). Sex-stereotyped diagnostic practices may shuttle these girls and women into the diagnostic category of eating disorders rather than autism.

Both lack of diagnosis and delayed diagnosis may help contribute to more negative outcomes in females with autism. The CDC reports that a higher proportion of females with ASDs have cognitive impairments, compared with males, among 8-year-old children in six US states (CDC, 2009; CDC, 2012). As bioethicists Krahn and Fenton (2012) note, "If girls on the Autism Spectrum are being systematically undiagnosed or improperly diagnosed, this would cut them off from ASD early intervention therapies that have proven beneficial to many children with autism in the short- and long-term" (p. 99).

Women who do receive an autism diagnosis are understudied. Clinical studies tend to select HFA and Asperger's participants – a population in which females are the minority. In their 2011 strategic plan for research, the IACC acknowledged, "Many studies of autism preferentially enroll higher-functioning individuals who do not have cognitive impairment, because of their ability to cooperate and participate in study-related tasks. However, these individuals represent only a subset of all individuals with autism, and lessons learned from them may or may not be generalizable to all individuals with ASD". The IACC (2011) also noted a troubling lack of research on girls and women with autism, writing, "Many studies of autism preferentially enroll males, who, due to a 4:1 increased prevalence, are easier to recruit. Without additional information about the biological features of ASD in females, it remains unclear whether the course of ASD is similar and whether currently used interventions are appropriate for females".

In sum, the 4:1 sex ratio ubiquitously cited in autism and sex differences research relies on two assumptions: (i) that the pronounced prevalence of males among HFA, Asperger's and average-to-high IQ individuals – representing 20 per cent of those on the autism spectrum – carries insight into the general etiology of the condition, and (ii) that current diagnosis rates of males and females reflect organic facts about autism and not gender stereotypes in diagnostic practices. These assumptions carry potential harms. They contribute

to the research emphasis on a small subset of those with autism, marginalizing those with substantial impairments – the majority of those living with autism. They also overlook the legitimate and poorly explored possibility of underdiagnosis of females and/or overdiagnosis of males with ASDs.

Finally, there is the question of autism and male math ability. EMB theorists use examples of autistic savants as well as of HFA and Asperger's individuals diagnosed as being on the autism spectrum to support the claim that autism accompanies innate interest in and talent for STEM. However, studies have shown that math ability seldom accompanies autism. Autistic savantism is rare; recent estimates report an incidence as low as 1 per cent (Hermelin, 2001). Autistic mathematical savants can exhibit incredible speed in mathematical calculation and memory for numbers. However, these arithmetic skills are not identical to the complex problem-solving skills required in high-level math, science and engineering. Most autistic savants are developmentally disabled and have severe general mental handicaps that prevent them from living independently, let alone succeeding professionally in science, even with accommodations (Heaton and Wallace, 2004; Treffert, 2009).

Systematic research on the abilities of individuals with HFA and Asperger's also offers little support for an association between autism and male math ability. Studies indicate that the vast majority of people with Asperger's struggle in arithmetic and mathematics (Whitby and Mancil, 2009). Most Asperger's students have average or weak mathematical ability compared with neurotypical individuals (Chiang and Lin, 2007) and strong verbal, not mathematical, skills compared with all other skills (Goldstein *et al*, 2001). Most students with HFA and Asperger's display weakness in problem-solving skills and applying math to real-world situations (Whitby *et al*, 2009). Although some HFA and Asperger's individuals on the autism spectrum are mathematically gifted, these skills are typically not generalized, but restricted to certain subtypes of mathematical ability (Jones *et al*, 2009; Burger-Veltmeijer *et al*, 2011).



## Grant-Funded Research and Peer-Reviewed Publications on Autism and Sex Differences

Despite these empirical and conceptual problems with claims about the male prevalence of autism, the 4:1 sex ratio and the EMB theory ground a rising research platform, as reflected by grant funding and publication trends over the past decade. US autism advocacy groups and federal agencies contribute hundreds of millions of dollars each year to projects investigating the biology of autism (Office of Autism Research Coordination (OARC), National Institute of Mental Health (NIMH) and the Interagency Autism Coordinating Committee (IACC), 2012) (Table 1). In 2010, the most recent date for which data are available, US federal agencies and private organizations together provided US$408 million for autism research (ibid.). The NIH spent $217 million on autism research in 2010, comparable to the $172 million spent on Parkinson's Disease research and much more than the $28 million allocated for Down Syndrome research (NIH, 2012a, b). Advocacy groups and private organizations have also significantly contributed to autism research funding, providing $74 million in 2010. Autism Speaks, one of the most prominent private autism advocacy organizations in the United States, funded 228 research projects in 2010 with an overall investment of

**Table 1:** Funding for autism research by agency/organization, 2010

| *2010 ASD research funding by agency/organization* | | |
|---|---|---|
| *Funding agency/organization* | *Number of projects* | *Total funding* |
| National Institutes of Health (NIH) | 545** | $217 143 701 |
| Simons Foundation (SF) | 123 | $53 729 921 |
| Health Resources and Services Administration (HRSA) | 82 | $43 303 150 |
| Department of Education (ED) | 139 | $30 432 564* |
| Centers for Disease Control and Prevention (CDC) | 30 | $19 698 859 |
| Autism Speaks (AS) | 228 | $18 476 890 |
| National Science Foundation (NSF) | 69 | $12 222 206* |
| Department of Defense (DoD) | 58 | $7 082 059 |
| Administration for Children and Families (ACF) | 1 | $1 877 959 |
| Agency for Healthcare Research and Quality (AHRQ) | 4 | $1 548 053* |
| Centre for Autism and Related Disorders (CARD) | 31 | $906 482 |
| Environmental Protection Agency (EPA) | 1 | $756 802 |
| Autism Research Institute (ARI) | 15 | $386 905 |
| Centers for Medicare & Medicaid Services (CMS) | 3 | $376 159 |
| Autism Science Foundation (ASF) | 13 | $245 000 |
| Organization for Autism Research (OAR) | 12 | $191 590 |
| Coalition for SafeMinds (SafeMinds) | 8 | $128 975 |
| Southwest Autism Research & Resources Center (SARRC) | 5 | $70 000 |
| Grand total | 1367 | $408 577 276 |

*Notes*: *Annual funding amounts for AHRQ, ED and NSF are estimated; **The NIH project number shown reflects unique NIH projects. Projects funded by more than one NIH institute ('co-funds') were combined and only counted as a single project. This approach differs from that used in the NIH RePORT database, where each co-fund is counted as a separate project when the data are exported to Excel.
*Source*: Office of Autism Research Coordination (OARC), National Institute of Mental Health (NIMH) and the Interagency Autism Coordinating Committee (IACC 2012).



$18 million (Office of Autism Research Coordination (OARC), National Institute of Mental Health (NIMH) and the Interagency Autism Coordinating Committee (IACC), 2012). Such an abundance of research funding has attracted investigators who frame their research to make it more relevant to autism. Citing statistics that autism affects boys between 4 and 10 times as often as girls, these investigators present genetic, hormonal and brain sex differences as potentially relevant to understanding the etiology and therapeutic treatment of autism.

Since 1988, the NIH has funded 217 research projects on autism and sex differences.[3] Funding for autism and sex differences research is a recent trend, with 47 per cent of these grants awarded between 2007 and 2011. These studies cite large sex differences in the prevalence of autism as a central motivation for research. An additional 8 projects on autism and sex differences have been funded by Autism Speaks since its founding in 2005.[4] Recent grant-funded research proposals provide strong evidence that autism is functioning as a biomedical research platform for basic sex differences research.

3 NIH Research Portfolio Online Reporting Tools: http://projectreporter.nih.gov/reporter.cfm. As of 6 July 2012. Exact search terms: autism And ("sex difference" Or "gender difference" Or "sex specific" Or "gender specific" Or "sexual difference" Or "sexual dimorphism" Or "sexual dimorphic" Or "sex dependent" Or "gender dependent" Or "sex based" Or "gender based" Or "sex ratio" Or "sex characteristics").

4 Autism Speaks Science Grant Search: www.autismspeaks.org/science/grant-search/. As of 6 July 2012.

In contrast to applied experimental, observational or epidemiological research in human populations in a clinical context, we define 'basic' sex differences research as studies in human or non-human molecular, cellular or biochemical systems in endocrinology, genetics, molecular biology and neuroscience. We found that grants for research on autism and sex differences are awarded in a range of disciplines, including genetics, endocrinology and the neurosciences, and for research in both human and non-human systems. Recipients include both seasoned autism researchers who have only recently begun to investigate sex difference and scientists who primarily conduct basic research on sex-specific biology and have only recently begun to relate their work to autism. Grant proposals ubiquitously cite the 4:1 sex ratio as a foundation for research.

For example, University of California, San Francisco geneticist Lauren Weiss received $270 375 from the Shriver Institute for her project "A sex-specific dissection of autism genetics". Weiss has published on autism genetics since 2003, but the sex ratio of autism is a new focus of her laboratory. The project proposal states:

> *Four times as many males as females are affected, for unknown reasons*. Thus, we may be able to leverage our knowledge about the primary genetic and hormonal determinants of sexual dimorphism in order to dissect a major source of heterogeneity in autism. […] The central hypothesis is that sexually dimorphic susceptibility to autism is reflected in sex differences of the genetic architecture of autism.
>
> (Weiss, 2012, emphasis added)

Similarly, Daniel Geschwind of University of California, Los Angeles primarily investigates autism genetics, and his lab has recently begun to investige sex difference. Donna Werling, a graduate student in the Geschwind lab, received a $31 561 grant from the NIMH for a project entitled "Investigation of sex differences associated with autism". The project description explicitly references the 4:1 male prevalence of autism as motivation:

> It is known that *ASDs affect at least four times as many males as females*, and that ASDs are highly heritable, indicating a strong genetic contribution. Continued identification of genes associated with ASDs has advanced our understanding of the role of genetics in ASDs, but the skewed sex ratio in prevalence remains unexplained. To this end, studying a candidate gene that shows sex differences in expression patterns or associated neural phenotypes may provide unique insights into ASD pathophysiology.
>
> (Werling, 2012, emphasis added)

University of Virginia behavioral geneticist Emilie Rissman also investigates genetic sex differences in her project "Sex chromosomes, epigenetics, and neurobehavioral disease", which received $678 841 from the NIMH. Rissman (2012) cites autism as the most relevant application of her work: "Given the large sex differences in the prevalence of several neurobehavioral diseases (for example, *autism is found 4 times more often in boys than in girls*), we focus on epigenetic modification of mechanisms that underlie sex differences in behavior" (emphasis added). Autism Speaks awarded Rissman (2008) $300 000 in 2008 for a similar project titled "Epigenetics, hormones and sex differences in autism incidence".

The interaction between genes, hormones and the environment is one focus of autism and sex differences research. Mount Sinai School of Medicine geneticist Jia Chen Chen (2006)

received $100 026 from Autism Speaks for a gene–hormone interaction study that explicitly cites the EMB theory of autism as the research model:

> *Autism occurs four times more frequently in males compared to females*, suggesting that a complex genetic predisposition, involving hormones, is involved […] since females have stronger empathizing capability, while males have stronger systemizing capability, an "extreme male brain" (EMB) theory may explain the genetic basis of autism.
>
> (emphasis added)

University of North Carolina psychiatrist John Gilmore received $85 979 from Autism Speaks for a project on testosterone and sex differences in brain anatomy. The project description states:

> *Autism occurs significantly more often in males than in females*, yet research on potential causes of the biased sex ratio is extremely limited. Multiple clues suggest that alterations in testosterone levels during development may contribute to this sex difference […] The proposed study will fill this crucial gap in our present knowledge by measuring early testosterone exposure and receptor sensitivity in a large population sample and relating them to development of regions known to be sexually dimorphic in childhood: the cerebrum, amygdala, hippocampus, and caudate.
>
> (Gilmore, 2006, emphasis added)

University of California, Davis public health scientist Irva Hertz-Picciotto received a $1 031 807 grant from the National Institute of Environmental Health Sciences for an investigation of childhood autism risks related to chemical exposure. The proposal identifies several chemicals with known hormonal effects as candidates for investigation. "Phthalates and bisphenol A are endocrine disruptors, the latter being estrogenic and the former, anti-androgenic. *Because of the 4:1 male-female ratio in autism*, sex steroids are hypothesized to play a role in susceptibility", they write (Hertz-Picciotto, 2012, emphasis added). Note that Phthalates and bisphenol A were chosen based on their sex-specific chemical action inside the body, not because boys encounter them more often than girls in gender-specific childhood environments. This reflects an understanding of autism's male prevalence as the result of innate biological sex difference rather than sex or gender differences in lived experience.

Other scientists primarily conduct basic research on sex-specific biological tissues, pathways and processes in non-human animal models, and have only recently begun to relate their work to autism. For example, University of Rochester neurobiologist Douglas Portman received a 2012 grant from the National Institute of General Medical Sciences for investigation of sex differences in the nervous system of the roundworm, *C. elegans*. In his grant proposal, Portman argues that work on sex differences in a very simple model organism might translate to autism research, writing, "These studies will identify genes and mechanisms that may have important roles in human mental health and neurological conditions, such as autism, mood disorders and chronic pain syndrome, that preferentially affect one sex over the other" (Portman, 2012). Although mood disorders and chronic pain are understood to be female prevalent (Gur *et al*, 2010; Lee, 2010; Seeman, 2010), Portman cites autism as the iconic male-biased mental health and neurological condition. Similarly, University of Massachusetts Amherst neuroendocrinologist Geert de Vries received a 2012 grant from the NIMH for basic

research on brain sexual differentiation in juvenile rats. In his proposal, he argues that this research may help to illuminate the neurological basis of "behavioral disorders that manifest themselves during development, such as autism spectrum disorders, [which] are often more common and severe in boys than in girls" (de Vries, 2012).

Physiologist Flavio Keller of the Università Campus Bio-Medico di Roma received $292 024 from Autism Speaks in 2006 for a study that investigates the effect of steroid hormones on neuron survival in animal models. The project description argues that this basic neuroscience research may be relevant to understanding why females are less susceptible to autism:

> This study will investigate the interaction between genetic vulnerability and gonadal steroid hormones on Purkinje cell survival, migration, and/or differentiation, which would account for the *biased sex ratio of autism* […] linking animal models with human pathological studies in an interdisciplinary fashion and studying the possible protective role of estrogen on genetic susceptibility to autism spectrum disorders.
>
> (Keller, 2006, emphasis added)

Keller (2008) received another $308 002 from Autism Speaks in 2008 for a project investigating the role of endogenous sex hormones, genetic susceptibility and environmental exposures in a mouse model of autism.

Trends in publications addressing autism and sex differences add to the picture of how autism is presently operating as a platform for basic sex differences research in genetics, endocrinology, molecular biology and the neurosciences. We used Thomson Reuters Web of Science to retrieve titles, abstracts and keywords of peer-reviewed publications on autism and sex differences research published since 1980. We used the topic field tag to search publication titles, abstracts, author keywords and Keywords Plus®, a Web of Science feature that includes words or phrases frequently used in the titles of an article's references. We limited the search to articles and reviews published between 1980 and 2011, to capture publication trends after the reintroduction of Asperger's in 1981.[5]

Using these methods, we identified 442 published articles and reviews addressing autism and sex difference. This is a subset of 16 331 publications on autism[6] and 97 982 publications on sex differences in general,[7] since 1980. We validated these data with cross-searches in the life sciences and medicine databases Scopus and Pubmed, which yielded similar numbers. Of the 442 publications on autism and sex difference that we identified, 86 per cent were published between 2001 and 2011, and the number of publications topically focused on



5 As of 12 July 2012. Exact search terms: TS = (autism AND ("sex difference*" OR "gender difference*" OR "sex specific" OR "gender specific" OR "sexual difference*" OR "sexual dimorph*" OR "sex dependen*" OR "gender dependen*" OR "sex based" OR "gender based" OR "sex ratio*" OR "sex characteristic*"). Refined by: Document Type = (ARTICLE OR REVIEW) Timespan = 1980–2011. Databases = SCI-EXPANDED, SSCI. Lemmatization = On. The Arts and Humanities Citation Index was excluded in an effort to focus on biomedical science publications. Search terms follow the recommendations of Moerman *et al* (2009) and Oertelt-Prigione *et al* (2010).

6 As of 12 July 2012. Exact search terms: TS = (autism). Refined by: Document Type = (ARTICLE OR REVIEW) Timespan = 1980–2011. Databases = SCI-EXPANDED, SSCI).

7 As of 12 July 2012. Exact search terms: TS = ("sex difference*" OR "gender difference*" OR "sex specific" OR "gender specific" OR "sexual difference*" OR "sexual dimorph*" OR "sex dependen*" OR "gender dependen*" OR "sex based" OR "gender based" OR "sex ratio*" OR "sex characteristic*"). Refined by: Document Type = (ARTICLE OR REVIEW) Timespan = 1980–2011. Databases = SCI-EXPANDED, SSCI. Lemmatization = On.

**Table 2:** Ranked journals that most commonly publish peer-reviewed research on 'autism and sex differences' compared with that journal's rank in 'all autism research' and 'all sex differences research'

| *Journal* | | *Autism and sex differences* | | *All sex differences* | | *All autism* | |
|---|---|---|---|---|---|---|---|
| | *5-year impact factor* | *Journal rank* | *Per cent of 422* | *Journal rank* | *Per cent of 97 982* | *Journal rank* | *Per cent of 16 331* |
| *Journal of Autism and Developmental Disorders* | 4.365 | 1 | 11.54 | 150 | 0.05 | 1 | 10.16 |
| *Personality and Individual differences* | 2.313 | 2 | 3.39 | 2 | 0.58 | 52 | 0.27 |
| ***Hormones and Behavior*** | ***4.126*** | ***3*** | ***2.26*** | ***10*** | ***0.42*** | ***81*** | ***0.09*** |
| *Research in Autism Spectrum Disorders* | 2.916 | 3 | 2.26 | 192 | 0.01 | 2 | 2.58 |
| *Behavioural Brain Research* | 3.512 | 4 | 2.04 | 18 | 0.33 | 31 | 0.50 |
| *PLOS One* | 4.537 | 5 | 1.81 | 17 | 0.33 | 17 | 0.78 |
| *Journal of Neuroscience* | 7.915 | 6 | 1.58 | 59 | 0.17 | 28 | 0.55 |
| *PNAS* | 10.472 | 6 | 1.58 | 22 | 0.28 | 24 | 0.66 |
| … | … | … | … | … | … | … | … |
| ***Psychoneuroendocrinology*** | ***5.264*** | ***9*** | ***0.91*** | ***31*** | ***0.23*** | ***83*** | ***0.08*** |

*Notes*: The endocrinology journals ***Hormones and Behavior*** and ***Psychoneuroendocrinology*** are among the top journals publishing research on 'autism and sex differences' and 'all sex differences'. In contrast, they rank 81 and 83, respectively, among journals that feature research on 'all autism'. (Web of Science data compiled by authors).

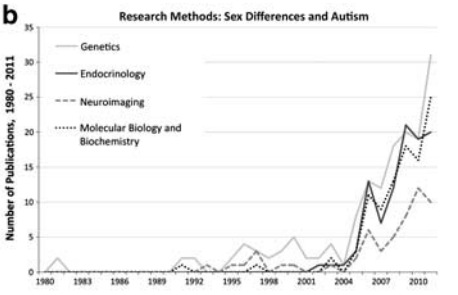


autism and sex differences has steadily increased since 2006. Although Baron-Cohen and colleague Sally Wheelwright have authored 10 per cent of all publications that mention autism and sex difference, the majority of published research on sex difference and autism is not theirs. Research on autism and sex difference is not the work of a few highly prolific investigators. Rather, we have found that research on autism and sex difference is an area of study conducted by researchers from a variety of fields, using a variety of methods.

The subset of studies on autism and sex differences has a different profile than autism research as a whole. We ranked journals that most commonly publish peer-reviewed research on "autism and sex differences" (442 publications), "all autism research" (16 331 publications) and "all sex differences research" (97 982 publications), since 1980. This yielded results (Table 2) consistent with the emergence of autism as a biomedical platform for sex differences research. For example, the publication profile of studies on 'autism and sex differences' contains a proportion of studies focused on endocrinology that is more similar to that of 'all sex differences research' than to 'all autism research'. The endocrinology journals *Hormones and Behavior* and *Psychoneuroendocrinology* are among the top journals publishing research on 'autism and sex differences'. These journals more commonly publish research on 'all sex differences' than research on 'all autism'. These findings suggest that autism and sex differences research is characterized by some methods (endocrinology) and research communities (as represented by major field-specific publication titles) that are more central to basic sex differences research than to autism research. Transfer nodes such as endocrinology represent a critical avenue by which autism is being taken up as a biomedical platform for research on sex differences.

a

| | Methods | | | | Study Subject | |
|---|---|---|---|---|---|---|
| | Genetics | Endocrinology | Neuroimaging | Molecular Biology & Biochemistry | Human | Non-Human Animal |
| Number of Publications | 155 | 98 | 55 | 99 | 356 | 63 |
| Percent of Total Publications | 35.0% | 22.1% | 12.4% | 22.4% | 80.4% | 14.2% |



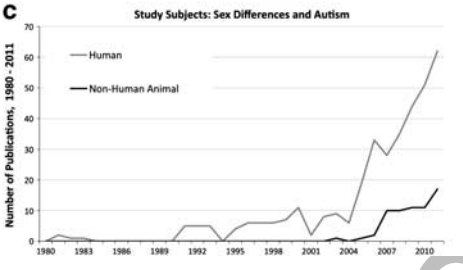




**Figure 2:** Methods used in 'autism and sex difference' research. (**a**) A substantial portion of research on autism and sex difference uses genetic, endocrinology, neuroimaging, and molecular biology and biochemistry methods. Fifteen percent of autism and sex difference publications study non-human animals. (**b**) Since 2004, the number of publications on autism and sex difference using genetic, endocrinology, neuroimaging, and molecular biology and biochemistry methods has increased. (**c**) In published studies of autism and sex difference, the use of non-human animals as research subjects has increased rapidly and recently. We interpret the use of non-human animals as an indicator of basic, as opposed to clinical, research. (Web of Science data, compiled and coded by authors).



To more thoroughly understand how autism functions as a biomedical platform for basic sex differences research, we employed two researchers to hand code the article titles, abstracts and keywords for methods (endocrinology, epidemiology, genetics or genomics, molecular biology and biochemistry, neurology, neuroimaging or fMRI, psychometrics) and study subjects (non-human animal or human) used in the set of 442 Web of Science articles on autism and sex differences. Although a comparative analysis would be ideal, a hand-coding effort is infeasible for the larger data sets for 'all autism research' (16 331 publications) and 'all sex differences research' (97 982 publications). Thus, our findings here are limited to an internal profile of the field of autism and sex differences research.

Coding results show that investigations of autism and sex difference are trending toward basic molecular research in non-human animal studies (Figure 2). Many autism and sex difference studies use multiple methods, and therefore the numbers that follow represent the non-exclusive presence or absence of a study method in articles in the data set analyzed. We find that methods outside 'psychometrics' – which we defined as the design, administration and interpretation of quantitative tests for the measurement of psychological variables such as intelligence, aptitude, behavior and personality traits – contribute to a considerable fraction of autism and sex differences research. Thirty-five per cent of publications on autism and sex differences research use genetic methods, 22.1 per cent use endocrinology methods, 12.4 per cent use neuroimaging methods and 22.4 per cent use

methods in molecular biology and biochemistry. Of autism and sex difference publications, 14.2 per cent study non-human animals, a characteristic we use as an indicator of basic, as opposed to clinical, research (Figure 2a).

Over time, we see an increase in the use of genetic, endocrinology, neuroimaging, and molecular biology and biochemistry methods (Figure 2b). The use of endocrinology and molecular biology methods is a particularly recent and fast-growing trend in autism and sex differences research. Between 1980 and 2001, no published research on autism and sex difference used endocrinology methods, and only two studies used molecular biology and biochemistry methods. In 2011, 20 studies used endocrinology methods and 25 used molecular biology and biochemistry methods. This increase is correlated with the rising use of non-human animals as research subjects in studies of autism and sex difference. No publications between 1980 and 2001 used animal research subjects, whereas 17 2011 publications used animals (Figure 2c). These data suggest that autism and sex difference studies are not solely investigating potential sex differences in the clinical manifestations of autism. Increasingly, they are pursuing the biological etiology of autism's male prevalence using non-human animals as research subjects and methods in genetics, endocrinology, neuroimaging, and molecular biology and biochemistry.



## Autism as a Biomedical Platform

Translational work between basic research and the clinic is characterized by the strategic launching of biomedical platforms. Keating and Cambrosio's classic example of a biomedical platform is immunophenotyping in cancer research. After the declaration of a 'War on Cancer', immunologists and others began to opportunistically frame and articulate their research programs in terms of their potential to cure cancer.

Autism has become a biomedical platform for sex differences research, offering an attractive opportunity for articulating the translational possibilities of basic sex differences research in a resource-competitive research environment. Autism, rather than other male-biased disorders, is particularly tractable as a platform for sex differences research at this time because of contextual, sociohistorical factors surrounding the rise of the concept of an autism spectrum. The notion that autism presents a toolbox for exploring the exceptional qualities of the male brain helps to support a positive autism archetype that recognizes special qualities or capabilities among those with an otherwise stigmatizing and disabling disorder. It also offers a biological explanation for male prevalence in science-related careers, a claim that finds a significant receptive audience in debates around this hot topic of popular, social scientific and public policy concern.

Analysis of privately and publicly funded research grants and publication trends over the past decade demonstrates how autism is emerging as a biomedical platform in basic molecular and cellular sex differences research in genetics, endocrinology and neuroscience. Autism has become a way that scientists investigating basic sex differences can articulate the potential medical benefits of their work, and that autism researchers can connect their findings with basic research. Although biomedical platforms are efficient at driving translational research forward, they are not "passive and transparent" (Keating and Cambrosio, 2003, p. 326), but actively entrench assumptions that may be deeply contested. Studies using autism

as a biomedical platform for basic sex differences research accept the same controversial premises as the EMB theory: that there is an exceptional male bias in the prevalence of autism, compared with other developmental disabilities, and that this bias has an organic basis linked to the genetic, hormonal or neurological mechanisms involved in normal differences between males and females. By citing the 4:1 male prevalence of autism as a research model for human sex differences research, biomedical investigations intentionally or unintentionally bring the confirmatory weight of the elite molecular biological sciences to the EMB theory and the harmful gender stereotypes about female ability in math, science and engineering it promotes.

The stereotype that males are more fit for math and science continues to hold women back. Social psychological evidence shows that belief in innate male superiority at math prompts females to assess their own math ability as lower than it actually is (Chatard *et al*, 2007; Coleman and Hong, 2008), to perform poorly on math-related tasks (Steele, 1997; Dweck, 2007), to feel like imposters in science settings (Clance and Imes, 1978) and to choose non-STEM careers (Holleran *et al*, 2011). Immense progress shown by women in STEM in recent decades evidences that low representation in STEM professions is at least in part a reflection of historical and cultural barriers against women in pursuing education and careers in STEM (European Commission Directorate-General for Research, 2009; United States National Science Foundation, 2012). Studies show that females have caught up to males in math performance over time and that gender gaps in math and spatial performance vary widely across cultures in a manner correlated with national gender equity measures (American Psychological Association, 2010; Kane and Mertz, 2011). Recent studies find no generalizable differences between males and females in innate math ability (Guiso *et al*, 2008; Hyde *et al*, 2008).

Our findings – that publications and funded grant proposals increasingly cite the 4:1 male prevalence of autism as a platform for basic sex differences research; that this claim of overwhelming male prevalence is empirically underdetermined and linked to the controversial addition of Asperger's individuals to the autism spectrum; and that highly speculative and harmful claims about innate sex differences in the brain related to math and science ability draw strength from autism and sex differences research – suggest the importance of a skeptical and cautionary stance toward the expanding deployment of autism as a biomedical platform for basic sex differences research.

Scientific claims about cognitive sex differences, autism and STEM ability are received in a high stakes social context. As sex differences researchers increasingly use autism as a biomedical platform to structure their research, they contribute to the entrenchment of controversial empirical and theoretical claims as foundational postulates in the funding structure and publication record of fields such as neuroscience, endocrinology and genetics. Lack of criticality about the use of autism as a biomedical platform for sex differences research contributes to a focus on the minority of autistic individuals considered 'high functioning', the marginalization of females with autism, and the perpetuation of stereotypes about women and the STEM professions. For these reasons, we urge sex differences researchers in the basic life sciences to critically engage with the empirical limitations and potential harms of the use of autism as a platform for basic sex differences research and apply a high burden of proof to the often opportunistic use of the autism platform in publications and grant proposals related to sex differences.

## Acknowledgements

The authors would like to thank Kendra Bechtel and Kate Womersley for research assistance and Steve Worthington and Ista Zahn of the Harvard Institute for Quantitative Social Science for assistance with the bibliometric data.

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