

# Chapter 2

## Progress in Understanding the Causes of Autism Spectrum Disorders and Autistic Traits: Twin Studies from 1977 to the Present Day

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### Introduction

This chapter provides a comprehensive review of twin studies in the autism field. While family studies have also made a substantial contribution to our understanding of autism, these have not been reviewed here for the practical reason of space and because several informative reviews of family studies of autism are available (e.g., Bailey, Palferman, Heavey, & Le Couteur, 1998; Sucksmith, Roth, & Hoekstra, 2011). It is also not within the scope of this chapter to include a systematic account of molecular genetic findings in ASD; the reader is directed to the following review papers (Abrahams & Geschwind, 2008; Betancur, 2011; Freitag, Staal, Klauck, Duketis, & Waltes, 2010; Geschwind, 2011).

In this chapter, we describe how the well-documented original twin studies of narrowly defined autism have been succeeded by twin studies of autism spectrum disorders (ASDs) and by a new wave of twin studies exploring the etiology of dimensional assessments of autistic traits in the general population. We discuss how this literature contributes to our understanding of the dimensional nature of autistic behaviors. Furthermore, we consider how twin research has added to our understanding of the overlap between autism and intellectual disability, language development, and psychiatric conditions, and how it has provided evidence for etiological heterogeneity in autistic symptoms. Finally, after considering some limitations and assumptions inherent in these twin studies, we provide suggestions for future research directions.

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## Current Issues

### *Autism Spectrum Disorders*

ASDs are a group of neurodevelopmental conditions characterized by impairments in social interaction, communication, and by restricted repetitive behaviors and interests (American Psychiatric Association, 2000). Diagnosis usually occurs in childhood and ASD diagnoses are usually extremely stable across the lifespan. The previous edition of the diagnostic statistical manual (DSM-IV, American Psychiatric Association 2000) distinguished the ASD subtypes autistic disorder, Asperger syndrome, and pervasive developmental disorder not otherwise specified (PDD-NOS). I The new DSM-5 edition, folds several subtypes into a single group called “autism spectrum disorder” (see [www.dsm5.org](http://www.dsm5.org)). ASDs are more common in males, with a male to female ratio of about 4:1 (Fombonne, 2006), and they can occur in individuals across the full range of cognitive ability from very low to very high IQ (Fombonne, 2006).

### *The Heritability of Autism, Autism Spectrum Disorders, and the Broader Autism Phenotype*

It is well established that twin studies of narrowly defined autism reported monozygotic (MZ) twin pairs to be more similar than dizygotic (DZ) twins in their concordance for autism (Bailey et al., 1995; Folstein & Rutter, 1977; Ritvo, Freeman, Mason-Brothers, Mo, & Ritvo, 1985; Steffenburg et al., 1989). Table 2.1 outlines the twin studies of narrowly defined autism and ASD. In the original Folstein and Rutter study including 21 twin pairs (11 MZ and 10 DZ pairs) (Folstein & Rutter, 1977), MZ twins, who share all of their genes, were 36 % concordant—that is, in just over a third of pairs both twins had autism. In DZ twins, who share on average half their DNA, there was 0 % concordance—that is, all twin pairs were discordant for diagnosis: one had autism, the other did not. The concordance rates were not found to be explainable by biological hazards associated with the twins’ birth. Model fitting in a later paper estimated the heritability of autistic disorder as 91–93 % (Bailey et al., 1995). It was also found that when criteria were widened to include individuals who show some but not all of the features of autism, this “broader autism phenotype” (BAP, as described by Folstein & Rutter, 1977), the MZ concordance increased to 92 % and the DZ concordance increased to 10 %, respectively (Bailey et al., 1995) (see Table 2.1).

Since the twin studies of narrowly defined autism, there have now been four twin studies incorporating all autism *spectrum* disorders (see Table 2.1). The first two twin studies of ASDs reported high MZ concordances (88–95 %) and DZ concordances of 31 % (Rosenberg et al., 2009; Taniai, Nishiyama, Miyachi, Imaeda, &

**Table 2.1** Twin studies of strictly defined autism and autism spectrum disorders (presented chronologically)

Study	Sample and measures			Results		Conclusions
	Sample ascertainment	N pairs, cases; IQ	Age, sex	Diagnosis	Concordance	
Folstein and Rutter (1977)	Systematic attempt to identify all twins with autism in the UK via letters to psychiatrists, twin registers, and autism society	21 pairs (11MZ, 10 DZSS), 25 cases; 48 % with IQ<50	5–23 years; 3.2:1	Criteria outlined by Kanner (1943) and Rutter (1971, 1977)	Autism: MZ, 36 %; DZ, 0 %. BAP: MZ, 82 %; DZ, 10 %. Biological hazards surrounding birth process did not explain concordance rates. In 12 of the 17 discordant pairs, one twin had experienced biological hazard—always the twin with autism diagnosis	Autism shows genetic influence. Genetic influences may be linked with a broader range of impairments. Concordances were not completely explained by biological hazards in the perinatal period, but they appeared to play a contributory role
Ritvo et al. (1985)	Via advert in autism society newsletter	40 pairs (23 MZ, 10 DZSS, 7 DZOS), 66 cases	3–31 years; 3.1:1	DSM III	Autism: MZ, 96 %; DZ, 24 %	Strong genetic influence on autism
Steffenburg et al. (1989)	Systematic attempt to identify all twins with autism in Denmark, Finland, Iceland, Norway, and Sweden via letters to child psychiatrists, twin registers, and autism society	21 pairs (11 MZ, 10 DZSS, 1 triplet set), 34 cases; 50 % with IQ<50	2–23 years; 1.6:1	DSM-III-R	Autism: MZ, 91 % (plus one set of identical triplets); DZ, 0 %. BAP: MZ, 91 %; DZ, 30 %. In the discordant pairs, always twin with autism who had more perinatal stress	Similar conclusions to Folstein and Rutter (1977, above), except that this study did not find evidence that the broader definition of impairments was more heritable than autism

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**Table 2.1** (continued)

Study	Sample and measures			Results		Conclusions
	Sample ascertainment	N pairs, cases; IQ	Age, sex	Diagnosis	Concordance	
Bailey et al. (1995)	Folstein and Rutter's (1977) sample was contacted and reassessed, and additional twins were identified using same methods	44 sets of twins and triplets (25 MZ, 20 DZSS, 2 triplet sets), 59 cases; 36.4 % nonverbal IQ < 50; 65.5 % verbal IQ < 30	NA; 3.4:1	ICD-10	Autism: MZ, 60 %; DZ, 0 %. BAP: MZ, 92 %; DZ, 10 %. Environmental causes of brain damage did not explain concordance rates. In discordant pairs, twin with autism experienced more biological disadvantage. Liability threshold modeling produced broad heritability estimates of 91–93 %	Replicated Folstein and Rutter's (1977) findings with larger sample including the original sample. Derived specific heritability estimate
Taniai et al. (2008)	Via child screening system in specific regions of Nagoya City, Japan, as well as referrals from nurseries, hospitals, and clinics	45 twin pairs (19 MZ, 14 DZSS, 12 DZOS); 46.5 % IQ < 70	3–6-year-olds; 3:1	Case vignettes	ASD: MZ, 95 %; DZ, 31 %. Continuous Childhood Autism Rating Scale scores showed heritability of 73 % for males and 87 % for females and modest nonshared environment (13–17 %). No evidence for the existence of sex-specific genetic influences	First twin study to provide MZ and DZ concordances for ASD. Reported high heritability for autistic symptoms assessed quantitatively in a clinically ascertained ASD sample

Rosenberg et al. (2009)	Voluntary Interactive Autism Network (IAN) online database for US residents	277 twin pairs (67 MZ, 120 DZSS; 90 DZOS); 23 % with intellectual disability	Age 18 or less (mean 7.7 years); 72 % male	Diagnostic information supplied by families	ASD: MZ, 88 %; DZ, 31 %. Severity concordance within ASD pairs: MZ, 96 %; DZ, 81 % (severity concordance defined as both twins had autism and/or PDD-NOS (PDD-NOS considered by authors as milder form of autism and as such grouped together) or both twins had Asperger syndrome (considered by authors as markedly different from PDD-NOS or autism), otherwise twins considered discordant. Parent-reported ASD diagnoses showed good agreement with SCQ and SRS questionnaires	Largest twin study of ASD showed high heritability of all ASDs. First study to rely on parent-reported diagnostic information
Lichtenstein et al. (2010)	Identified from the Child and Adolescent Twin Study in Sweden (CATSS), part of the Swedish Twin Registry	117 twin pairs (29 MZ, 48 DZSS; 40 DZOS); 128 cases, 34 % with learning disorders	Age 9 or 12, 4:1	ASD diagnosis on basis of parent interview on Autism—Tics, AD/HD, and other Comorbidities inventory (A-TAC)	ASD: MZ, 39 % (47 % for males only, not enough data for females only); DZ, 15 % (14 % for males, 20 % for females). <sup>a</sup> Liability threshold models estimated heritability of ASD at 80 % and nonshared environmental influences explained remaining 20 % of variance. Did not discriminate between different types of ASD diagnoses	Large representative twin study of ASD. Inclusion of model fitting provided specific estimates of genetic and environmental influences. Parent-report measure has good reliability and validity information but was not suitable for discriminating ASD subtypes

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Table 2.1 (continued)

Study	Sample and measures			Results		Conclusions
	Sample ascertainment	N pairs, cases; IQ	Age, sex	Diagnosis	Concordance	
Hallmayer et al. (2011)	Systematic attempt to identify all twins with ASD born in California between 1987 and 2004 using Department of Developmental Services records	192 twin pairs (54 MZ, 58 DZ, 80 DZOS), 242 probands (autism or ASD), IQ information not provided	Mean age 12 years; 2:1	Diagnostic criteria based on criteria from both the ADOS and ADI-R	Strict autism (narrow): MZM, 58 %; DZM, 21 %; MZF, 60 %; DZF, 27 %; ASD (broad): MZM, 77 %; DZM, 31 %; MZF, 50 %; DZF, 36%. <sup>a</sup> Liability threshold models estimated heritability of autism and ASD at 37 % and 38 %, respectively, with large shared environmental component (55 % for autism, 58 % for ASD) and small amount of nonshared environmental influences	Largest population-based twin study of ASD. First study to employ ADOS and ADI-R diagnostic assessment tools. Concordances closely mirror those from previous studies but the model-fitting result, particularly the large shared environmental component identified, contrasts to findings from all other autism and ASD twin studies to date

Note: Percentages refer to calculated pairwise concordance rates unless otherwise stated. Ratio of males to females presented in age and sex column. All study samples are independent with exception of Folstein and Rutter (1977) and Bailey et al. (1995)

NA information not available, MZ monozygotic twins, DZ dizygotic twins, DZSS same-sex DZ twins, DZOS opposite-sex DZ twins, ASD autism spectrum disorders, BAP broader autism phenotype, PDD-NOS pervasive developmental disorder not otherwise specified, SCQ social communication questionnaire, SRS social responsiveness scale, ADOS autism diagnostic observation schedule, ADI-R autism diagnostic interview-revised

<sup>a</sup>Probandwise concordances given, as per the original publication

Sumi, 2008). These DZ concordances for ASD are notable for being higher than in any previous twin studies of autism, whereas the MZ concordances are similar to those reported in some of the previous studies. The first ASD twin study employed a sample of children with ASD from Japan who were diagnosed using DSM-IV criteria (Taniai et al., 2008). Because no structured interview was available in Japanese, the children were diagnosed using semi-structured summaries (case vignettes) of all available psychiatric and diagnostic information. Using the Childhood Autism Rating Scale as a quantitative assessment of autistic symptoms, this study reported heritability estimates of 73 % for males and 87 % for females. It is unknown how diagnoses made by case vignettes in Japan compare to the standard Western diagnostic instruments. Apart from methodological differences there may also be subtle cultural differences in the expression, diagnostic practice, and prevalence of ASDs (Grinker, 2007; Grinker et al., 2012; Kim et al., 2011). The second ASD twin study relied on parent report of ASD diagnoses through a US-based voluntary online register (Rosenberg et al., 2009). This is a less systematic or reliable ascertainment method than employed in the previous twin studies, but has the advantage of giving a large sample size (with 277 twin pairs it is the largest twin study of ASD published so far). The twin concordances from this second ASD twin study (MZ, 88 %; DZ, 31 %) are highly similar to those from the first ASD study from Japan, described above.

Finally, the more recent third and fourth twin studies of ASD are notable for having both relatively large and systematically obtained population samples from Sweden and California, respectively. Both studies reported concordances as well as liability threshold model-fitting analyses (Hallmayer et al., 2011; Lichtenstein, Carlström, Råstam, Gillberg, & Anckarsäter, 2010). In the Swedish study, the concordances for all ASDs (the measure did not distinguish different types of ASD) were 39 % for MZ twins and 15 % for DZ twins; liability model-fitting analyses suggested a heritability of 80 %, thus again indicating strong genetic influences on ASD (Lichtenstein et al., 2010). The Californian study (Hallmayer et al., 2011) distinguished strict autism from broader ASD and reported MZ and DZ twin concordance rates that were largely similar to previous studies. For narrowly defined autism, the MZ vs. DZ concordance rates were 58 % vs. 21 % (males) and 60 % vs. 27 % (females), compared with 77 % vs. 31 % (males) and 50 % vs. 36 % (females) for broader ASD. These concordance rates are remarkably similar to the rates reported by Rosenberg et al. (2009) and Taniai et al. (2008), with the exception of the relatively low concordance for broad ASD in MZ females (although the confidence intervals around this estimate were large due to limited sample size). Despite the similarities in concordance rate findings, the liability threshold model-fitting analyses employed by Hallmayer et al. (2011) produced a more modest heritability (37 % for autism and 38 % for ASD) and a large shared environmental component (55 % for autism and 58 % for ASD; Hallmayer et al., 2011). This is the first and only twin study to report substantial shared environmental influences on diagnosed autism or ASD. The contrasting results from this Californian twin study compared to all the other twin studies of autism and ASD that have included model-fitting analyses—in particular the finding of a large shared environmental component—require further

explanation. Possible reasons for the different results in this study may involve the characteristics of the Californian twin sample or the specific assumptions employed in the modeling, including the ascertainment probability. The participation rate in this study was only 17 %, and although the authors could rule out various sources of potential ascertainment bias, it remains a question whether the sample under study was a true reflection of the Californian population as a whole. A notable characteristic of the Californian study was its use of the autism diagnostic observation schedule (ADOS) and autism diagnostic interview-revised (ADI-R) diagnostic tools to identify cases. The ADOS involves observational assessments of behavior, and the combination of these two instruments has come to be considered one of the most well-respected methods of diagnosing ASD in recent years.

In sum, since the original twin studies showed the high heritability of autistic disorder, three new studies have reported twin concordances or model-fitting results to suggest a high heritability for ASD, while one study has suggested that shared environment may play a prominent role in ASD.

### *Autistic Traits in Community Samples*

Findings from broader autism phenotype studies in first-degree relatives of people with autism (Sucksmith et al., 2011) revealed that these relatives may show elevated rates of behavioral and personality traits characteristic of ASDs. Quantitative scales assessing these so-called autistic traits, such as the Childhood Autism Spectrum Test (CAST; Williams et al., 2008), Autism-Spectrum Quotient (AQ; Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001), and Social Responsiveness Scale (SRS; Constantino, 2002), are continuously distributed in community samples throughout the normal range to the clinical extreme and show high internal consistency (e.g., Hoekstra, Bartels, Cath, & Boomsma, 2008; Skuse, Mandy, & Scourfield, 2005). Relatives of individuals with ASDs show, on average, elevated levels of autistic traits compared to control families (e.g., Bishop, Maybery, Wong, Maley, & Hallmayer, 2006; Constantino et al., 2006) suggesting that subclinical autistic traits share familial influences with diagnosed ASD. Since common genetic variants (that are, by definition, present in a significant proportion of the general population) are thought to play a role in the etiology of autism (e.g., Alarcón et al., 2008; Anney et al., 2010; Ronald, Butcher, et al., 2010; Wang et al., 2009; Weiss et al., 2009), it is argued that understanding the etiology of individual differences in autistic traits in the general population may aid our understanding of the causes of clinically diagnosed autism.

Table 2.2 describes twin studies of autistic traits assessed in general population and community samples. These studies report that autistic traits, as assessed using quantitative scales such as the CAST, AQ, and SRS, show heritability estimates ranging from 36 to 90 % in twin samples ranging from age 2 to age 18. The general trend is for heritability to vary between 60 and 90 % for parent- and teacher-rated autistic traits in middle childhood and older (Constantino & Todd, 2000, 2005;



**Table 2.2** Twin studies of autistic traits (presented chronologically)

Sample and measures					Results	Conclusions
Study	Sample	N pairs	Age; sex	Measure		
Constantino and Todd (2000)	Community sample, Missouri twin study	232 pairs (98 MZ, 134 DZ)	7–15 years; all male	SRS: 65 items. Parent report	Twin correlations: MZM, 0.73; DZM, 0.37. Strong additive genetic influence (76 %), moderate nonshared environmental influence (24 %). No significant shared environmental or nonadditive genetic influence	Autistic traits are highly heritable in males
Constantino and Todd (2003)	Community sample, Missouri twin study	788 pairs (268 MZ, 270 DZSS, 250 DZOS)	7–15 years; 43.7 % male	SRS. Parent report	Twin correlations: MZM, 0.73; DZM, 0.37. MZF, 0.79; DZF, 0.63; DZOS, 0.59. Modest genetic influences (48 %) and significant moderate shared and nonshared environmental influences (32 % and 20 %, respectively)	Autistic traits for both males and females show moderate heritability (48 %). Unlike the previous study, significant shared environmental influences were found
Constantino and Todd (2005)	Community sample, Missouri twin study	285 pairs (89 MZF, 69 DZF, 127 DZOS)	8–17 years; 22.3 % male (from male twins in DZOS pairs). Parents: aged 30–55, 50 % male	SRS child and adult versions; maternal report of twins and spousal report of parents	For combined parent and child samples: high heritability (87 % males, 73 % females), modest shared environment (12 % males, 10 % females) and nonshared environment (0 % males, 17 % females), assortative mating estimate = 0.29. Significant parent-offspring intraclass correlations were also reported	Autistic traits are highly heritable in children and adults. Evidence of assortative mating. Conclusions based on largely female twin sample

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Table 2.2 (continued)

Sample and measures					Conclusions	
Study	Sample	N pairs	Age; sex	Measure		
Ronald et al. (2005)	Representative UK sample, Twins Early Development Study (TEDS)	3,138 pairs with teacher data; 3,996 pairs with parent data	Age 7; 48 % male	DSM-IV-based social and nonsocial questionnaires, parent and teacher report	High heritability of parent- and teacher-rated social and nonsocial autistic traits (62–76 %), modest nonshared environment (25–38 %). Modest genetic overlap between social and nonsocial autistic traits (genetic correlation = 0.07–0.40) and modest nonshared environmental overlap (nonshared environment correlation = –0.02–0.18)	First twin study of social and nonsocial components separately showed they are both individually heritable but show limited genetic overlap
Skuse et al. (2005), see also Scourfield, Martin, Lewis, and McGuffin (1999)	Representative UK sample, Cardiff Study of All Wales and North of England Twins	670 pairs (278 MZ, 180 same-sex DZ, and 198 DZOS)	5–17-year-olds (M = 10.6 years); 48 % male	Social and Communication Disorders Checklist (93), parent report	Twin correlations: MZ, 0.73; DZM, 0.38. Heritability, 74 %; nonshared environmental influence, 26 %	Social cognitive skills show high heritability and no shared environment influence

Ronald, Happé, Bolton, et al. (2006), Ronald, Happé, Price, et al. (2006)	Representative UK sample, TEDS	3,419 pairs; sample included representative proportion of children with ASD	Age 8; 49 % male	CAST, parent report	High heritability for autistic traits in whole sample (81–86 %) as well as for extreme autistic traits using >85 %, >90 %, >95 %, and >98 % cutoffs, using both DeFries-Fulker analyses (group heritabil- ity = 64–73 %) and liability threshold models (heritabil- ity = 86–92 %). Autistic trait subscales (social impairments, communication impairments, RRBIs) all show high heritability individually. No evidence for shared environmental influences. Nonshared environment modest but significant (14–19 %). Multivariate models indicated modest genetic overlap between subscales (genetic correlations = 0.18–0.50)	Large twin study of autistic traits confirms their high heritability in general population and in extreme groups
Hoekstra, Bartels, Verweij, et al., 2007	Representative Dutch sample, subsample of the Netherlands Twin Register	380 twin pairs, 94 siblings, 128 parents of twins	Twins, 18 years; siblings, range 10–35 years, average 18 years; 47 % male	Dutch AQ, self- report	Twin correlations: MZM, 0.59; DZM, 0.36; MZF, 0.51; DZF, 0.43; DZOS, 0.35; all twin-sibling pairs, 0.28. Substantial heritability (57 %) and moderate nonshared environmental influences (43 %) on self-reported autistic traits in late adolescence. No evidence for different genetic influences on males and females	First twin study of late adolescence confirms substantial heritability in this age group. No evidence for assortative mating for autistic traits

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**Table 2.2** (continued)

Study	Sample and measures				Measure	Results	Conclusions
	Sample	N pairs	Age; sex				
Ronald, Happé, et al., 2008	Representative UK sample, TEDS	2,586 pairs with teacher data; 3,259 pairs with parent data; 3,109 pairs with self-report data	Age 9; 49 % male		Abbreviated CAST; parent report, teacher report, and self-report	Correlations between raters were significant but moderate ( $r=0.16-0.33$ ). High heritability for parent ratings (82–87 %), moderate for teacher (69 %), and modest for child self-report (36–47 %). Shared environment influences found only for male self-report data (18 %). Genetic overlap was significant but moderate across all raters (average genetic correlation between raters = 0.40)	Heritability estimates differ depending on type of rater. Different raters pick up on partly different genetic phenotypes
Edelson et al. (2009)	Community sample, Boston University Twin Project	313 pairs, 145 MZ, 168 DZ	Age 2; 53 % male		Child Behavior Checklist (CBCL), pervasive developmental problems scale, parent report	Twin correlations: MZ, 0.58; DZ, 0.38. Moderate heritability (40 %), significant shared environment (20 %), nonshared environment (40 %)	First twin study of autistic traits in young children. Moderate heritability and significant shared and nonshared environmental influences in this age group
Stulp et al. (2010)	Representative US sample, Wisconsin Twin Panel	1,211 pairs (414 MZ, 410 same-sex DZ, 387 DZOS)	Ages 2–3; 50 % male		Eight items similar to items from Modified Checklist for Autism in Toddlers (M-CHAT), parent report	Twin correlations: MZM, 0.62; DZM, 0.25; MZF, 0.53; DZF, 0.34; DZOS, 0.44. Using categorical data, liability threshold models estimated heritability at 44 %, shared environment as 32 %, and nonshared environment as 24 %; but with a more extreme threshold, these values were 74 %, 19 %, and 7 %, respectively	Autistic behaviors in toddlers (such as a lack of pointing, looking, and imitating) show moderate genetic influence and significant shared and nonshared environmental influences

Ronald et al. (2011)	Representative Swedish sample, CATSS	6,223 pairs (1,788 MZ, 1,728 DZSS, 2,024 DZOS, 683 exclusions/ missing data)	Two indepen- dent samples of twins, one aged 9 years, one aged 12 years; 51 % male	Autism symptom items from the Autism—Tics, AD/HD, and other Comorbidities inventory (A-TAC), parent report	Autism symptoms divided into three subscales based on factor analysis of items. Heritabilities of three autism symptoms 49–76 %; remaining variance explained by nonshared environment. Multivariate common pathway model fit the three autism symp- toms best, showing common genetic and nonshared environmen- tal influences on each symptom domain, but also symptom-specific genetic and nonshared environmen- tal influences that could not be dropped from the model. Similar results across gender and age	The core symptoms of autism, when assessed in the general popula- tion, show modest overlap and have partly separate genetic influences
Robinson et al. (2011)	TEDS (as above)	5,968 pairs (2,126 MZ, 1,952 DZSS, 1,890 DZOS)	Age 12; 50 % male	CAST	Moderate-to-high heritability for autistic traits at age 12 in general population (72 % males, 53 % females). High heritability did not differ for extreme 5 %, 2.5 %, and 1 % quantitatively defined extreme-scoring groups	Evidence for shared etiology between extreme scores and normal variation

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Table 2.2 (continued)

Study	Sample and measures				Conclusions	
	Sample	N pairs	Age; sex	Measure		
Lundström et al. (2012)	CATSS (as above)	11,535, (28 % MZ, 36 % DZSS, 34 % DSZOS)	Two independent samples of twins, aged 9 years and aged 12 years; 51 % male	A-TAC	High heritability of autistic traits in general population (71 %). Two validated cutoffs for ASDs and two quantitatively defined cutoffs (9 % and 12 %) all showed similar high heritability. Cross-twin cross-cutoff correlations indicated substantial genetic overlap across thresholds. A high group heritability (59 %) was reported	ASDs and autistic traits share the same genetic susceptibilities. ASDs represent extreme of continuous variation in autistic traits

Note: Studies that used the same sample (as noted above) are not independent  
MZM monozygotic males, DZM dizygotic males, MZF MZ females, DZF DZ females, DZOS DZ opposite-sex pairs, SRS social responsiveness scale, CAST Childhood Autism Spectrum Test, AQ Autism-Spectrum Quotient, TEDS Twins Early Development Study, CATSS Child and Adolescent Twin Study in Sweden. RRBIs restricted repetitive behaviors and interests

Lundström et al., 2012; Robinson et al., 2011; Ronald, Happé, Bolton, et al., 2006; Ronald, Happé, & Plomin, 2005; Ronald, Happé, & Plomin, 2008; Skuse et al., 2005), with self-report assessments of autistic traits giving more moderate heritability estimates (32–57 %; Hoekstra, Bartels, Verweij, & Boomsma, 2007; Lundström et al., 2011; Ronald, Happé, et al., 2008). The two twin studies of early childhood, on 2-year-olds, also reported moderate heritabilities (40 and 44 %) of parent-rated autistic traits (Edelson & Saudino, 2009; Stilp, Gernsbacher, Schweigert, Arneson, & Goldsmith, 2010).

Shared environmental influences are the environmental influences common to both twins that make children growing up in the same family more similar. Some studies in middle-to-late childhood report modest shared environmental influences ranging from 10 to 32 % (Constantino & Todd, 2000, 2003, 2005; Ronald, Happé, et al., 2008), but the majority find no significant effects (see Table 2.2). All studies report modest to moderate influences of the nonshared environment, defined as environmental influences that make children growing up in the same family different, and which by default include measurement error in their term.

Twin research has demonstrated the magnitude of the role of both genetic and environmental influences on autistic traits across development, both measured in the general population and in the extremes of this population. Extremes analyses (presented by Lundström et al., 2012; Robinson et al., 2011; Ronald, Happé, Price, Baron-Cohen, & Plomin, 2006; see Table 2.2) consistently suggest that there is a genetic link between ASDs, impairments at the quantitative extreme of the distribution of autistic traits, and variation in autistic traits in the general population. For example, in a recent UK study, the high heritability of autistic traits at age 12 did not differ for extreme 5, 2.5, and 1 % quantitatively defined extreme-scoring groups (Robinson et al., 2011). In a Swedish sample, similar findings were reported and cross-twin cross-cut-off correlations suggested considerable genetic overlap across varying severity thresholds for autistic symptoms (Lundström et al., 2012).

In sum, twin studies of autistic traits have been important in supporting the notion of autism as a continuously distributed trait, a position that has been championed by a number of autism researchers (Baron-Cohen et al., 2001; Constantino & Todd, 2003; Gillberg, 1992; Hoekstra et al., 2008; Ronald, Happé, Bolton, et al., 2006; Ronald & Hoekstra, 2011; Skuse et al., 2005).

### ***“MZ Differences” Design***

Twin studies of autism, broader ASDs, and autistic traits consistently demonstrate that nonshared environment plays a modest but potentially important causal role. MZ twins are not 100 % similar on autism, broader ASDs, BAP, or autistic traits. The most effective way to identify nonshared environmental influences is to employ an MZ differences design. Because MZ twins are genetically identical at the DNA sequence level (but may show differences in gene expression due to, e.g., differences in DNA methylation levels; Jirtle & Skinner, 2007), any differences between two identical twins are due to nonshared environment.

Nonshared environmental influences are defined as environmental influences that make children growing up in the same family different and can include epigenetic processes, gene expression, illnesses, intra- and extrauterine environment, and measurement error. If *de novo* mutation events (e.g., rare *de novo* copy number variants, e.g., Sebat et al., 2007) or single nucleotide variants (Neale et al., 2012; O’Roak et al., 2012; Sanders et al., 2012) which have been linked to autism took place after the MZ twins separated, thus inducing differences between the twins, these effects will also be included in the nonshared environmental component. As such interpretations of nonshared environmental effects should always be considered in light of this definition.

A handful of studies have used structural MRI methods to report brain differences between MZ twins discordant for a narrow definition of autism.<sup>1</sup> Fourteen MZ pairs, nine of whom were clinically discordant for strictly defined autism, were examined and some neuroanatomical differences associated with this discordance (such as cerebellar volume) were reported. There was however also strong concordance across these pairs, for example, in cerebral gray and white volumes (Kates et al., 2004). Recently specific brain regions including the prefrontal cortex, amygdala, and hippocampus were examined, again finding that the degree of within-pair neuroanatomical concordance varied by brain region (Mitchell et al., 2009). The same sample has also been used to explore gyrification (cortical folding) patterns (Kates, Ikuta, & Burnette, 2009). Further research that attempts to replicate these interesting findings is needed.

One of the most well-replicated associations, in terms of putative risk factors, is between ASD and perinatal obstetric complications (Kolevzon, Gross, & Reichenberg, 2007; Ronald, Happé, Dworzynski, Bolton, & Plomin, 2010). Perinatal obstetric complications could be a result of preexisting genetic abnormalities in individuals who later develop ASD, could be a causal environmental risk factor, or could be both. To address whether perinatal obstetric complications could be an environmental risk factor for autistic traits, MZ twins in the UK-based TEDS sample who were discordant for postnatal birth complications (e.g., one twin had been in intensive care, the other had not) were compared on their later autistic trait scores. In some cases, significant correlations were observed between the two “difference” scores, that is, the twin with more postnatal birth complications had more autistic traits at a later age compared to their co-twin (Ronald, Happé, et al., 2010). In the Swedish CATSS sample, a co-twin control design was used to show that birth weight was modestly associated with autistic traits and risk of ASDs (Losh, Esserman, Anckarsäter, Sullivan, & Lichtenstein, 2012). These findings do not rule out that *some* birth weight and postnatal birth complications associated with autism or autistic traits could be due to genetic factors, but, if replicated, suggest that birth weight and postnatal complications can have a causative influence on a child’s later autistic traits and risk of ASD, above and beyond the influence of a child’s DNA

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<sup>1</sup>Case studies of single twin pairs with ASD have been omitted from this review. Although case studies are useful at a descriptive level, statistical results cannot be derived from individual pairs.



code. This would fit with the predictions from twin studies, which consistently find evidence for nonshared environmental effects on autism and autistic traits.

Finally, a sample of three MZ pairs discordant for ASD diagnoses (one twin in each pair had autism; the other had some autistic traits and was described as “not quite autistic” or “broad spectrum”) has been studied in relation to their gene expression profiles (Hu, Frank, Heine, Lee, & Quackenbush, 2006; Sarachana, Zhou, Chen, Manji, & Hu, 2010) and their methylation profiles (Nguyen, Rauch, Pfeifer, & Hu, 2010). Both gene expression and epigenetic changes can occur as a result of genetic or environmental influences. The combination of phenotypically discordant genetically identical MZ twins and gene expression or epigenetic profiling allows for the discovery of biological mechanisms underlying nonshared environmental influences on autism (because DNA code is controlled for in the MZ differences design). Because MZ twins discordant for ASD are relatively rare, an inherent challenge of these MZ differences studies is how to employ a sample that has more participants than measured variables. Two options are to collaborate by combining samples and to study autistic traits rather than diagnosed ASD (see, e.g., Ronald, Happé, et al., 2010). Nevertheless, this is a promising field for further research.

### *Multivariate Twin Studies of Autism and Autistic Traits*

In the following sections, we consider what twin research has added to our understanding of the overlap between autism and intellectual disability, language development, and psychiatric conditions, and how it has provided evidence for etiological heterogeneity in autistic symptoms.

### *Autism and Intellectual Disability*

Intellectual disability ( $IQ \leq 70$ ) is common in ASD. However, people with ASD are found along the entire spectrum of intellectual ability and prevalence estimates of intellectual disability in ASD vary widely, with older studies suggesting that around 70 % of people with ASD also have intellectual disability (Chakrabarti & Fombonne, 2005; Fombonne, 2006) and more recent studies giving a substantially lower prevalence estimate of intellectual disability (e.g., 38 % in the most recent estimates from the US-based Autism and Developmental Disabilities Monitoring Network; Baio et al., 2012). Twin studies can help to elucidate whether autism and intellectual disability share common etiological influences. So far, three studies from two different research groups have explored the genetic overlap between autistic traits and intellectual abilities. Nishiyama et al. (2009) examined the genetic correlation ( $r_g$ ) between IQ and autistic traits in 45 young twin pairs in which at least one twin had an ASD diagnosis. The genetic correlation gives an estimate of the extent to which the set of genetic influences on one trait overlaps with the set of genetic influences

on another trait. A correlation of 1.0 implies complete overlap, while a correlation of 0 suggests that the sets of genes are entirely independent. Nishiyama et al. (2009) reported a very strong negative genetic correlation ( $r_g = -0.95$ ), suggesting that the genes affecting the risk for autism and the genes influencing IQ largely overlap, acting to increase risk for autism and decrease propensity for intellectual development. Due to the small sample size, the confidence intervals (CI) varied widely (the 95 % CI was between  $-1.00$  and  $-0.60$ ). Moreover, the authors put forward that the genetic correlation they reported may be inflated because of the inclusion of severely intellectually disabled children who only had a mild degree of autism and had received a PDD-NOS diagnosis. On the other hand, the findings fit in well with studies of rare gene variants, which suggest a large overlap between rare gene variants for autism and rare gene variants for intellectual disability (see Betancur, 2011 for a review).

It has been suggested that the association between intellectual disability and autism may be inflated in clinical samples, since the probability of clinical ascertainment is greatly increased in individuals expressing both conditions (Skuse, 2007). These possible effects of clinical ascertainment bias (Boomsma, Busjahn, & Peltonen, 2002) can be avoided by studying the association between autistic traits and IQ in the general population. A community-based twin study (Hoekstra, Happé, Baron-Cohen, & Ronald, 2009) examined the extent to which extreme autistic traits (defined by a score in the top 5 % of the population on a measure of autistic traits) were related to intellectual difficulties (defined by a score in the bottom 5 % on measures of intelligence and academic achievement). Both extreme traits showed only a modest degree of genetic overlap; this was true for both parent- and teacher-rated autistic traits and for both poor academic achievement and low IQ scores ( $r_g$  ranging between 0.04 and 0.44). A follow-up study explored the longitudinal association between autistic traits and IQ using data from the twin population sample as a whole (Hoekstra, Happé, Baron-Cohen, & Ronald, 2010). A stable set of genetic influences could explain the stability of autistic traits over time (at ages 8, 9, and 12 years), while another set of genetic influences explained the stability in IQ scores over time (ages 7, 9, and 12 years). The genetic overlap between these two sets of genetic influences was only modest ( $r_g = -0.27$ ; 95 % CI  $-0.34$  to  $-0.22$ ) and was mainly accounted for by pragmatic communication difficulties characteristic of autism. This study was limited in that it included few cases with severe or profound intellectual disabilities, as it was drawn from a population-based sample. It may be that genetic influences involved in causing autism in people with severe intellectual impairment are somewhat distinct from the genetic influences causing autism in people with normal or near-normal intelligence and that the genetic influences causing autism in the severely intellectually impaired also impact on IQ. Although further studies are needed in this area, this is one hypothetical scenario that would reconcile the different findings in Nishiyama et al. (2009) and Hoekstra et al. (2009, 2010). The rare gene variants that have so far been implicated in autism (Betancur, 2011) and especially rare gene variants with a role in synaptic functioning (Persico & Bourgeron, 2006) are likely

candidates to explain the genetic overlap between autism and intellectual disability. So far, much less is known about the genetic variants that can affect the risk for autism, but spare intellectual functioning.

### *Autism and Early Language Problems*

Delays in the development of speech and language are the most common early signs of autism recognized by parents (De Giacomo & Fombonne, 1998). There is large variability in language ability between children on the autism spectrum, varying from children with no useful speech (in about 20 % of children with autism) to children with Asperger syndrome (as defined by the DSM-IV; American Psychiatric Association, 2000) who do not show any significant general language delay and may have a large vocabulary. Twin studies have demonstrated a moderate to high heritability for language (see Stromswold, 2001 for a review) and specific language impairment (Bishop, 2002).

Similar to the studies into the overlap between autism and IQ, twin studies can shed a light on the genetic correlation between language delay and autism. Dworzynski et al. (2007, 2008) studied the association between early language (at ages 2, 3, and 4 years) and subsequent autistic traits at age 8 in a general population sample. Early language problems (indexed by language scores in the bottom 5 % of the population) were only modestly related to later autistic traits, most notably autistic pragmatic communication problems. This phenotypic correlation was entirely explained by genetic influences; the genetic correlation between extreme autistic traits and early language problems was modest ( $r_g=0.33$ ) (Dworzynski et al., 2008). Analyses using the data from the whole sample reported a modest to moderate overlap between the genetic influences on language delay and the genetic effects on autistic traits (Dworzynski et al., 2007). Further twin studies are warranted that assess the association between language development and ASD or autistic traits measured at similar developmental ages.

### *Autism and Psychiatric Conditions*

Comorbidity is common in child psychiatric conditions, and autism is no exception. For example, between 24 and 59 % of individuals with autism are thought to also have an anxiety disorder (Weisbrot, Gadow, DeVincent, & Pomeroy, 2005), and in a large UK study, 28 % of individuals with ASD met the criteria for ADHD (Simonoff et al., 2008). Twin studies of autistic traits have developed some interesting hypotheses concerning the causes of this comorbidity.

Table 2.3 outlines twin studies of psychiatric comorbidity in ASD and autistic traits. As shown in the table, significant genetic overlap has been reported between

**Table 2.3** Twin studies of psychiatric comorbidity in autism and autistic traits

Study	Comorbid trait/ disorder	Sample description, age, and size	Measures	Key findings
Constantino et al. (2003)	ADHD	Community sample (Missouri Twin Project), 7–15-year-olds; <i>N</i> =219 male twin pairs	CBCL Attention Problems subscale and Social Responsiveness Scale, parent report	All CBCL subscales explained 43 % of variance in autistic traits. Attention problems explained the most variance, but despite this significant overlap, some genetic influences remained specific to autistic traits. Genetic correlation was not reported
Reiersen et al. (2008)	ADHD	Community sample (subsample of Australian Twin Register), 18–33-year-olds; <i>N</i> =674 twins (275 complete pairs)	Abbreviated Social Responsiveness Scale and DSM-IV ADHD items, self-report	Genetic correlation between autistic traits and ADHD behaviors=0.72. Substantial genetic overlap between adult self-reported autistic and ADHD traits
Ronald, Simonoff, et al. (2008)	ADHD	Population-based sample (TEDS), including children with suspected ASD and ADHD. 8–9-year-olds; <i>N</i> =6,771 pairs	Conners' DSM-IV subscales, parent report; Strengths and Difficulties subscale, teacher report; Childhood Autism Spectrum Test (CAST), parent and teacher report	Genetic correlations between autistic traits and ADHD behaviors=0.54–0.57 (depending on sex and rater) in general population. In diagnosed children, genetic correlation=0.62. Substantial genetic overlap between autistic traits and ADHD traits and between ASD and ADHD diagnoses, in middle childhood
Ronald, Edelson, et al. (2010)	ADHD	Community sample (Boston University Twin Project), 2-year-olds; <i>N</i> =312 pairs	CBCL, pervasive develop- mental problems and ADHD subscales, parent report	Genetic correlation between autistic traits and ADHD behaviors=0.27
Lichtenstein et al. (2010)	ADHD, developmen- tal coordina- tion disorder, tic disorder, learning disorders	Population-based sample (CATSS) screened for disorders, 9- and 12-year-olds, original <i>N</i> =8,429 pairs	Autism—Tics, AD/HD, and other Comorbidities inventory (A-TAC), parent report used to identify individuals with neuropsychiatric disorders	High genetic correlations reported between ASD and all neuropsychiatric disorders studied (ADHD, developmen- tal coordination disorder, tic disorder, learning disorders). Highest genetic overlap was observed between ASD and ADHD, with over three-quarters of the variance attributable to genetic influences on ASD shared with ADHD, and a genetic correlation of 0.87

Lundström et al. (2011)	ADHD, anxiety, conduct problems, depression, substance abuse	CATSS (child sample, as above), 11,222 individuals, and the Study of Twin Adults: Genes and Environment (STAGE) adult sample, 18,349 individuals	A-TAC was used for the child sample, self-rated DSM-IV-based questions for the adult sample	All other mental health problems (ADHD, anxiety, conduct problems, depression (adult sample only), substance abuse (adult sample only)) showed considerable genetic overlap with autistic traits (genetic correlations ranged from 0.38 to 0.60). Overlap in environmental influences was also present. The proportion of the phenotypic correlation explained by genetic influences was higher in the child than adult samples between autistic traits and ADHD, anxiety, and conduct problems
Hallett et al. (2009)	Anxiety-related behaviors	Population-based sample (TEDS), 8–9-year-olds, $N = 3,233$ twin pairs	CAST; anxiety-related items, based on Anxiety-Related Behaviors Questionnaire, parent report	Genetic correlation between autistic traits and anxiety-related behaviors = 0.12–0.19; shared environmental correlation = 0.96–1.00
Hallett et al. (2010)	Anxiety-related behaviors	Population-based sample (TEDS), 8-year-olds followed longitudinally to age 12, $N = 5,876$ – $7,834$ twin pairs	CAST; anxiety-related items, based on Anxiety-Related Behaviors Questionnaire, parent report	Longitudinal cross-lag associations were explored within a twin model. An asymmetric bidirectional association between autistic-like and internalizing traits across ages 8 and 12 was found, suggesting some “phenotypic causality.” Both traits were moderately to highly heritable, but were largely independent with regard to their genetic overlap. Autistic-like communication difficulties made the most significant contribution to later internalizing traits

(continued)

**Table 2.3** (continued)

Study	Comorbid trait/ disorder	Sample description, age, and size	Measures	Key findings
Hallett et al. (2012)	Subtypes of anxiety-related behaviors	TEDS (as above), 7–8-year-olds, 7,311 pairs	Subscales of the CAST; subtypes of anxiety-related behaviors, parent report	Distinguishable patterns of overlap between the three autistic-like traits (social difficulties, communication problems, and repetitive/restricted behaviors) and four subtypes of internalizing traits (social anxiety, fears, generalized anxiety, negative affect); autistic-like communication difficulties and restricted repetitive behaviors correlated most strongly with generalized anxiety and negative affect both phenotypically and genetically. Conversely, social difficulties showed low overlap with internalizing behaviors
Moruzzi et al. (2011)	Clumsiness	Sample from Italian Twin Registry, 5–17-year-olds, 398 pairs	CBCL items used to derive clumsiness and autistic subscales	Genetic correlation between autistic traits and clumsiness traits = 0.63
Jones et al. (2009)	Psychopathic traits	Community sample (subsample of TEDS), 9-year-olds; $N = 642$ pairs	Antisocial Process Screening Device and CAST, parent report	Genetic correlation between autistic traits and psychopathic traits = 0.43
Hoekstra, Bartels, Hudziak, et al. (2007)	Withdrawn behavior and social problems	Community sample (subsample of the Netherlands Twin Register), 18-year-olds; $N = 424$ pairs + 206 non-twin siblings	Youth Self Report; Autism-Spectrum Quotient, self-report	Withdrawn behavior and social problem subscales were the most important predictors of autistic traits in the Youth Self Report measure. Genetic correlation between autistic traits and social problems = 0.71; genetic correlation between autistic traits and withdrawn behavior = 0.56

*Note:* Studies that used the same sample (as noted above) are not independent  
*TEDS*: Twins Early Development Study, *CATSS*: Child and Adolescent Twin Study in Sweden, *ADHD*: attention deficit hyperactivity disorder, *CBCL*: Child Behavior Checklist, *CAST*: Childhood Autism Spectrum Test

autistic traits and ADHD traits in the general population (Constantino, Hudziak, & Todd, 2003; Lundström et al., 2011; Reiersen, Constantino, Grimmer, Martin, & Todd, 2008; Ronald, Edelson, Asherson, & Saudino, 2010; Ronald, Simonoff, Kuntsi, Asherson, & Plomin, 2008) as well as between children who appear to meet diagnostic criteria for ASD and ADHD according to parent report (Lichtenstein et al., 2010; Ronald, Simonoff, et al., 2008). The genetic correlations between autistic traits and ADHD behaviors reported in these studies were all substantial ( $r_g$  between 0.53 and 0.87), apart from a more modest estimate ( $r_g=0.27$ ) found in young twins (24-month-olds) (Ronald, Edelson, et al., 2010).

Multivariate twin models on autistic traits and anxiety have also been reported. According to findings from the UK TEDS sample, rather than genetic influences playing a major role in their overlap (as appeared to be the case between ASD and ADHD), autistic traits and anxiety-related behaviors share some common environmental influences and also display phenotypic interaction over time (Hallett, Ronald, & Happé, 2009; Hallett, Ronald, Rijdsdijk, & Happé, 2010). As shown in Table 2.3, genetic correlations between autistic traits and anxiety-related behaviors in middle childhood were low ( $r_g$  between 0.12 and 0.19) suggesting that these types of psychopathology co-occur for reasons other than shared genetic pathways (Hallett et al., 2009). In a Swedish population sample, somewhat higher genetic overlap was reported between autistic traits and anxiety traits in both child and adult samples ( $r_g$  0.53 and 0.51, respectively) (Lundström et al., 2011). In a more recent analysis of specific subtypes of autistic traits and internalizing traits, autistic-like communication difficulties and restricted repetitive behaviors correlated most strongly with generalized anxiety and negative affect both phenotypically and genetically (Hallett, Ronald, Rijdsdijk, & Happé, 2012). Conversely, social difficulties showed low overlap with internalizing behaviors. In the only twin study of comorbid mental health problems in autistic traits in late adolescence (Hoekstra, Bartels, Hudziak, Van Beijsterveldt, & Boomsma, 2007), autistic traits were found to be significantly related to withdrawn behavioral problems and social problems. Autistic traits and anxiety/depressive behaviors also correlated modestly, but this correlation ceased to be significant after the effects of social and withdrawn behavioral problems were taken into account in the regression model. Substantial genetic overlap between both withdrawn behaviors and social problems with autistic traits was found. Overall, the results to date suggest that autistic traits and anxiety behaviors do not appear to share as much genetic overlap as autistic traits and ADHD, but the somewhat mixed results may reflect different measures used for anxiety behaviors as well as different age groups.

Lastly, new avenues of research are investigating genetic and environmental overlap between autistic traits and other conditions such as tic disorder and developmental coordination disorder (Lichtenstein et al., 2010). Psychopathic tendencies have been shown to share modest genetic overlap with autistic traits in a twin sample in middle childhood (Jones et al., 2009), and clumsiness was reported to show genetic overlap with autistic traits in an Italian twin sample (Moruzzi, Ogliari, Ronald, Happé, & Battaglia, 2011).



## ***Degree of Genetic and Environmental Overlap Between Different Autistic Symptoms***

ASDs are characterized by a triad of symptoms in the domains of social impairments, communication impairments, and restrictive repetitive behaviors and interests (RRBIs). Several groups of researchers have suggested that autism is best understood as a disorder of “multiple deficits” (Bishop, 1989; Goodman, 1989; Happé, Ronald, & Plomin, 2006; Mandy & Skuse, 2008; Wing & Wing, 1971), while other researchers argue that autistic symptoms together represent a single underlying dimension (e.g., Constantino et al., 2004). Understanding which of these models is most accurate has many implications, for example, for how best to define ASD subtypes, for understanding familial risk, and for designing management and treatment options.

It is notable that the autism phenotype “splinters” among family members who share proportions of the proband’s genetic makeup. That is, relatives often show mild versions of just part of the autism phenotype, for example, social impairments, without communication difficulties, or RRBIs. Thus family studies suggest that different causative factors influence the three components (e.g., Bolton et al., 1994). While the majority of factor analytic studies support the notion of two, three, or more dimensions underlying autistic symptoms (see reviews by Happé & Ronald, 2008; Mandy & Skuse, 2008), a minority of studies report a single dimension underlying autistic symptoms (for example, Constantino et al., 2004).

Four twin studies from a large general population twin sample have reported that the three sets of autistic symptoms are all highly heritable individually but are caused by largely different sets of genetic influences, when assessed in the general population in middle and late childhood, both dimensionally (Robinson et al., 2011; Ronald et al., 2005; Ronald, Happé, Bolton, et al., 2006) and at the impaired 5 % extreme (Robinson et al., 2011; Ronald, Happé, Price, et al., 2006). The genetic correlations were all modest to moderate in these studies (Robinson et al., 2011; Ronald et al., 2005; Ronald, Happé, Bolton, et al., 2006; Ronald, Happé, Price, et al., 2006). This finding has been replicated across two other samples (Edelson, Ronald, & Saudino, 2009; Ronald, Larsson, Anckarsäter, & Lichtenstein, 2011). Using a sample of twins with ASD who had been diagnosed using a parent interview, a similar modest degree of genetic overlap between the different ASD symptoms has been reported (Dworzynski, Happé, Bolton, & Ronald, 2009). In another study of twins diagnosed with ASD, social dysfunction and nonverbal communication symptoms were reported to show a modest degree of common genetic influences (Mazefsky, Goin-Kochel, Riley, & Maes, 2008). The comparison of symptom profiles within MZ pairs who are concordant for ASD is another potentially informative approach. However, the two studies of this kind so far have presented contradictory findings, and the small sample sizes mean that statistical comparisons between twin similarity estimates were limited (Kolevzon, Smith, Schmeidler, Buxbaum, & Silverman, 2004; Le Couteur et al., 1996).



The implication of these multivariate twin studies of autism symptoms and autistic traits is that the autism “triad,” that is, the three core sets of symptoms that defined ASD in the DSM IV, may be on average largely fractionable, and causal explanations should be sought for each symptom group separately, rather than for autism as a whole (Happé et al., 2006; Happé & Ronald, 2008). Molecular genetic research has begun to explore the possibility of symptom-specific genetic influences in autism using candidate gene studies, linkage, and genome-wide association (Alarcón et al., 2008; Brune et al., 2006; Ronald, Butcher, et al., 2010). Studying subphenotypes, or endophenotypes that are relevant to autism, may aid the identification of genes associated with specific heritable facets of the condition.

### ***Assumptions of the Twin Design for Studying Autism and Autistic Traits***

*Generalizability of Twin Studies for Studying Autism and Autistic Traits.* Some studies have suggested that the process of twinning may be a risk factor for the development of autism (Betancur, Leboyer, & Gillberg, 2002; Greenberg, Hodge, Sowinski, & Nicoll, 2001; but see Visscher, 2002). However, large population-based studies do not support these findings (Croen, Grether, & Selvin, 2002; Hallmayer et al., 2002; Hultman, Sparen, & Cnattingius, 2002). While a recent study that compared autistic traits across singleton and twin samples reported no major effect of twinning on autistic traits (Curran et al., 2011), one earlier study reported evidence that male twins may show slightly more autistic traits compared to male singletons (Ho, Todd, & Constantino, 2005). When singletons and twins come from two different samples, the two samples are not necessarily matched for age, IQ, or social economic status. In a twin family study that also included the siblings of the twin pairs, which has the advantage that it controls for possible confounding effects of social economic status or parental education, mean self-reported autistic trait scores were found to be similar in twins and non-twin siblings (Hoekstra, Bartels, Verweij, et al., 2007). In another study, there were no significant twin-sibling mean differences on measures of social impairments or RRBI for teacher- or parent-rated data in 7-year-olds, with the exception of parent ratings of DZ twins, who showed significantly higher social impairments (Ronald, 2006). As such, three out of four of these studies suggested, for the most part, that level of autistic traits is unrelated to being born a twin or singleton.

*Assortative Mating.* The classical twin design assumes random partner selection, i.e., that partners do not actively or passively select each other based on their phenotype. Positive assortative mating (a positive correlation between partners' phenotypes) leads to a greater resemblance in DZ twins and non-twin siblings, while MZ resemblance remains unaltered, resulting in attenuated heritability estimates. Five studies to date have examined assortative mating for autistic traits in the general population or in clinical samples, with contrasting results. Constantino and Todd

(2005) found a spousal correlation of 0.38 for autistic traits as measured using the SRS in the general population. Two subsequent studies using the SRS in parents of a child with autism found spousal correlations of respectively 0.26 (Virkud, Todd, Abbacchi, Zhang, & Constantino, 2009) and 0.34 (Schwichtenberg, Young, Sigman, Hutman, & Ozonoff, 2010). In contrast, Hoekstra, Bartels, Verweij, et al., 2007 and Pollmann, Finkenaier, and Begeer (2010) found near-zero partner correlations in general population samples using the full-scale AQ and the AQ-short. The latter two studies relied on self-report, while the studies using the SRS asked spouses to rate each other's autistic traits. Shared beliefs or perceptions about the couple's relationship may have inflated the spousal correlation in these studies. In contrast to the lack of resemblance on the AQ-short ( $r=0.03$ ), Pollmann et al. (2010) did find significant spousal correlations for relationship satisfaction ( $r=0.32$ ), relationship intimacy ( $r=0.28$ ), and partner trust ( $r=0.21$ ), strengthening the idea that the studies using spousal report may have mainly picked up shared beliefs about the relationship quality, rather than resemblance for autistic traits per se. An alternative explanation for these conflicting findings would be that self-report assessment of autistic traits as employed by Hoekstra, Bartels, Verweij, et al., 2007 and Pollmann et al. (2010) may underestimate assortative mating. Various twin registers around the world have now started to include data on siblings, spouses, and children of twins, so that many more family relationships can be modeled in the future. In the so-called extended twin family designs (see, e.g., Eaves, 2009; Maes et al., 2009), it will be possible to test directly the possible effects of assortative mating.

## Conclusions and Future Directions

Our understanding of the causes of autism, broader ASD, and autistic traits measured on quantitative scales is continually evolving through new discoveries, and it is argued that twin studies have added considerably to this research field. This literature provides new evidence regarding the dimensional nature of autistic behaviors; why ASD and autistic traits co-occur with intellectual disability, language delay, and other psychiatric disorders; and etiological heterogeneity of autistic symptoms. Although more research is needed in this area, the findings reviewed here have provided specific and testable hypotheses for molecular genetic autism research. Example hypotheses include that a substantial proportion of genetic risk factors associated with ADHD will also be associated with risk for ASD, that different genetic causal pathways will be associated with different types of autistic symptoms, and that the common genetic variants influencing the risk for autism are likely to be substantially distinct from the genetic causes of intellectual disability.

Despite the considerable impact of twin studies on our understanding of the etiology of ASD and autistic traits, further research is needed to settle existing contradictory findings and to address so far unresearched questions. For example, twin studies of psychiatric comorbidity could explore the degree to which genes and environment explain co-occurrence of other so far neglected comorbid symptoms

and conditions such as conduct problems, sleep problems, antisocial behavior, psychotic experiences, and depression. It would also be intriguing to explore the etiological architecture underlying RRBIs, which may comprise several different behavioral subdomains. Further work could teach us more about developmental change and continuity in genetic and environmental influences on ASD and autistic traits, particularly in early childhood, for which there are only two cross-sectional twin studies of autistic traits to date (Edelson & Saudino, 2009; Stilp et al., 2010), and adulthood, for which only one twin study has been published (Lundström et al., 2011). One longitudinal analysis, albeit with limited power due to a small sample (95 male twin pairs), suggests that change over time in autistic traits from early childhood to adolescence is explained by mostly genetic, and to a lesser extent, nonshared environmental influences (Constantino et al., 2009).

The types of measures used to assess features of autism need to be further developed. Age-appropriate measures that reliably capture autistic traits at different time points in life are necessary to conduct reliable longitudinal analyses. Moreover, the comparability of measures of dimensional autistic traits with measures used in clinical samples is an important consideration. The field awaits with interest the results of further twin studies of ASD using the ADOS and ADI-R clinical measures. Novel approaches to measurement were employed in a study that related autistic traits to lab measures of orientation and engagement in 2-year-olds (Edelson & Saudino, 2009) and two studies of older children that have employed cognitive assessments in theory of mind (Ronald, Viding, Happé, & Plomin, 2006) and emotion attribution (Jones et al., 2009) in relation to autistic traits. Further studies including cognitive phenotypes related to autism are needed to examine the association between specific cognitive abilities and autistic traits. Such studies will also be instrumental in integrating psychological and biological explanations of autism. Moreover, studies focusing on special abilities (Vital, Ronald, Wallace, & Happé, 2009) can teach us more about some of the superior characteristics associated with the autism phenotype.

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