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REVIEW PAPER

ASD Validity

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Abstract ASD research is at an important crossroads. The ASD diagnosis is important for assigning a child to early behavioral intervention and explaining a child's condition. But ASD research has not provided a diagnosis-specific medical treatment, or a consistent early predictor, or a unified life course. If the ASD diagnosis also lacks biological and construct validity, a shift away from studying ASD-defined samples would be warranted. Consequently, this paper reviews recent findings for the neurobiological validity of ASD, the construct validity of ASD diagnostic criteria, and the construct validity of ASD spectrum features. The findings reviewed indicate that the ASD diagnosis lacks biological and construct validity. The paper concludes with proposals for research going forward.

Keywords DSM-5 · ASD · Autism · Diagnosis · Validity · Comorbidity · Heterogeneity

The goal of the DSM-3 nosology (American Psychiatric Association 1980) was to create reliable and standard categorical psychiatric diagnoses (Robins and Guze 1970). However, in the past 30 years, clinical, genetics, and neuroscience findings have revealed that the DSM diagnoses are not biologically valid. The National Institutes of Mental Health (NIMH) responded by proposing the Research Domain Criteria (RDoC) framework for a brain-based transdiagnostic psychiatric symptom nosology (Cuthbert and Insel 2013; Insel et al. 2010; Lilienfeld and Treadway 2016). Peterson (2015) and Weinberger et al. (2015) argued that the RDoC could not replace the DSM-5 psychiatric nosology (American Psychiatric Association 2013) or the parallel International Classification of Diseases (ICD) psychiatric nosology (World Health Organization 2012). But "For the foreseeable future, RDoC is not envisioned as a system of psychiatric classification in its own right. Instead, in the near term, RDoC and DSM-ICD are expected to coexist. Nevertheless, RDoC is intended to provide scaffolding for a large-scale research program that will ultimately yield an alternative to DSM-ICD" (Lilienfeld and Treadway 2016, p. 445).

RDoC advocates accept that DSM-5/ICD psychiatric categories remain necessary in clinical practice, but argue that researchers should shift to RDoC study designs immediately. They assert that studying psychiatric categories lacking biological validity blocks the discovery of brain bases for psychopathology and thus cannot lead to effective medical treatments for specific psychiatric symptoms (Cuthbert and Insel 2013; Insel et al. 2010; Lilienfeld and Treadway 2016; Yee et al. 2015). Against this RDoC imperative for biological validity, Weinberger et al. (2015) countered that current DSM-5 psychiatric behavioral diagnoses were valid when they yielded effective medical treatment, clear prognosis, and a life course specific to a diagnosis.

Autism spectrum disorder (ASD) research has been productive (Dawson 2016; de la Torre-Ubieta et al. 2016; Szatmari et al. 2016), but no ASD research findings have met the validity criteria of Weinberger et al. (2015). DSM-5 ASD research has found no specific effective pharmacotherapy or other medical treatment (Na Young and Findling 2015). The only broadly successful ASD treatment has been early behavioral intervention

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programs (Kasari 2015; Schreibman et al. 2015; Smith and Iadarola 2015; Volkmar et al. 2014), but these treatments are not unique to ASD (Losinski et al. 2014), and the long-term effectiveness of these programs is not yet known (Fernell et al. 2011, 2014). Researchers who studied infant siblings of children with ASD concluded no single early behavior could predict ASD diagnoses (Zwaigenbaum et al. 2015), and ASD has been found with widely varied trajectories of development (Fountain et al. 2012; Lord et al. 2015) and varied life outcomes (Fein et al. 2013; Helles et al. 2015; Steinhausen et al. 2016).

ASD research is at a crucial decision point. The ASD diagnosis remains necessary in the clinic to assign a child to early behavioral intervention and to explain a child's condition. But researchers must decide whether to continue studying ASD-defined samples or not. Given that ASD lacks any diagnosis-specific medical treatment, any consistent early predictor, or any specific life course, if the ASD diagnosis also lacks biological and construct validity, a shift away from studying ASD-defined samples would be warranted.

Consequently, this paper reviews recent findings for ASD biological and construct validity. This paper is not a meta-analysis; instead it brings together competing and unresolved findings. The first section examines evidence for the neurobiological validity of ASD. The second section outlines evidence for the construct validity of ASD diagnostic criteria. The third section explores evidence for the construct validity of ASD spectrum features beyond ASD diagnostic symptoms. The paper concludes that the evidence reviewed does not provide support for the neurobiological or construct validity of the ASD diagnosis, and therefore the ASD diagnosis should be disbanded in research.

Does ASD Have Neurobiological Validity?

The ASD diagnosis would be biologically valid if all or nearly all individuals diagnosed with ASD shared one or a few related brain impairments. Researchers have tried different means to find a unitary ASD brain impairment. Researchers have measured the brain structures of idiopathic ASD, defined as having no known genetic or environmental cause. Researchers have proposed and tested models of unitary ASD brain impairment. Researchers have sought brain impairments unique to each core ASD diagnostic symptom. Researchers have looked for an independent ASD brain impairment in syndromic ASD, defined as occurring with known genetic and environmental syndromes. Fifth, researchers have grouped ASD genetic risk genes theorized to produce a narrowed set of disrupted brain circuits.

Brain Validity Research Approach 1: Is There a Specific ASD Brain Impairment?

Findings for ASD global and regional brain sizes have been varied. Riddle et al. (2016) found that 443 individuals with ASD had a 2.17 % increase in gray matter compared to 390 typically developing (TD) individuals, but found no group difference in white matter. However, when Riddle et al. (2016) compared matched subsamples of 300 ASD and TD children, no differences between TD and ASD white matter *or* gray matter were found. Vasa et al. (2012) reported that only 8 of 73 individuals diagnosed with ASD had any atypical brain features. Lenroot and Yeung (2013) reported that the majority of individuals diagnosed with ASD had typical brain and head size. However, in other studies, approximately 10 to 24 % of individuals diagnosed with ASD had persisting macrocephaly (Gillberg and de Souza 2002; Lainhart 2015; Nebel et al. 2015; Sacco et al. 2015; Tammimies et al. 2015). In addition, a number of studies have reported that 3 to 15 % of individuals with ASD had persisting microcephaly (Gillberg and de Souza 2002; Nebel et al. 2015; Roullet et al. 2013; Stevens et al. 2013).

Although Riddle et al. (2016) found no regional brain differences in 443 individuals with ASD compared to 390 TD individuals, Lefebvre et al. (2015) noted that many studies had found significantly smaller corpus callosum in ASD than TD controls. By contrast, Lefebvre et al. (2015) found no difference in corpus callosum size in their sample of 694 individuals with ASD compared to TD controls. Studies of the amygdala in ASD have reported significantly "increased, decreased and preserved volumes" of the amygdala (Bellani et al. 2013, p. 3). Similarly, Stigler et al. (2011) noted that studies have reported increased, decreased, and typical (preserved) volumes for the fusiform gyrus in ASD.

D'Mello et al. (2015) reported that ASD was characterized by reduced gray matter in the cerebellum in lobule VII. However, a consensus paper on the cerebellum in ASD (Fatemi et al. 2012) concluded that only a subgroup of ASD had atypical cerebellar anatomy, and this was a smaller cerebellar vermis volume and fewer Purkinje cells. Studies of the brainstem in ASD have reported both typical and atypically smaller volumes of brainstem gray matter (Jou et al. 2013). Despite evidence for abnormal auditory brainstem response (ABR) in ASD (Rosenhall et al. 2003; Lukose et al. 2015), Jou et al. (2013) concluded that ASD brainstem studies were conflicting and inconclusive.

Summary ASD global and regional brain structures are varied and do not provide brain structure biological validity for ASD.

To date, no unitary atypical brain size or volume has been found for ASD, and no unitary atypical ASD regional brain structure has been found. Equally important, varied ASD electrophysiology findings (Billeci et al. 2013) and varied ASD molecular neurochemistry findings (Zürcher et al. 2015) stand against the idea that there is any shared single ASD brain impairment in electrophysiology or molecular neurochemistry.

Of course, research has not uncovered the full complexity of human brain development, functions, and networks (Sporns and Betzel 2016). When much more is known about the

emergence of regional functions and connectivity of the brain, it may be possible in the future to establish a unitary model of ASD brain impairment.

Brain Validity Research Approach 2: Is There a Replicated ASD Brain Impairment Model?

Hundreds of unitary models of ASD brain impairment have been theorized and studied. For example, Baron-Cohen et al. (2015) proposed that ASD stemmed from fetal steroidogenic abnormalities. Fishman et al. (2014) proposed that ASD resulted from atypical overconnectivity of the brain's mirror neuron regions and theory of mind regions. By contrast, Khan et al. (2015) proposed that ASD resulted from underconnectivity in local brain regions when activated by a "functionally relevant task" (p. 1407). Mullins et al. (2016) posited that mutations in the FMR1 gene and TSC genes disrupt long-term depression (LTD) and long-term potentiation (LTP), and therefore, these mutations in ASD cause atypical LTP and LTD processes that impair the excitation-inhibition balance in brain development and function which determines ASD (Mullins et al. 2016).

Robertson et al. (2015) claimed that the "prime suspect" single cause for ASD was disrupted GABAergic signaling that impaired neurodevelopment and cortical computations. However, Estes and McAllister (2015) theorized that ASD was caused by atypical immune system factors that converged on the MEF2 and mTOR signaling hubs and thus disrupted the brain's developmental synaptic function and plasticity. Irimia et al. (2014) theorized a basis for ASD brain impairment in atypically greater misregulation of nSR100-dependent microexons. Focusing on early visual attention in ASD, Klin et al. (2015) posited that the developmental failure of the reward-based interactional eye fixation to co-opt the brain's innate reflexive eye fixation caused ASD.

Because these eight theories explain different aspects of ASD brain function, they are not necessarily mutually exclusive. However, there has been no attempt to synthesize any subset of these eight theories, or synthesize any subset of prior unitary ASD brain theories (Waterhouse 2008). Most importantly, no unitary brain impairment theory to date has been replicated to become a standard explanation of ASD brain disruption.

The theory with the most active support argues that ASD results from impaired brain connectivity that is likely to have been preceded by early brain overgrowth (Solso et al. 2015; Stoner et al. 2014; Venkataraman et al. 2015). Although the underconnectivity theory has been studied for more than 15 years (Just et al. 2004) and has many supporters (Anderson 2013; Dawson 2016; Ecker et al. 2015; Green et al. 2015; Shen et al. 2013), nonetheless, this theory has not become standard because there is as much evidence against the theory as there is for it.

Supporting the existence of early ASD brain overgrowth, Ecker et al. (2015) asserted that, on average, toddlers with ASD have "a larger brain volume than typically developing children" (p. 1), and Shen et al. (2013) and Anderson (2013) reported that ASD was characterized by atypical early brain overgrowth. Sussman et al. (2015) reported that early brain overgrowth was limited to males with ASD, and Chaste et al. (2013) found that the subgroup of ASD with an atypically larger head circumference expressed greater symptom severity and lower IQ.

Counter to the early brain overgrowth model, though, Chaste et al. (2013), Raznahan et al. (2013), and Cederlund et al. (2014) all concluded that very few children with ASD had early brain overgrowth, and Raznahan et al. (2013) reported that larger ASD head circumference was not found when local TD controls were used. Lainhart (2015) reviewed research and noted that only "a very small subgroup of ASD children" (p. 79) had larger brain volumes. In a meta-analysis, Sacco et al. (2015) found only 5.7 % of individuals with ASD had macrocephaly and just 9.1 % had brain overgrowth. Tammimies et al. (2015) also found that only 63 of 258 children with ASD had macrocephaly. Also countering the ASD early brain overgrowth model, 3 to 15 % of individuals diagnosed with ASD have been born with microcephalic brains (Nebel et al. 2015; Roullet et al. 2013; Stevens et al. 2013). Most importantly, the generalizability of the ASD early brain overgrowth model is limited by the evidence that the majority of individuals diagnosed with ASD have typically developing head and brain growth (Lenroot and Yeung 2013; Nebel et al. 2015; Riddle et al. 2016; Vasa et al. 2012).

Supporting the malconnectivity component of the currently dominant model, Dawson (2016) asserted that "long-range connections between different brain regions are weaker in people with ASD" (para. 4). Venkataraman et al. (2015) determined that ASD brain malconnectivity occurred in two networks: a language network including temporal lobe areas and a "social-person" network including temporal and parietal areas. Venkataraman et al. (2015), however, found no impairment in ASD frontal lobe connectivity. Conversely, Kitzbichler et al. (2015) reported that ASD malconnectivity was centered in frontal lobe-linked connections.

Counter to both Kitzbichler et al. (2015) and Venkataraman et al. (2015), though, Redcay et al. (2013) reported finding no evidence for atypical connectivity in ASD. Tyszka et al. (2014) also stated that their ASD sample showed, "no evidence at all for altered connectivity at the whole-brain level" (pp. 7–8). Kirkovski et al. (2015) found no differences between high functioning individuals with ASD and typical controls in white matter in major tract bundles determined by any method: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), or axial diffusivity (AD). Koldewyn et al. (2014) reported finding no general impaired white matter in ASD. Lefebvre et al. (2015) found no differences between 694 individuals diagnosed with ASD and typical controls in the largest white matter tract in the brain—the corpus

callosum. The researchers questioned whether any regional ASD malconnectivity model could be meaningful because most of the brain is involved in connectivity (Lefebvre et al. 2015).

Another problem for standardizing the overgrowth-malconnectivity model is that there are so many different versions of this model (Fishman et al. 2014; Kennedy et al. 2015; Khan et al. 2015; Kitzbichler et al. 2015; Venkataraman et al. 2015). As noted by Kennedy et al. (2015), "the connectivity hypothesis has been vague ever since its inception… slowly morphing from a theory about underconnectivity in ASD, to one about distal underconnectivity paired with local overconnectivity, to one about atypical connectivity in either direction (or both)" (p. 81).

Summary No ASD brain impairment model has been adequately replicated to become standard, and thus, no existing model provides neurobiological validity for ASD.

Despite intense research efforts, the malconnectivity model has not been successfully replicated (Ecker et al. 2015; Kennedy et al. 2015; Khan et al. 2015; Lefebvre et al. 2015), and neither has any of the myriad other unitary ASD brain impairment models. Moreover, none of these models has accounted for the variation in ASD global and regional brain structures, or the variation in ASD electrophysiology findings (Billeci et al. 2013), or the variation in neurochemistry findings (Zürcher et al. 2015).

Brain Validity Research Approach 3: Is Each ASD Diagnostic Symptom Caused by a Distinct Brain Impairment?

Many studies have looked for the biological validity of individual ASD diagnostic and associated nondiagnostic symptoms (Anderson et al. 2014; Boucher 2011; Brunsdon and Happé 2014; Chen et al. 2015; Harrop et al. 2013; Hormozdiari et al. 2015; Jason et al. 2015; Pina-Camacho et al. 2012; Shuster et al. 2014).

Is ASD Social Impairment Linked to a Unique Brain Impairment?

DSM-5 defines ASD diagnostic social impairment as persistent impaired social reciprocity, with impaired social nonverbal communication behaviors, along with an inability to develop and maintain relationships. Pina-Camacho et al. (2012) analyzed multiple studies of the association between ASD symptoms and brain impairments and reported that ASD diagnostic social impairment was linked to four distinct regional brain dysfunctions. The face-fusiform area (FFA) was found as the basis for ASD social impairment, and the frontotemporal cortical networks including mirror neuron system circuits were found as the basis for ASD social impairment (Pina-Camacho et al. 2012). Still other findings implicated dysfunction of the anterior cingulate cortex (ACC) in ASD social impairment, and finally, some research suggested that ASD social behaviors were impaired by disruptions in the subcortical amygdala-hippocampal network (Pina-Camacho et al. 2012).

In addition to the brain regions reported by Pina-Camacho et al. (2012), Ecker et al. (2012) claimed that ASD diagnostic social impairment was specifically linked to "a significant decrease in gray matter volume in a large cluster located in the occipital and medial parietal regions" (p. 202). However, Ecker et al. (2015) later asserted that impaired ASD social communication resulted from dysfunctions in Broca's and Wernicke's areas, while impaired ASD social/emotional comprehension resulted from dysfunctions in frontotemporal regions and the amygdala.

Zilbovicius et al. (2013) reported that ASD diagnostic social impairment was linked to abnormalities in the superior temporal sulcus (STS), including decreased gray matter and hypoperfusion at rest. Maillard et al. (2015) found that diagnostic ASD social impairment and chromosomal number variant (CNV) 16p11.2 carrier social impairment were both linked to brain dysfunctions in left and right putamen, insula, posterior cingulate, thalamus, and superior temporal gyrus. By contrast, Byrge et al. (2015) reported that five (of 17) individuals diagnosed with ASD all had profound diagnostic social impairment but none of the five shared any specific atypical brain dysfunction. Instead, these five individuals expressed five different idiosyncratic brain responses to observed social interaction (Byrge et al. 2015).

Ameis and Catani (2015) reported that three different methods yielded different brain bases for ASD social impairment. Ameis and Catani (2015) noted that while neuropathology studies found frontolimbic pathways linked to ASD diagnostic social impairment, MRI imaging studies did not. Instead, Ameis and Catani (2015) reported that MRI imaging studies found early atypical brain growth and atypical volume of frontal white matter linked to ASD social impairment. Finally, fMRI findings differed from both neuropathology and MRI findings, linking ASD diagnostic social impairment to decreased temporal lobe activity and decreased frontal lobe activity. Ameis and Catani (2015), in turn, theorized that the brain basis for ASD diagnostic social impairment was disrupted uncinate fasciculus and thalamic projections to prefrontal and temporal lobes.

Are ASD Diagnostic Repetitive Behaviors, Restricted Interests, and Resistance to Change, Together Identified as the RRBs, Linked to a Unitary Brain Impairment?

The DSM-5 ASD diagnosis now requires the presence of two of four behaviors of any of the RRBs, and/or atypical sensory

responsiveness. Pina-Camacho et al. (2012) reviewed multiple studies of the brain basis of the RRBs and reported that six distinct brain regions had been linked to ASD RRBs. One brain region was the frontocerebellar network, and another region was the frontostriatal system (Pina-Camacho et al. 2012). Four more regions linked to the RRBs were the anterior and posterior cingulate, some posterior parietal regions, the posterior regions of corpus callosum, and the cerebellar vermis and peduncles (Pina-Camacho et al. 2012).

The RRBs have also been linked to specific frontal lobe structural abnormalities (Ecker et al. 2012), and the RRBs have been linked to atypical caudate overgrowth (Langen et al. 2014). By contrast, Doyle-Thomas et al. (2014) reported that RRBs in general were associated with atypically low choline/creatine in the thalamus, whereas ASD social impairment was not. In addition, Gabriels et al. (2013) reported that the general severity of RRBs was inversely correlated with daytime cortisol levels.

Are ASD Nondiagnostic Symptoms Linked to Specific Brain Impairments?

Although ASD diagnostic criteria specifically exclude many neurodevelopmental symptoms such as intellectual disability (ID), language delay, language impairment, attention deficits, and seizures, more than 96 % of those diagnosed with ASD actually express one or more of these symptoms and/or other non-ASD symptoms (Lundström et al. 2015b). The prevalence of non-ASD neurodevelopmental symptoms varies. ADHD symptoms were found in 17 to 83 % of individuals with ASD (Matson et al. 2013; Nebel-Schwalm and Worley 2014). ID has been reported in 50–70 % of individuals with ASD (Matson and Williams 2014). Nearly 100 % of individuals diagnosed with ASD have been found to exhibit mutism, or language delay, or language impairment (Boucher 2012). Finally, 40 % with ASD have experienced seizures (Amiet et al. 2013), and 60 % with ASD have exhibited epileptiform brain activity (Mulligan and Trauner 2014).

Variation in the pathophysiology of non-ASD epilepsy is very similar to the variation in the pathophysiology of epilepsy in ASD (Amiet et al. 2013; Blackmon 2015; Stafstrom and Carmant 2015). Some epilepsy is the result of malformations of cortical development (MCDs), including focal cortical dysplasia and heterotopias, and these malformations have been found in ASD (Blackmon 2015).

Attention problems are inherent in some ASD criteria, such as the preoccupation with unusual objects, and up to 83 % of those with ASD have expressed ADHD symptoms (Nebel-Schwalm and Worley 2014). However, before DSM-5, ASD and ADHD could not be diagnosed together in one individual. Johnson et al. (2015) reported that frontal lobe impairments and hypo- and hyperconnectivity have been reported for both ASD and ADHD. Johnson et al. (2015) also noted that some studies found slower early brain size increase in both ADHD and ASD.

Up to 70 % of individuals with ASD express ID, and some of the comorbidity of ASD and ID is known to stem from shared gene risk factors. For example, 17 % of all ID risk genes with de novo loss of function (LoF) mutations are also reported for ASD (Vissers et al. 2016). Both ASD and ID have been found with gene variants that cause impairment in many aspects of brain development and function, including neurogenesis, neuronal migration, synaptic function, and regulation of transcription and translation (Vissers et al. 2016).

Mayes et al. (2015) found that language impairment in children without ASD was associated with atypical structure and function in traditional language regions including the inferior frontal gyrus, posterior superior temporal gyrus, and caudate nucleus. As noted earlier, Venkataraman et al. (2015) reported that ASD included impaired brain connectivity in language regions including right temporal pole, left posterior cingulate cortex, left supramarginal gyrus, and left middle temporal gyrus. ASD has also been found with both decreased and increased rightward functional activation of language cortex (Joseph et al. 2014).

Summary Each of the two ASD core diagnostic symptoms has been found with multiple varied brain impairments; thus, each core ASD diagnostic symptom lacks neurobiological validity.

Neither core ASD diagnostic symptom has been linked to a single consistent brain impairment. Moreover, nondiagnostic symptoms commonly found with ASD, such as ID, ADHD, language impairments, and seizures, each occur with varied brain impairments.

That ASD social impairment is found with so many varied brain impairments may reflect the many different and interconnecting brain systems that shape typical human social behaviors (Barrett and Satpute 2013; Doré et al. 2014). The varied brain impairments, in turn, may, in part, reflect the myriad genes that regulate the structure and function of social brain systems (Weitekamp and Hofmann 2014; Westberg and Hasse Walum 2015).

The many varied brain impairments found with the RRBs may be consonant with the variation in the types of RRBs. The RRBs include stereotyped movements, repetitive manipulation of objects, repetitive self-injurious behavior, specific object attachments, compulsions, rituals and routines, an insistence on sameness in the environment, repetitive use of language, as well as narrow and circumscribed interests (Bishop et al. 2013; Leekam et al. 2011). Given this wide range of RRB behaviors, it is possible that, in part, different forms of RRBs may be caused by different brain dysfunctions.

Finally, nondiagnostic symptoms found with ASD such as ID and language dysfunction have many different brain bases reflecting the wide variation in ASD etiology.

Brain Validity Research Approach 4: Are Syndromic ASD Diagnostic Symptoms Caused by an Independent Unique ASD Brain Impairment?

Syndromic ASD is found with a known genetic or environmental syndrome, such as fragile X syndrome (FXS) or valproate syndrome. Syndromic ASD occurs with Mendelian single gene syndromes, CNV syndromes, and environmental syndromes. Although syndromic ASD has been estimated to account for only 5 to 25 % of all cases of ASD (Adviento et al. 2014; de la Torre-Ubieta et al. 2016; Jeste and Geschwind 2014), more forms of syndromic ASD continue to be identified (Adviento et al. 2014; Richards et al. 2015; Roullet et al. 2013; Smile et al. 2013; Yu and Berry-Kravis 2014; Yuen et al. 2015). In addition, syndromic and idiopathic ASD brain impairments have been reported that are similar (Adviento et al. 2014; Blackmon 2015; D'Angelo et al. 2015; Guilmatre et al. 2014; Klusek et al. 2015; Sala et al. 2015).

The key question is whether syndromic ASD diagnostic symptoms are caused by an independent brain impairment unique to ASD. For example, when ASD occurs with cerebral palsy (Smile et al. 2013), are ASD diagnostic symptoms caused by an ASD-specific brain connectivity problem? Or are ASD diagnostic symptoms caused by characteristic cerebral palsy gray matter injuries, brain malformations, and focal vascular insults? If syndromic ASD symptoms do not result from an independent ASD-specific brain impairment, then ASD diagnostic symptoms in syndromic ASD must result from widely varied brain impairments.

Peters et al. (2013) and Tye and Bolton (2013) argued for an independent unique ASD brain impairment in syndromic ASD. Peters et al. (2013) asserted that in syndromic ASD with tuberous sclerosis complex (TSC), the TSC brain tubers and TSC malorganization of the brain caused TSC symptoms, but that brain underconnectivity was independently and uniquely causal for ASD alone. The researchers found that underconnectivity occurred in syndromic ASD with TSC, and in idiopathic ASD, but not in TSC alone. Similarly, Lainhart (2015) claimed that syndromic ASD with TSC and idiopathic ASD both expressed the ASD-specific reduced long-range connectivity with increased short-range connectivity.

However, Jeste and Geschwind (2014), Hall et al. (2010), and Adviento et al. (2014) proposed that syndromic ASD arose from the syndrome's brain impairments. Specifically, for the case of syndromic ASD with TSC, Jeste and Geschwind (2014) argued that the TSC brain tubers and TSC malorganization of the brain that caused TSC symptoms also simultaneously caused ASD symptoms. Jeste and Geschwind (2014) argued that both ASD and TSC symptoms resulted from TSC tubers that occurred in the temporal, frontal, and occipital cortex and in the cerebellum, because these tubers cause many brain impairments, including disorganized axonal tracts, increased axonal growth, abnormal myelination, aberrant synapse formation, and aberrant white matter organization. Similarly, for syndromic ASD with FXS, Hall et al. (2010) argued that an individual with FXS who expressed ASD symptoms did not have two disorders, but had one genetic disorder, FXS, that caused one brain impairment, the lack of fragile X mental retardation protein (FMRP) that, in turn, caused both FXS symptoms and ASD symptoms. Gabis and Pomeroy (2014) also supported the single brain impairment model of syndromic ASD with evidence suggesting that ASD symptoms expressed in syndromic ASD likely resulted from a unitary "biological or neural pathway" (p. 297).

Genetic Syndromic ASD Has Been Found with Varied Brain Impairments

There are many forms of genetic syndromic ASD (Cederlöf et al. 2014; Kern et al. 2015; Plasschaert et al. 2015; Poot 2015; Richards et al. 2015). The fact that many different genetic syndromes do yield ASD diagnostic symptoms is the result of locus heterogeneity, wherein different gene variants produce the same phenotype, or the same phenotypic trait or symptom. Syndromic ASD has been found with genetic syndromes called RASopathies that are caused by mutations in Ras/mitogen-activated protein kinase (Ras/MAPK) expression genes. Adviento et al. (2014) reported that ASD occurred in four RASopathies: neurofibromatosis type 1 (NF1), Noonan syndrome (NS), Costello syndrome (CS), and cardio-facio-cutaneous syndrome (CFC). Syndromic ASD has also been found with the Shankopathies, which are genetic syndromes caused largely by mutations in *SHANK2*, and *SHANK3* genes (Guilmatre et al. 2014; Leblond et al. 2014; Sala et al. 2015). Many genetic variants, like the mutations in *SHANK2* and *SHANK3*, have pleiotropic effects, that is, a single mutation results in a variety of phenotypes. A mutation in *SHANK3* has the pleiotropic effect of generating four separate diagnostic phenotypes: ASD, schizophrenia (SCZ), severe ID, and epilepsy (Guilmatre et al. 2014; Leblond et al. 2014; Sala et al. 2015). Hommer and Swedo (2015) noted that *SHANK3* mutations, and the 22q11.2 deletion syndrome, and duplications at the Williams syndrome locus (7q11.23) all pleiotropically generated both the ASD and SCZ phenotypes. However, the ACD and SCZ phenotypes had disrupted deep layer cortical projection neurons in different brain locations; in ASD, the disruption occurred in the prefrontal and primary motor-somatosensory regions, but in SCZ, the disruption occurred in the dorsolateral and ventrolateral prefrontal cortical regions (Hommer and Swedo 2015).

ASD has frequently been reported with the Phelan-McDermid syndrome caused by the CNV chromosome 22q13 deletion that disrupts the gene *SHANK3*. The SHANK protein regulates synaptic cell adhesion molecules and cell scaffolding in brain development via dendrites and

glutamatergic synapses. *SHANK2* and *SHANK3* gene mutations reduce the total number of dendritic spines and synapses on neurons, and the lack of mature glutamatergic synapses appears to cause the impaired brain function that results in ID and ASD symptoms.

In a meta-analysis of 168 papers, Richards et al. (2015) reported varied rates of syndromic ASD across 11 genetic syndromes. Richards et al. (2015) reported that of those diagnosed with Rett's syndrome (RTT), 61 % were found to have ASD diagnoses, and of those with Cohen's syndrome, 54 % had ASD, while for Cornelia de Lange syndrome, 43 % had ASD. Richards et al. (2015) also noted that of those with TSC, 36 % were diagnosed with ASD; for those with Angelman's syndrome, 34 % had ASD; for CHARGE syndrome, 30 % had ASD; and also 30 % of males with FXS were found to be diagnosed with ASD. Richards et al. (2015) further reported that 18 % of those diagnosed with NF1 had ASD diagnoses, and the rate of ASD for Down's syndrome was 16 %, for NS was 15 %, and for Williams' syndrome was 12 %. Finally, the researchers reported that 11 % of those found with the 22q11.2 deletion syndrome met the criteria for an ASD diagnosis.

Genetic syndromes found with ASD diagnostic symptoms also occur without ASD diagnostic symptoms. For example, the Cornelia de Lange syndrome, which is caused by mutations in *NIP-BL*, *SMC3*, and X-linked *SMC1A* and *HDAC8* genes, occurs with and without ASD diagnostic symptoms (Moss et al. 2012). However, with or without ASD diagnostic symptoms, Cornelia de Lange syndrome involves ID, social anxiety, and mutism. Similarly, the RASopathy syndromes NS, CS, and CFC have all been reported with and without ASD diagnostic symptoms. With or without ASD diagnostic symptoms, NS, CS, and CFC are consistently characterized by atypical head and face development, brain lesions, and impaired cognition.

Research has demonstrated that syndromic ASD and idiopathic ASD may cause similar brain impairments. As noted above, ASD occurs with four Ras/MAPK syndromes: NF1, NS, CS, and CFC. However, ASD has also occurred with CNVs and single nucleotide polymorphisms (SNPs) that disrupt the Ras/MAPK pathway (Adviento et al. 2014). These CNVs and SNPs do not technically cause a RASopathy syndrome such as Noonan syndrome; nonetheless, these CNVs and SNPs result in the same brain impairments as those found with the RASopathy syndromes. Similarly, while syndromic ASD occurs with *SHANK* gene mutations, idiopathic ASD has been found with mutations in neuroligin genes, including *NLGN2* and *NLGN3*, and mutations in neurexin (*NRXN*) genes, whose deleterious effects on synaptic cell adhesion molecules and cell scaffolding are very much like the deleterious effects of SHANK gene mutations and the Phelan-McDermid 22q13 deletion.

Another example linking syndromic and idiopathic ASD is that some individuals with idiopathic ASD have expressed hyperarousal, dampened parasympathetic tone, and atypical reactivity, and these same symptoms have been found for syndromic ASD with FXS (Klusek et al. 2015). In syndromic ASD with FXS, these arousal and reactivity deficits result from brain dysfunction caused by the genetic mutation of the *FMR1* gene, and therefore, Klusek et al. (2015) argued that these symptoms in idiopathic ASD must result from brain impairments that are similar to those caused by *FMR1* gene mutations.

Genetic syndrome risk factors and individual nonsyndromic genetic mutations may also together contribute to an individual case of autism, and multiple nonsyndromic genetic mutations may also operate together (De Rubeis and Buxbaum 2015; Jiang et al. 2013; Lim et al. 2013; Murdoch and State 2013; Sanders et al. 2015), such that "each individual gene accounts for a small fraction of ASD" (Lim et al. 2013, p. 240). Combinations of CNVs also work together to cause ASD. For example, D'Angelo et al. (2015) reported that ASD was linked to both the CNV 16p11.2 BP4-BP5 duplication and the CNV 16p11.2 BP4-BP5 deletion. However, D'Angelo et al. (2015) found that those individuals who had the duplication of 16p11.2 BP4-BP5 also had many additional deleterious CNVs, but those with the 16p11.2 BP4-BP5 deletion did not have additional deleterious CNVs. This indicated that the duplication form had less damaging brain effects, because it required the presence of additional deleterious CNVs to produce a brain impairment that could yield ASD diagnostic symptoms.

Similarly, syndromic ASD brain impairment may be burdened by the additional deleterious effects of other gene variants. Wassink et al. (2014) studied syndromic ASD with FXS in relation to a low activity allele of the *MAOA* gene that is linked to impaired arousal regulation, aggression, impaired social communication skills, and cortical enlargement. Wassink et al. (2014) found that when individuals with syndromic ASD with FXS, idiopathic ASD, and FXS without ASD carried the low activity *MAOA* allele, all three groups had identical atypical increases in gray matter and white matter. Thus, the *MAOA* allele functioned identically in three different diagnoses—idiopathic ASD, ASD with FXS, and FXS alone.

Environmental Syndromic ASD Has Been Found with Varied Brain Impairments

There are fewer defined environmental ASD syndromes than genetic ASD syndromes, but there are numerous ASD environmental risk factors (Boukhris et al. 2015; Croen et al. 2011; Grabrucker 2013; Hviid et al. 2013; Lyall et al. 2014; Maramara et al. 2014; Ornoy et al. 2015; Rossignol et al. 2014; Schieve et al. 2014). Ornoy et al. (2015) reviewed ASD environmental risk factors and reported 17 significant prenatal, perinatal, and postnatal risk factors: maternal inflammation and immune activation, rubella, cytomegalovirus

(CMV), influenza, fever, diabetes, folic acid deficiency, toxoplasmosis; exposure to ethanol, cocaine, valproic acid, misoprostol, thalidomide, antidepressant serotonin reuptake inhibitors (SSRIs); and exposure to pesticides, insecticides, and air pollution. Also, Maramara et al. (2014) found 15 significant ASD prenatal, perinatal, and postnatal risk factors in a single study sample: father's age, mother's age, maternal drug and alcohol use, maternal hypertension during pregnancy, gestational diabetes, vaginal bleeding, cesarean section, prematurity, induced labor, prolonged labor, lack of infant oxygen during delivery, low birth weight, newborn jaundice, and newborn infection.

Though not every ASD environmental risk factor is identified as a syndrome, many environmental syndromes have been identified. For example, Roullet et al. (2013) reported that ASD was seven times more frequent in infants born to mothers who took valproic acid during their first trimester to control epilepsy, or as a mood stabilizer for bipolar disorder. Children with fetal valproate syndrome (FVS) who express ASD symptoms are likely to have ID, microcephaly, and varied other physical disabilities. In addition, children with fetal alcohol syndrome (FAS) have also expressed ASD symptoms (Stevens et al. 2013). FAS is found with an atypically smaller brain, and an impaired, or atypically small, or missing corpus callosum.

Kuzniewicz et al. (2014) reported that ASD is associated with prematurity, and the risk of ASD increases with decreasing gestational age at birth: the rate of ASD was three times higher in infants born at less than 27 weeks gestational age. Kuzniewicz et al. (2014) also reported that intracranial hemorrhage (ICH) in premature infants was also associated with a higher rate of ASD.

Even pollution has been linked to ASD. Kalkbrenner et al. (2014) theorized that five chemicals contributed to ASD by disrupting endocrine system development: polychlorinated biphenyls (PCBs), flame retardants, nonstick chemicals, bisphenol A (BPA), and phthalates. However, pollution risk findings have been variable. Boggess et al. (2016) pooled heavy metals and organic pollutants into a single variable of xenobiotic exposure and reported that xenobiotic exposure level correlated with severity of ASD communication impairment ($p = .02$) and ASD social impairment severity ($p = .05$). Conversely, Guxens et al. (2015) found no link between prenatal air pollution and ASD in a study of 8000 children.

Volk et al. (2014), however, demonstrated that if individuals homozygous for the C allele of the *MET* gene were exposed to air pollution, they had an increased ASD risk rate of 2.9 (1.0–10.6). The C allele of the *MET* gene reduces gene transcription by 50 %, disrupting the brain's structural networks, resting state connectivity, and social-emotional information processing. The process by which the C allele of the *MET* gene reduces gene transcription is likely to be further disrupted by the xenobiotics in air pollution. This and other gene variant-environment interaction findings suggest that xenobiotics may add to existing genetic vulnerability.

Summary Evidence indicates that many varied brain impairments cause syndromic ASD diagnostic symptoms, thus providing no neurobiological validity for ASD.

The ASD diagnosis has been found with more than 100 genetic and environmental syndromes, and these syndromes are found with varied brain impairments. Although similar brain impairments have been reported for some types of syndromic and idiopathic ASD, the wide variation in syndromic ASD brain impairments argues that there is no unitary brain basis for ASD diagnostic symptoms. Moreover, the etiology of brain impairments in both syndromic and idiopathic ASD is complex. Syndromic ASD may occur with additional deleterious syndromic or nonsyndromic genetic mutations, and syndromic and idiopathic ASD brain impairments may stem from the interaction of multiple genetic risk factors, or from the additive effect or interaction of multiple genetic and environmental risk factors.

Brain Validity Research Approach 5: Do Multiple ASD Genes Disrupt Few Brain Circuits?

Some researchers have theorized that a network or networks of multiple ASD risk genes disrupt just a few impaired brain circuits or pathways in ASD (Chen et al. 2015; de la Torre-Ubieta et al. 2016; Ecker et al. 2015; Geschwind and State 2015; Parikshak et al. 2013; Ruggeri et al. 2014; Willsey et al. 2013). For example, de la Torre-Ubieta et al. (2016) stated "evidence from known mutations does suggest significant convergence in the pathways in which the mutations are found" (p. 349). Willsey et al. (2013) predicted that ASD risk genes together would yield, "a much smaller set of underlying pathophysiological mechanisms" (p. 1004), and Geschwind and State (2015) also proposed that ASD genetic risk factors would converge on only a few "specific molecular pathways or brain circuits" (p. 9).

There is evidence that ASD risk gene variants do converge on specific brain tissue in development (Parikshak et al. 2013; Willsey et al. 2013). Willsey et al. (2013) reported that nine ASD risk genes were expressed in one brain development layer at a shared time of mouse fetal brain growth. Parikshak et al. (2013) reported that ASD risk genes were linked to "laminae containing postmitotic neurons during early fetal development…(and) upper-layer glutamatergic neurons in adult cortex" (p. 1118). Ziats and Rennert (2016) lauded the findings of Willsey et al. (2013) and Parikshak et al. (2013) for providing evidence "that a few common mechanisms may ultimately relate the heterogeneous set of ASD candidate genes to one another" (p. 4).

However, there are limits to the explanatory power of the "multiple genes-few brain circuits" model because "the function of most known genes is not fully understood; the grouping of affected genes is often arbitrary; and the concepts of pathways and networks are based on biochemistry, which may not be appropriately capturing the complex scenarios of the true biological system" (Vissers et al. 2016, p. 5). Most of the nearly 800 identified ASD risk genes (Butler et al. 2015) are not yet well understood, and the full extent of polygenicity for ASD is not yet known. It could be that ASD polygenicity is as great as that found for schizophrenia (SCZ). Loh et al. (2015) reported SCZ was so polygenic that most of the human genome contained SCZ-linked loci, raising the concern that a future more powerful analysis could link SCZ to the entire human genome, making genetic analysis effectively uninformative.

Yet another difficulty for the ASD multiple genes-few brain circuits model is that there are many known functional gene pathway groups. For example, Wen et al. (2016) found ASD risk genes in pathways for cell signaling, metabolism, neuroactive ligand-receptor interaction, and nervous system development. Wen et al. (2016) noted yet another ASD genetics inference problem. The researchers reported that the MAPK signaling pathway and the calcium signaling pathway that were central to the ASD pathway network were integrated by "ASD genes that encode proteins functioning in multiple steps" (Wen et al. 2016, p. 16). Because these proteins affect multiple body systems and thus can cause problems throughout the body, Wen et al. (2016) concluded that ASD symptoms were likely to be caused "by underlying more pervasive processes that are *not specific to* ASD brain or behavior features" (p. 13).

Another concern is that some "multiple genes yielding few disrupted brain circuits" models have not addressed known variation in ASD brain impairments. For example, Parikshak et al. (2013) stated that gene variants disrupted laminae in fetal development that resulted in upper-layer glutamatergic neuron malconnectivity that was the malconnectivity that defined ASD. However, Parikshak et al. (2013) did not discuss the evidence that many with ASD have no brain malconnectivity (Redcay et al. 2013; Tyszka et al. 2014). Thus, the Parikshak et al. (2013) model cannot apply to ASD in general. Parikshak et al. (2013) also proposed that the chromatin remodeling ASD risk gene *ARID1B* caused the corpus callosum abnormalities that characterized ASD. Here again, Parikshak et al. (2013) did not discuss evidence that many with ASD have no corpus callosum abnormalities (Lefebvre et al. 2015). Consequently, the role of the *ARID1B* risk gene in ASD cannot be generalized.

Finally, models of multiple genes disrupting a few brain circuits have ignored ASD environmental risk factors. For example, de la Torre-Ubieta et al. (2016) stated that ASD genetic risk factors caused "deficits in neurogenesis, cell fate, neuronal migration and morphogenesis during fetal development and dysregulated synaptic function" (p. 349). This inventory does not include intracranial hemorrhage effects found in ASD diagnosed with extreme prematurity (Kuzniewicz et al. 2014), or the brain cysts and apoptosis of neurons infected with cytomegalovirus (CMV) found for ASD occurring with congenital CMV infection (Engman et al. 2015).

While evidence suggests that gene variants are the dominant cause of the pathophysiology of ASD symptoms, just as gene variants have been found to be the dominant cause for most human traits and disorders (Polderman et al. 2015), there are significant findings for many ASD environmental risk factors (Boukhris et al. 2015; Grabrucker 2013; Lyall et al. 2014; Maramara et al. 2014; Ornoy et al. 2015; Rossignol et al. 2014; Schieve et al. 2014). Moreover, heritability studies have variably calculated ASD environmental risk factor influence at 7 to 35 % (Tick et al. 2016), 5 to 44 % (Colvert et al. 2015), 50 % (Sandin et al. 2014), and 55 % (Hallmayer et al. 2011). Huguet et al. (2016) reviewed ASD findings and proposed a specific distribution of ASD risk factors: 49.8 % common inherited variants, 2.6 % rare inherited CNVs and SNVs, 6.6 % de novo SNVs, 2.9 % de novo CNVs, and 38.1 % environmental risk factors. Huguet et al. (2016) considered the de novo SNVs and CNVs to be environmental and thus 52.4 % of ASD had genetic causes, and 47.6 % had environmental causes. Most importantly, gene-environment interactions have been identified for ASD (LaSalle 2013; Jeste and Geschwind 2014; Volk et al. 2014).

Summary "Multiple gene-few brain circuits" models are premature and lack explanatory coverage; thus, these models cannot provide neurobiological validity for ASD.

The "multiple gene-few brain circuits" models are premature and insufficiently explanatory because ASD risk gene functions in networks are complex and not yet fully understood. There are hundreds of ASD risk genes, and there is evidence for gene-gene and gene-environment interaction in ASD etiology. It is also possible that ASD polygenicity is so extreme as to hinder specific causal inferences, and possible that ASD symptoms result from gene variants causing systemic processes that are "not specific to ASD" (Wen et al. 2016, p. 13).

Do ASD Diagnostic Criteria Have Construct Validity?

The two core ASD diagnostic criteria of social impairment and ASD RRBs and/or atypical sensory responsiveness would have construct validity if these diagnostic symptoms were invariantly expressed together or were expressed together without additional nondiagnostic symptoms. Research to determine the links between the ASD diagnostic criteria has

taken different approaches. One approach documented the separate expression of the two core ASD diagnostic symptoms in affected individuals. Another research approach looked for what causes ASD diagnostic social impairment and ASD RRBs to uniquely occur together. A third research approach investigated whether ASD diagnostic criteria occur in TD children. A fourth approach looked for the comorbidity of ASD diagnostic symptoms with symptoms of other psychiatric and neurodevelopmental disorders.

Criteria Validity Research Approach 1: Do ASD Diagnostic Symptoms Occur Independently in Affected Individuals?

Kanner (1943, 1951) asserted that autism social withdrawal always occurred with the obsessive desire for the preservation of sameness. Although Kanner's claim of an invariant bond between these core symptoms provided construct validity for the infantile autism diagnosis, subsequent research has not supported Kanner's claim. No invariant link between ASD social impairment and ASD RRBs has been discovered (Frazier et al. 2014; Harrop et al. 2013; Pina-Camacho et al. 2012; Shuster et al. 2014). Many who express ASD diagnostic social impairment do not express the need for the preservation of sameness or any of the RRBs (Brennan et al. 2015; Kim et al. 2014; Kulage et al. 2014; Mandy et al. 2011; McPartland et al. 2012; Ventola et al. 2006). For example, in comparing toddler diagnostic instruments, Ventola et al. (2006) found that when a diagnostic instrument required RRBs, a majority of the children who had clinical autism diagnoses did not meet DSM-IV-TR autistic disorder (AD) diagnostic criteria (American Psychiatric Association 2000). However, all clinically diagnosed children were correctly diagnosed with AD when assessed by instruments that did not require the expression of RRBs (Ventola et al. 2006).

In a study of 256 children with DSM-IV-TR pervasive developmental disorder-not otherwise specified (PDD-NOS), Mandy et al. (2011) found that 97 % of those with PDD-NOS expressed AD diagnostic social impairment, but only 3 % expressed AD RRBs. Comparing DSM-IV-TR and DSM-5 diagnostic categories, McPartland et al. (2012) reported that most individuals previously diagnosed with Asperger's syndrome or PDD-NOS did not meet DSM-5 ASD diagnostic criteria, but would meet DSM-5 criteria if the requirement for RRBs was eliminated. Similarly, Kim et al. (2014) reported that nearly all individuals with a prior diagnosis of AD, Asperger's disorder, or PDD-NOS diagnosis who did not meet DSM-5 ASD criteria did express ASD social impairment, but did not express two of the four RRBs and/or atypical responsiveness.

Individuals who express ASD diagnostic social impairment but no RRBs or one RRB are in diagnostic limbo (Happé et al. 2006; Hus et al. 2007; Lam et al. 2008; Mandy and Skuse 2008; Szatmari et al. 2006; Watt et al. 2008). These individuals might meet criteria for the new DSM-5 social communication disorder (SCD) diagnosis (Smith et al. 2015). However, Bishop (2014) claimed that the DSM-5 category of language disorder was flawed, and Norbury (2014) warned that the SCD diagnosis would confusingly overlap with the ASD diagnosis because many diagnosed with SCD express full ASD social impairment and also express one of the two required RRBs and/or atypical sensory responsiveness.

ASD Social Impairment and RRBs Form Independent Factors

ASD criteria have been shown to form independent factors (Frazier et al. 2014). Frazier et al. (2014) reported a two-factor model with one factor for each core ASD diagnostic criterion. Similarly, Harstad et al. (2015) reported finding one ASD social impairment factor and one RRBs factor. Shuster et al. (2014) reviewed 36 factor analytic studies of ASD symptoms and concluded that ASD social interaction impairment formed one factor, while RRBs formed a separate independent factor.

Separate factors for the ASD core criteria have been replicated despite mixed evidence for the intercorrelations of ASD symptoms. Although some researchers have reported positive correlations between social impairment and RRBs (Frazier et al. 2014; Lam et al. 2008; Szatmari et al. 2006; Watt et al. 2008), other researchers reported finding no or limited associations between social impairment and the RRBs (Harrop et al. 2013; Hus et al. 2007; Mandy and Skuse 2008; Veatch et al. 2014).

Distinct Subgroups Have Been Identified Within ASD Social Impairment

Wing and Gould (1979) reported finding three distinct types of ASD social impairment—aloof, active-but-odd, and passive. More recently, Scheeren et al. (2012) identified two social impairment subgroups in higher functioning ASD, individuals with active-but-odd interaction, and individuals with aloof social interaction. Corbett et al. (2014) reported two ASD social-cortisol level groups: the ASD low social motivation group engaged in less social play and expressed higher levels of cortisol in interaction, and the ASD moderate social motivation group engaged in relatively more social play and expressed lower levels of cortisol in interaction.

Pierce et al. (2015) reported finding two ASD social attention subgroups: 80 % of toddlers with ASD preferred to look at dynamic social images, but 20 % of toddlers with ASD strongly preferred to look at dynamic geometric images. Pierce et al. (2015) noted that none of the children in comparison groups, including "toddlers with typical development, language delay, and global developmental delay as well as unaffected siblings of toddlers with ASD" (p. 6), preferred

to look at dynamic geometric images. Bishop et al. (2016) reported finding two clusters of ASD social impairments. One cluster included basic social communication deficits in eye contact, facial expression, shared enjoyment, and gesture that Bishop et al. (2016) identified as characterizing true core ASD. These social skills were relatively more "intact in … children with severe intellectual disability, early trauma/neglect, prenatal teratogenic exposure, (and) extreme prematurity" (Bishop et al. 2016, p. 5). The other cluster of social impairments included impaired quality of social reciprocity and impaired social rapport that Bishop et al. (2016) stated was more prevalent than the first cluster of social impairments in non-ASD neurodevelopmental disorders.

Distinct Subgroups Have Been Identified Within the ASD RRBs

Some factor analyses of the RRBs have reported multiple subgroups (Esbensen et al. 2009; Mirenda et al. 2010; Frazier et al. 2014). Leekam et al. (2011) noted an age stratification in the RRBs where, "lower level RRBs are more apparent in younger and more developmentally delayed cases, and preoccupations, special interests, and obsessions more often found in older and more able cases" (p. 564). This developmental split in the RRBs has appeared as two clusters: a younger motor cluster with stereotyped movements and repetitive manipulation of objects; and an older cognitive cluster with compulsions, rituals, insistence on sameness, and circumscribed interests (Bishop et al. 2013; Georgiades et al. 2010; Leekam et al. 2011).

Summary The independence of ASD symptoms in clinical autism does not support the construct validity of an invariant link between core ASD diagnostic symptoms.

Many who express ASD diagnostic social impairment do not express two of the RRBs and/or atypical sensory responsiveness, and therefore, ASD does not have construct validity based on an invariant link between the two core diagnostic symptoms. Equally important, there is no adequate clinical diagnosis for individuals who nearly meet all criteria for ASD.

Criteria Validity Research Approach 2: Do the Two Core ASD Diagnostic Criteria Occur Together in the Absence of Other Symptoms?

As reviewed in the section above, ASD social impairment and ASD RRBs do not have an invariant link, and many individuals exhibit ASD diagnostic social impairment but express none or only one of the RRBs. Consequently, Happé et al. (2006), Boucher (2011), Shuster et al. (2014), and Brunsdon and Happé (2014) all raised the concern that no brain impairment had been found that caused *only* the ASD social impairment and ASD RRBs to occur together, and no theory had explained why the core ASD diagnostic symptoms did occur together. Boucher (2011) and Shuster et al. (2014) argued for studying core symptoms separately, and Waterhouse (2013) recommended studying ASD social impairment alone.

Brunsdon and Happé (2014) argued that there was no unitary basis for ASD diagnostic symptoms because each ASD diagnostic symptom was linked to "different genes, neural patterns and cognitive components that influence distinct behavioral symptoms" (p. 27). The claim of different neural patterns for each symptom is supported by the evidence discussed above that each ASD diagnostic symptom has been found with a different set of varied brain impairments (Harrop et al. 2013; Hormozdiari et al. 2015; Jason et al. 2015; Pina-Camacho et al. 2012; Shuster et al. 2014; Zilbovicius et al. 2013). However, existing evidence argues that ASD social impairment and the RRBs are very unlikely to be generated by separate genes in one individual. Although studies of TD twins found social impairment and RRBs to be independently heritable (Robinson et al. 2011; Ronald et al. 2011), this is not true for syndromic ASD with FXS, RTT, TSC, the RASopathies, the Shankopathies, FAS, or ASD with extreme prematurity. In these and other cases of syndromic ASD, a specific gene mutation or prenatal event appears to cause both ASD social impairment and RRBs as well as other symptoms. In addition, individual SNPs, such as those that disrupt the Ras/MAPK pathway (Adviento et al. 2014), also appear to cause both core diagnostic symptoms in idiopathic ASD. Finally, where multiple risk genes combine to cause ASD, it has not yet been determined that one gene or set of genes yields social impairment while another gene or set of genes yields the RRBs and/or atypical sensory responsivity (Jiang et al. 2013; Lim et al. 2013; Murdoch and State 2013; Sanders et al. 2015).

ASD diagnostic symptoms are expressed together because ASD genetic and nongenetic risk factors cause brain impairments that yield both ASD diagnostic symptoms (Chen et al. 2015; Ornoy et al. 2015) and at rates above chance (Happé et al. 2006). However, ASD risk factors do not cause *only* ASD social impairment and RRBs to be expressed together at rates above chance. In fact, fewer than 5 % of individuals with ASD have been found to express ASD diagnostic social impairment and RRBs together without any non-ASD symptoms (Lundström et al. 2015b), and/or minor physical anomalies (MPAs) (Tammimies et al. 2015), and/or MCAs (Timonen-Soivio et al. 2015). More than 95 % of individuals with ASD express ASD diagnostic symptoms along with ADHD, ID, epilepsy, language impairment, motor dysfunctions, attention deficits, anxiety, varied medical conditions, and many other symptoms (Coleman and Gillberg 2012; Lundström et al. 2015b; Pine et al. 2008; Richards et al. 2015; Waterhouse 2013). Because the vast majority of those diagnosed with ASD also express one or more non-ASD symptoms, ASD lacks the construct validity that would be

provided by diagnostic symptom co-expression in the absence of other symptoms.

Counter to this, however, Rutter (2014) argued that "there is a problem in defining autism on the basis of particular features without considering a broader pattern" (p. 55) of non-ASD symptoms found with ASD. Rutter (2014) argued that ADHD, ID, epilepsy, language impairment, and other nondiagnostic symptoms provided ASD with a validating pattern of ASD-specific nondiagnostic symptoms. However, this validating pattern of non-ASD symptoms is not one consistent pattern, but instead, non-ASD symptoms vary widely from one diagnosed individual to another. Moreover, these associated symptoms stand against the construct validity of a unique co-expression of ASD symptoms. Most importantly, ADHD, ID, epilepsy, and language impairment occurring with ASD symptoms are linked to varied brain impairments that stand against the biological validity of ASD (Gabis and Pomeroy 2014; Jeste and Geschwind 2014; Klusek et al. 2015; Peters et al. 2013).

Summary Because nearly 100 % of those with ASD also express non-ASD symptoms, there are too few instances of the unique co-expression of just the two ASD core diagnostic symptoms to provide construct validity for the ASD diagnosis.

ASD core diagnostic symptoms occur alone together without other nondiagnostic symptoms in vanishingly few individuals. Consequently, there is insufficient coverage for ASD construct validity based on unique ASD symptom co-expression. Some researchers have proposed to make ASD more homogeneous by refining ASD diagnostic criteria (Bishop et al. 2016; Sonuga-Barke 2016) and by developing more sensitive ASD diagnostic screening instruments (Bone et al. 2016). However, it is unlikely that the many nondiagnostic symptoms such as ADHD, ID, epilepsy, and language impairment that occur with ASD that stem from varied ASD brain impairments caused by varied ASD risk factors (Kida and Kato 2015) will be eliminated by refinement of the ASD criteria or refinement of ASD screening measures.

Criteria Validity Research Approach 3: Do ASD Diagnostic Criteria Occur Independently in Typical Children?

Many very young TD children express RRBs, including restricted interests, repetitive motor behaviors, change resistance, and/or atypical sensory responsiveness (Camarata 2014; Harrop et al. 2013; Van Hulle et al. 2012). In fact, Harrop et al. (2013) noted that young TD children and young children diagnosed with ASD express similar rates of RRBs. However, RRBs disappear in typically developing children after they "serve the purpose of developmental mastery" (Harrop et al. 2013, p. 3). Thus, RRBs in older children with ASD may be evidence for developmental delay or evidence of atypical limits to development (Camarata 2014; Harrop et al. 2013). However, only extremely shy but otherwise typically developing children show severe social withdrawal in that they "rarely initiate social contacts with available playmates, tend to withdraw from social interactions" (Coplan et al. 2013, p. 862).

Happé et al. (2006) found modest or weak correlations between ASD social impairment symptoms and RRBs in typically developing 7- and 8-year-old twins. Posserud et al. (2013) reported separate factors for social impairment and RRBs in a sample of 10,220 typically developing adolescents. Conversely, Constantino and Charman (2015) concluded that ASD "characteristic traits and symptoms… are as highly inter-related in the general population as they are in ASD syndromes" (p. 7), and asserted that ASD traits were continuous; therefore, any boundary between TD and ASD was arbitrary.

Summary The independence of the two core ASD symptoms in typical children stands against the construct validity of a general invariant link of ASD diagnostic symptoms in TD.

RRBs are commonly expressed in young typically developing children (Harrop et al. 2013), but ASD social withdrawal is extremely rare in typical development (Coplan et al. 2013). These findings and TD twin study findings (Robinson et al. 2011; Ronald et al. 2011) argue against a general invariant coupling of ASD social impairment and ASD RRBs in TD.

Criteria Validity Research Approach 4: Is ASD Comorbid with Other Psychiatric Disorders?

The DSM-III nosology (American Psychiatric Association 1980) triggered an increase in the comorbidity of diagnoses because DSM-III divided complex psychiatric phenotypes into fixed diagnostic categories with specific required symptoms. As a result, often more than one diagnosis was needed to cover the full range of an individual's symptoms (Maj 2005).

Skokauskas and Frodl (2015) found moderately high levels of comorbidity of ASD and bipolar disorder (BPD). Levy et al. (2010) found that 39 % of those with ASD expressed anxiety and mood disorder symptoms, compared with only 4 % of controls. Pine et al. (2008) reported that 57 % of children with BPD, 38 % of children with major depressive disorder (MDD), and 25 % of children with anxiety disorder expressed ASD symptoms. Croen et al. (2015) reported that 54 % of adults with ASD were diagnosed with an additional psychiatric disorder, including anxiety (29 %), BPD (11 %), depression (26 %), SCZ (8 %), and OCD (8 %).

OCD and ASD symptoms have been reported to be comorbid in frequencies ranging from 1.5 to 81 % and OCD

compulsions have parallels in ASD insistence on sameness and ASD repetitive behaviors (Meier et al. 2015; Stone and Chen 2015). Surprisingly, although OCD is often found with increased gray matter volumes in the caudate nuclei (Meier et al. 2015), the OCD-like insistence on sameness in ASD without OCD has been linked to every subcortical region *except* the caudate (Eisenberg et al. 2015).

Half of those diagnosed with SCZ have expressed ASD diagnostic social impairment (Matsuo et al. 2015), and social cognitive impairment was found to be the same in Asperger's disorder and SCZ (Lugnegård et al. 2013), as well as the same in ASD and SCZ (Eack et al. 2013). Moreover, SCZ was diagnosed in 2.4 % of those with ASD (Kohane et al. 2012). Evidence also has indicated that if one parent was diagnosed with SCZ, there was an increased risk for having a child with ASD (Larsson et al. 2005).

Multiple complex developmental disorder (MCDD) is a psychosis prodrome disorder leading to overt psychosis or SCZ that is often found with ASD or PDD symptoms, as well as with panic, explosive emotional behaviors, magical thinking, easy confusability, and paranoid preoccupations (Ad-Dab'bagh and Greenfield 2001; de Bruin et al. 2007; Kyriakopoulos et al. 2015; Sprong et al. 2008; Oranje et al. 2013; Ziermans et al. 2009). MCDD is not a DSM-5 diagnosis, and the brain basis of MCDD remains unknown. Oranje et al. (2013) reported no deficits in P50 wave suppression and prepulse inhibition (PPI) of the startle reflex in MCDD with ASD suggesting that there were no SCZ-like sensory gating problems. Ziermans et al. (2009) also found no abnormalities in brain gray matter or white matter in MCDD with PDD.

Summary Comorbidity of psychiatric symptoms in ASD stands against ASD construct validity.

The comorbidity of SCZ, BPD, MDD, OCD, MCDD, and anxiety symptoms in ASD (along with symptoms of ID, epilepsy, language impairment, motor dysfunctions, and others) stands against the construct validity of the ASD diagnosis by demonstrating that most complete ASD phenotypes are inadequately covered by the two core ASD diagnostic symptoms. One likely contributor to such high ASD comorbidity is that ASD shares risk genes with other disorders (Brandler and Sebat 2015).

Do Shared Features Provide Construct Validity for an ASD Spectrum?

An ASD spectrum of related disorders would have construct validity if the spectrum had features common to all diagnosed with ASD beyond simply the ASD diagnostic symptoms. Researchers have looked for five types of unifying ASD features. One line of research has looked for a consistent early behavioral or biological predictor shared by all with ASD. A second line of research has looked for a consistent developmental course or life outcome for ASD. A third line of research has looked for a single predictive recurrence risk for possible future siblings of those with ASD. A fourth line of research has looked for a consistent broader ASD phenotype (BAP) in siblings and parents. Finally, a fifth line of research has looked for valid subgroups within the ASD spectrum.

Feature Validity Research Approach 1: Is There a Consistent Early ASD Predictor?

Yirmiya and Charman (2010) observed that little is known about "the prodrome of ASDs" (p. 450), and Reeb-Sutherland and Fox (2015) noted that studies attempting to predict which infant siblings would go on to develop ASD "had little success reliably identifying behavioral markers during infancy that predict the later manifestation of ASD" (p. 390). Volkmar and Reichow (2014) suggested that one difficulty for early ASD diagnosis was "the broad range of severity and associated communicative and cognitive disability" (p. 11). Barbaro and Dissanayake (2013) reported that at 12 months, deficits in pointing, waving, imitation, eye contact, and name response were significant markers for an ASD diagnosis, but that by 24 months, only deficits in eye contact remained a reliable index of ASD.

Elsabbagh and Johnson (2016) reported that social impairment was not a key early characteristic of ASD, which instead included five features: (1) head lag when an infant is pulled up to sitting, (2) atypically high sensitivity to sensory experience, (3) trouble with consonants in earliest language, (4) atypically slower ability to shift away attention, and (5) general atypically lower level of activity. Similarly, in a study of young siblings of individuals with ASD, Sutera et al. (2007) reported that ASD diagnostic social and communicative skills were *not* predictive but that motor skills were predictive of later diagnostic outcome.

A consensus panel of ASD researchers reported there was no "single behavioral sign or a single developmental trajectory that is predictive of all diagnoses of ASD" (Zwaigenbaum et al. 2015, p. S37), and the panel asserted that ASD heterogeneity made it unlikely that any defining early ASD behavioral marker will ever be found.

As discussed in the first section of this paper, a dominant theory has argued that ASD results from early brain overgrowth with later impaired brain connectivity (Solso et al. 2015). Consequently, early brain overgrowth has been proposed as the primary biomarker for ASD (Anderson 2013; Ecker et al. 2015; Shen et al. 2013). However, as previously outlined, early brain overgrowth is rare in ASD. The meta-analysis of Sacco et al. (2015) found macrocephaly in less than 6 % of ASD, and also, as reported earlier, Chaste et al. (2013), Raznahan et al. (2013), and Cederlund et al. (2014)

found no evidence that ASD was characterized by early brain overgrowth.

Jones and Klin (2013) argued that early decline in eye fixation would be the best single biomarker of ASD. The researchers claimed this biomarker reflected that a disrupted reward-based interactional eye fixation regulatory system was the core ASD brain impairment (Klin et al. 2015). Reeb-Sutherland and Fox (2015), however, suggested that atypical eyeblink conditioning was a possible single ASD biomarker, and Jeste et al. (2015) proposed that EEG patterns might be a possible biomarker for ASD.

Small and Pelphrey (2015) proposed, "Innate olfactory behaviors may provide a link between early emerging sensory motor behaviors and the social deficits that characterize ASD" (p. R675). Rozenkrantz et al. (2015) reported that longer time sniffing an unpleasant odor was 81 % accurate in differentiating children with ASD from typically developing children, and Rozenkrantz et al. (2015) and Small and Pelphrey (2015) suggested that a sniff test could serve as an effective single biomarker for ASD.

However, Varcin and Nelson (2016) argued that "The heterogeneity inherent to ASD necessitates… sets of markers, rather than a single marker" (p. 127). Glatt et al. (2012) identified a blood-based gene expression profile of 48 genes that reliably identified young children with ASD. Taylor et al. (2014) and Ruggeri et al. (2014) proposed large panels of biomarkers to include markers such as head circumference above the 97th percentile, long-range functional hypoconnectivity and short-range hyperconnectivity, ERP-measured speed of response to human faces, elevated blood serotonin (5-HT) levels, and autoantibodies against a range of brain antigens localized in GABAergic neurons. However, Varcin and Nelson (2016) concluded that "Biomarkers with sufficient sensitivity and specificity for clinical application are yet to be identified in ASD" (p. 124).

Summary There is no consistent early behavioral or brain predictor for ASD; thus, these findings do not support construct validity for an ASD spectrum.

Ideally, clinicians use early symptoms to determine prognosis and assign individuals to treatment. However, ASD research has discovered many varied early behaviors and varied brain markers, and no consistent predictor pattern has been found. Panels of multiple biomarkers have been proposed to help net ASD heterogeneity.

Feature Validity Research Approach 2: Is There One ASD Developmental Course?

Understanding the developmental course of ASD is crucially important for managing life care and planning treatment. However, ASD occurs with many varied developmental paths (Fountain et al. 2012; Lord et al. 2015), and there is no one consistent life outcome (Fein et al. 2013; Helles et al. 2015; Steinhausen et al. 2016). Variation in ASD developmental course has ranged from typical development in infancy that becomes atypical in early childhood, to marked infant impairment in social and cognitive skills that changes to become optimal adaptive functioning in adulthood (Anderson et al. 2014; Fein et al. 2013; Fountain et al. 2012; Helles et al. 2015; Howlin et al. 2013; Levy and Perry 2011; Lord et al. 2015; Yirmiya and Charman 2010).

Predictors of ASD Outcome Are Varied

Although Howlin et al. (2013) reported that ASD childhood IQ was not a predictor of adult outcome in their sample, nonetheless, many researchers have found that IQ was a good predictor, or even the best predictor of outcome in ASD (Hedvall et al. 2014; Jones et al. 2014; Magiati et al. 2014). Billstedt et al. (2007) reported that childhood IQ and social communication before age 5 were the strongest predictors of adult outcome in ASD. Anderson et al. (2014) reported that 25 % of higher IQ children with ASD experienced notably improved functioning at age 19, but that lower functioning children with ASD did not have comparable improvement.

Rates of Recovery from ASD Are Varied

Howlin et al. (2013) determined that long-term follow-up studies indicated that a majority of adults with ASD had not recovered. Steinhausen et al. (2016) conducted a meta-analysis of ASD adolescent and adult outcome studies and determined that 19.7 % had a good outcome, 31.1 % had a fair outcome, but 47.7 % of those with ASD had a poor outcome. Fein et al. (2013) reported that good or optimal outcomes for ASD ranged widely, from about 1 % to nearly 50 %.

Blumberg et al. (2015) reported that 13 % of 1607 individuals diagnosed with ASD in childhood no longer met criteria for ASD: 9 % had been initially misdiagnosed and 4 % "lost" their ASD due to treatment or maturation. Helles et al. (2015) found that 24 % of individuals diagnosed initially with Asperger's disorder no longer met criteria for any developmental disorder. However, developmental changes are complex. For example, Olsson et al. (2015) found that a majority of preschool children who were clinically judged to be recovered from an early ASD diagnosis were rediagnosed with ASD or other neurodevelopmental disorders just 4 years later. Fein et al. (2013) recruited 34 adults who had been diagnosed with ASD as children, but whose behavior was now comparable to that of typical adults. Magiati et al. (2014) reviewed 18 ASD adult outcome studies and reported that 50 % of adults with ASD were able to live independently.

Summary Existing evidence for varied developmental courses and life outcomes does not provide construct validity for an ASD spectrum.

The findings for outcome and developmental trajectories suggest that the ASD diagnosis does not identify a consistent specifiable developmental course or life outcome.

Feature Validity Research Approach 3: Is There a Unitary ASD Recurrence Risk?

The assumption that ASD was a unitary entity led to efforts to establish a single recurrence risk rate for ASD. Recurrence risk is the likelihood that a second child with ASD would be born in a family where a child has already been diagnosed with ASD. No consistent recurrence risk for ASD has been established, and rates have varied from 6 to 19 % (Grønborg et al. 2013; Ozonoff et al. 2011; Ronemus et al. 2014; Rosti et al. 2014; Werling and Geschwind 2013).

However, Matsunami et al. (2014) asserted that no single inheritance model for ASD could be correct, because many varied forms of genetic transmission occur with ASD, and Ronemus et al. (2014) noted that ASD genetic transmission recurrence risk must vary for families with one child with ASD (simplex) and families with more than one child with ASD (multiplex). An example of varied genetic transmission was reported by Jiang et al. (2013), who found multiple varied ASD inheritance patterns in just 16 families: 12 rare X-linked deleterious variants, 7 rare deleterious autosomal-dominant mutations, 13 deleterious missense mutations, and 15 de novo deleterious mutations. Another problem for recurrence rate determination was discovered by Grønborg et al. (2013), who found increased ASD risk in maternal half-siblings, indicating that environmental factors unique to the mother's pregnancy history may contribute to ASD recurrence risk.

Summary Recurrence risk findings do not provide construct validity for an ASD spectrum.

Researchers have identified many varied ASD genetic risk factors with varied transmission patterns, and because there are also many varied ASD environmental risk factors, no single recurrence risk can ever be determined for the ASD diagnosis.

Feature Validity Research Approach 4: Is There a Consistent Broader Autism Phenotype (BAP)?

The assumption that ASD was a unitary disorder led researchers to look for a unitary BAP in families of individuals diagnosed with ASD. The BAP is theorized to be the expression of attenuated ASD symptoms in family members. However, BAP symptoms have been found to be as heterogeneous as ASD symptoms and have included cognitive, language, and social skill impairments, as well as attenuated and nonattenuated psychiatric symptoms (Sucksmith et al. 2011).

Do Siblings of Individuals with ASD Express Varied BAP Symptoms?

Ozonoff et al. (2014) reported that 28 % of siblings of individuals with ASD expressed a BAP consisting of mild social impairment. However, Sucksmith et al. (2011) reported that BAP symptoms in siblings were quite varied and included impaired social responsiveness, impaired mental state recognition, impaired basic emotion recognition, impaired face processing, language delay, pragmatic language impairment, atypical eye gaze patterns, and impaired joint attention. Szatmari et al. (2016) concluded that the siblings of children with ASD express a significant "variability in terms of both type and severity" (p. 183) of BAP symptoms.

Taylor et al. (2015) reported that in families with two or more children with ASD, the undiagnosed siblings had significantly greater social impairment and pragmatic language impairment than did undiagnosed siblings in families where only one child was diagnosed with ASD.

Do Parents of Individuals with ASD Express Varied BAP Symptoms?

Cruz et al. (2013) reviewed studies of BAP in parents of individuals with ASD and found widely varied BAP symptoms in parents, including pragmatic language impairment, lack of friends, difficulties in planning, impaired working memory, and impaired detection of emotions in face expressions. Cruz et al. (2013) also noted a great variation in BAP symptom prevalence, ranging from no parent deficits in skills such as reading and spelling to more than 40 % of parents expressing some form of pragmatic language deficit.

Losh et al. (2008) examined specific features of BAP in parents, including overconscientiousness, rigidity, aloofness, anxiety, hypersensitivity, tactlessness, pragmatic language deficits, speech deficits, and lack of friendships, and discovered four general deficit trait factors: language, rigidity, anxiety, and sociability. Losh et al. (2008) reported a high prevalence of BAP symptoms in their samples. In the sample of parents who had more than one child diagnosed with ASD, 92 % of parents expressed at least one BAP symptom, and in the sample of parents with a single child diagnosed with ASD, 66 % of parents expressed at least one BAP symptom.

Losh et al. (2008) reported that in families with more than one child diagnosed with ASD, parents were four times as

likely to express two or more of the deficit traits than parents with a single child diagnosed with ASD. Similarly, Bernier et al. (2012) reported that in families where more than one family member was diagnosed with ASD, more undiagnosed family members expressed BAP symptoms. Woodbury-Smith et al. (2015) looked for a genetic link between parents' BAP and presence of specific CNVs in their children diagnosed with ASD, but could only find, "a small number of CNVs transmitted from BAP parents to ASD offspring" (p. 196).

Summary Varied BAP findings provide no construct validity for an ASD spectrum.

Pisula and Ziegart-Sadowska (2015) reviewed sibling studies and concluded that evidence was, "insufficient to formulate final conclusions regarding BAP characteristics in siblings of people with ASD" (p. 13250). Cruz et al. (2013) similarly concluded that findings for BAP in parents were so varied that "further studies should be conducted before there is a definition of which traits are undoubtedly part of the group of BAP characteristics" (p. 261). It is likely that widely varied brain dysfunctions in family members with BAP result in varied constellations of social, language, cognitive, and psychiatric symptoms.

Feature Validity Research Approach 5: Are There Valid ASD Spectrum Subgroups?

Researchers have proposed that ASD includes biologically valid subgroups (Aldinger et al. 2015; Brandler and Sebat 2015; Ellegood et al. 2015; Georgiades et al. 2013; Williams et al. 2014; Whitehouse and Stanley 2013; Williams and Bowler 2014). Williams et al. (2014) predicted that ASD would eventually become a set of biologically valid subgroups defined "by genetic and/or neurological…findings" (p. 339), and Brandler and Sebat (2015) predicted that ASD would naturally disband into valid "quanta of separate genetic disorders" (p. 502).

Researchers have subtyped many aspects of ASD. There has been ASD gender subgrouping (Halladay et al. 2015; Ypma et al. 2016), ASD brain feature subgrouping (Piras et al. 2014; Hahamy et al. 2015), ASD behavior subgrouping (Chaste et al. 2015; Kim et al. 2016; Veatch et al. 2014), ASD developmental course subgrouping (Fountain et al. 2012; Lord et al. 2015), ASD behavior and brain feature subgrouping (Lombardo et al. 2015), ASD MPAs subgrouping (Tammimies et al. 2015), ASD MCAs subgrouping (Timonen-Soivio et al. 2015), and ASD risk gene variant subgrouping (Hormozdiari et al. 2015; Krumm et al. 2014; Noh et al. 2013).

Males and females are valid biological subgroups. Males with ASD show more aggression and repetitive behaviors, while females with ASD express more mood disorders, and that females with ASD have greater cognitive impairment than males with ASD (Jeste and Geschwind 2014). There is a sex ratio of four or five males for every female with ASD (Halladay et al. 2015; Jeste and Geschwind 2014; Romano et al. 2016; Ypma et al. 2016). Romano et al. (2016) asserted that male genetic variants make them more vulnerable to ASD risk factors than are females. Jeste and Geschwind (2014) proposed that a possible reduced female vulnerability, termed the female protective effect (FPE), arises from genes in females that are found on the sex chromosomes, and the effects of sex hormones themselves. Halladay et al. (2015) noted support for the FPE in that females with ASD carry a higher number of dnCNVs and de novo loss of function point mutations than do males with ASD.

However, the sex ratio of males and females in ASD has not been adequately explained by either increased male vulnerability or a special female protective factor (Halladay et al. 2015; Ypma et al. 2016). For example, at the lowest level of ID, the male-female ASD sex ratio is 1:1. In addition, different etiologies have different sex ratios. Syndromic ASD with RTT includes only females, and syndromic ASD with FXS includes only males. Taking ASD apart by etiologies will likely reveal that the current overall ASD sex ratio is composed of many different separate sex ratios that vary by etiology, sex chromosome gene effects, and sex hormone effects.

Tammimies et al. (2015) divided children diagnosed with ASD into three groups: those with many MPAs, those with few MPAs, and those with some MPAs. Children with few MPAs had fewer molecular diagnoses than the children with many MPAs (Tammimies et al. 2015). However, there was genetic heterogeneity in each of the three ASD MPA subgroups, including varied de novo mutations and other varied molecular diagnoses (Tammimies et al. 2015).

Similarly, Chaste et al. (2015) found that subgrouping ASD by distinct phenotypes did not result in finding sets of genetic variants that were unique to distinct clinical phenotypes. In fact, fewer and greater numbers of overlapping genetic variants were reported across the ASD phenotypic groups. Chaste et al. (2015) nonetheless argued that clinical phenotypes must have some "power for discovering genetic associations" (p. 781).

Summary ASD subgroups have been insufficiently homogeneous to provide construct validity for an ASD spectrum.

Despite many efforts to form valid subgroups of ASD, no ASD subgroups have become standard, and no ASD subgroup has yet achieved adequate internal homogeneity (Chen et al. 2015). Thus, to date, ASD has not been subdivided into valid subgroups that together would provide construct validity for the ASD spectrum. Males and females are valid biological

subgroups, but the sex ratio of males and females in ASD has not been adequately explained, and different ASD etiologies have different sex ratios.

Conclusion: ASD Lacks Neurobiological and Construct Validity—What Should Be Done?

Table 1 summarizes the 14 groups of findings reviewed in this paper that together argue that ASD lacks neurobiological and construct validity. No unitary ASD brain impairment or replicated unitary model of ASD brain impairment exists. ASD core diagnostic symptoms are not uniquely linked and are only very rarely expressed without nondiagnostic symptoms. ASD has no reliable early predictor, no unitary developmental course, no unitary life outcome, no unitary recurrence risk, no unitary pattern of BAP features, and no standard homogeneous subgroups.

In sum, these findings suggest that neurodevelopmental social impairment exists in varied forms with varied etiologies and varied pathophysiologies, but the ASD diagnostic criteria do not identify a valid entity. These findings argue that a shift away from studying ASD-defined samples is warranted. However, even though ASD lacks neurobiological and construct validity, ASD is supported by the powerful existential validity of wide, and perhaps increasing, clinical coverage. In 1989, Ritvo et al. reported that 4 in 10,000 were diagnosed with autism (Ritvo et al. 1989). Now, 1 in 68 children are diagnosed with ASD (Blumberg et al. 2013; Braun et al. 2015; Centers for Disease Control and Prevention 2012; Christensen et al. 2015; Christensen 2016; Lundström et al. 2015a; Hansen et al. 2015; Kim et al. 2011; Kim 2014). This wide coverage has helped to sustain the belief that ASD is a unitary entity, but coverage cannot compensate or substitute for missing neurobiological and construct validity.

In fact, despite its wide coverage, ASD has two coverage problems. ASD is underinclusive because its coverage excludes those with ASD diagnostic social impairment who do not fully meet the criteria for RRBs and/or atypical sensory responsiveness. ASD is overinclusive because some of the increase in ASD coverage has come from diagnostic substitution (Navon and Eyal 2016) or even, possibly, the force of social exchange (Liu and Bearman 2015). Polyak et al. (2015) reported that in the USA between 2000 and 2010, even though the proportion of total diagnoses did not change, ASD diagnoses increased 331 %, while ID *decreased* 31 %, emotional disturbance *decreased* 22 %, and learning disability *decreased* 19 %. Polyak et al. (2015) concluded "diagnostic recategorization toward autism is occurring, potentially confounding estimates of autism prevalence" (p. 4), and the researchers asserted that diagnostic substitution revealed that developmental diagnoses were fungible.

Table 1 Summary of varying, inconsistent, and unresolved findings for studies of ASD brain impairments, ASD symptoms, and ASD spectrum features

Research questions	Answer	Research study findings
ASD brain research has not provided evidence for the neurobiological validity of ASD		
Are there any consistent global or regional brain structures implicated in ASD?	No	ASD global and regional brain structure findings have been varied and conflicting.
Have any theories of a unitary ASD brain impairment been replicated to become standard?	No	None of the ASD unitary brain impairment models has been adequately replicated to become standard.
Are individual ASD symptoms linked to specific brain impairments?	No	Each ASD diagnostic symptom and nondiagnostic symptom has been found with varied brain impairments.
Is there a consistent unique ASD brain basis for syndromic ASD?	No	Syndromic ASD has been found with a wide range of brain impairments caused by risk factors for the associated syndromes.
Do a set of ASD risk genes cause impairment in just a few related brain circuits?	No	Multiple gene-few brain circuits models are premature and have not addressed environmental causes for ASD or variant ASD brain impairments.
ASD symptom research has not provided evidence for the construct validity of ASD diagnostic symptoms		
Do ASD diagnostic symptoms occur together in isolation?	No	ASD diagnostic symptoms have occurred with non-ASD symptoms in 96 % of individuals diagnosed with ASD.
Do ASD diagnostic symptoms invariantly occur together in clinical autism?	No	ASD social impairment has frequently occurred in individuals with clinical autism who do not express the required diagnostic RRBs and/or atypical sensory responsivity.
Do ASD diagnostic symptoms occur together in typically developing children?	No	Most typical children have expressed RRBs in early childhood, but ASD social impairment is quite rare in typically developing children.
Is the ASD diagnosis found with comorbid psychiatric symptoms and disorders?	Yes	ASD has been shown to share symptoms with many psychiatric diagnoses.
ASD feature research has not provided evidence for the construct validity of the ASD spectrum		
Is there any consistent early behavioral feature or brain marker that predicts an ASD diagnosis?	No	There is no consistent early behavioral or brain predictor for an ASD diagnosis.

Table 1 (continued)

Research questions	Answer	Research study findings
Is there a consistent developmental course or life outcome for ASD?	No	ASD is found with varied developmental courses and varied life outcomes.
Is there a single recurrence risk for ASD?	No	ASD does not and cannot have a single recurrence risk rate because there are so many different forms of genetic transmission and because so many environmental risk factors cause ASD.
Is there a consistent ASD broader autism phenotype (BAP)?	No	BAP symptoms in siblings and parents of children with ASD have been found to vary widely.
Is there any set of valid ASD subgroups?	No	Existing ASD subgroups have shown a lack internal homogeneity and have not been adequately replicated.

Proposals for Future Research: Disband the ASD Diagnosis, Study Individual Variation, and Revise Instruments and Health Records

Disband the ASD Diagnosis in Research

ASD should be disbanded in research because it lacks validity, and finding effective medical treatments requires the analysis of individual variation in valid pathophysiological mechanisms linked to specific risk factors in complete neurodevelopmental phenotypes (Kennedy et al. 2015; London 2014; Volkmar and McPartland 2015; Waterhouse and Gillberg 2014). Because the ASD diagnosis is defined by just two symptoms from an individual's complete set of symptoms, an ASD-defined sample is widely over-inclusive, capturing many different "lifelong conditions that can arise from a complex combination of multiple genetic and environmental factors" (Dawson 2016, para. 1), in which "the genetic architecture of ASD seems to be different from one individual to another" (Huguet et al. 2016, p. 118), and there are many individually varied "connections between brain and behavior" (Kennedy et al. 2015, p. 81). In sum, the heterogeneity of risk factors, brain impairments, and non-diagnostic symptoms in an ASD-defined sample blocks valid scientific inference.

Study Individual Variation in Brain Impairments in Neurodevelopmental Disorders

There is no catalog of brain impairments for neurodevelopmental disorders because much past research was based on the belief that each neurodevelopmental disorder had its own specific brain impairment (Bourgeron 2015a). Jeste and Geschwind (2014) highlighted the need for a catalog of brain impairments in genetic research by inserting a question mark where (ASD) brain impairments should have been listed (Jeste and Geschwind 2014, Fig. 1, p. 75). Individual variation in brain impairments reflects variation in risk factors, and as argued for RDoC, pathophysiology variation is not aligned with diagnostic categories but is a focus for specific medical treatment.

Revise Instruments and Health Records for Neurodevelopmental Disorders

Disbanding the ASD diagnosis will require new screening, evaluations, and health records for all neurodevelopmental disorders to include social impairment and RRBs and sensory atypical responsivity independent of the ASD diagnosis. Many forms of electronic health records (EHRs) have been outlined (Castillo et al. 2015; McCoy et al. 2015; Simon et al. 2014).

Gillberg (2010) proposed "Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations" or ESSENCE, to include early appearing difficulties in general development, communication and language, social interrelatedness, motor coordination, attention, activity, behavior, mood, and/or sleep. ESSENCE disorders include ASD, ADHD, ID, BPD, oppositional defiant disorder (ODD), specific language impairment (SLI), learning disabilities (LD), nonverbal learning disabilities (NVLD), tic disorders, behavioral phenotype syndromes, rare epilepsy syndromes, and reactive attachment disorder. Gillberg (2010) found that comorbidity resulted in most children having two or more diagnoses. Empirical support for ESSENCE (Bourgeron 2015b; Hatakenaka et al. 2016) has demonstrated that it effectively documents the variation and complexity of neurodevelopmental disorder symptoms.

London (2014) similarly recommended that research should study DSM-5 neurodevelopmental disorders as a whole, but proposed a multiaxial model that would allow for the identification of specific symptoms such as sensory overresponsiveness and ID, allow for possible etiologic factors such as genetic findings or infection during pregnancy, allow for functional assessment, and also allow for treatment outcome history. Most importantly, London (2014) noted that this reformulated nosology would direct researchers and clinicians to attend to an individual's specific symptoms and not force researchers to assign a categorical diagnosis. Instead an inventory of individual symptoms and risk factors would provide a template suitable for clinical use in lieu of a diagnostic category.

Drawbacks and Benefits of Disbanding ASD in Research

Disbanding ASD in research is likely to be reductive and uncomfortable. Most painfully, many existing ASD group

findings and ASD theories will be irrelevant for future transdiagnostic studies, and future studies will likely be based on varied grouping factors, making study findings less comparable. There will also likely be conflicting interests as clinicians continue to use DSM-5 ASD, while researchers develop new types of studies that aggregate multiple neurodevelopmental diagnoses. However, Zhao and Castellanos (2016) argued that many large sample studies of psychiatric diagnoses have been unproductive exactly because they studied traditional DSM diagnoses. Zhao and Castellanos (2016) argued that "Neuropsychiatric disorders are frequently transdiagnostic with distinct subtypes likely among all disorders" (p. 432); therefore, large-scale imaging and genetics studies should benefit from exploring multiple neurodevelopmental diagnoses together.

Most importantly, Lilienfeld and Treadway (2016) noted that although DSM-5 diagnoses have captured much of individuals' impairments, RDoC research is likely to yield "stratified medicine, in which interventions are tailored to individuals within well-defined subgroups" (p. 447), something that should be the central focus for all future research on neurodevelopmental disorders.

Compliance with Ethical Standards All procedures performed in reviewed studies conducted by the authors involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Research reports reviewed herein have included statements that informed consent was obtained from all individual participants included in the study.

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