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BRIEF REPORT

Brief Report: An Autistic Spectrum Subtype Revealed Through Familial Psychopathology Coupled with Cognition in ASD

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Abstract This study identified a possible autistic spectrum subtype expressed through family psychopathology coupled with autistic probands' cognitive functioning (i.e., an endophenotypic profile). Participants included 24 children with Autism Spectrum Disorder (ASD) and 49 children with Learning Disorder (LD). There were significantly higher rates of Mood and Anxiety Disorder in first degree maternal relatives and of LD and Attention-Deficit Hyperactivity Disorder in first degree paternal relatives of ASD probands. Significantly higher visuospatial functioning was noted in all ASD probands for which there were higher rates of Mood Disorder on the maternal side suggesting a possible marker for an ASD subtype and indicating that maternal psychopathology may have a neuroprotective effect on visuospatial functioning.

Keywords Pervasive development disorder · Autistic disorder · Asperger syndrome · Neuropsychology · Cognition · Phenotype · Endophenotype

Introduction

Autism spectrum disorders (ASD) are developmental disorders characterized by abnormalities in communication, social functioning, and a repetitive, restricted behavioral repertoire (Koczat et al. 2002). ASD are extremely prevalent with the Center for Disease Control and Prevention (MMWR Surveillance Summary 2007) recently reporting the prevalence at approximately 1 in 150, making its etiology and early identification an urgent public health concern.

Neurobiological mechanisms of ASD have focused on abnormalities in the cerebrellum and brain stem (Courchesne et al. 1994; Courchesne et al. 1994), frontal and parietal lobes (Courchesne et al. 1993), and hippocampus and amygdala (Aylward et al. 1999). Serotonergic and GABAergic mechanisms are involved in the pathophysiology of ASD (McDougle et al. 2005). Neurobiological mechanisms implicated support cognitive functions altered in ASD and bolster theories of executive dysfunction (Hughes et al. 1997; Ozonoff and Strayer 1997), weak central coherence (CC) (Happe et al. 2001), and abnormalities of theory of mind (ToM) (Baron-Cohen and Hammer 1997). Nonetheless, the etiology and genetic origins of ASD remain elusive.

Delayed progress in revealing the genetic determinants of ASD has been partially due to a lack of emphasis on the development of endophenotypes; indicators of processes mediating between the genotype and phenotype (Glahn et al. 2007; Gottesman and Gould 2003). Endophenotypes may be neurophysiological, biochemical, endocrinological, neuroanatomical, or neuropsychological. Endophenotypes can be viewed as measurable components that emerge when a psychiatric disorder is dismantled (Gottesman and Gould 2003). Endophenotypic markers are less complex than the phenotype and are more readily linked to specific genetic loci. Risk genes for psychiatric illness can be transmitted without expression of the clinical phenotype or can be partially expressed as in the broader autism phenotype (BAP), a wider but milder range of social, communicative, and behavioral patterns identified in

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family members of ASD probands (Hughes et al. 1999). The proband is the affected individual through whom a family with a genetic disorder is ascertained. The identification of phenotypes based on neurocognitive profiles and quantitative biological markers (e.g., neuroimaging) that may be moderated by familial or environmental triggers is a promising approach. That is, illuminating these endophenotypic variables may assist with the identification of the genetic determinants of ASD.

Cognitive abnormalities in ASD follow a triad of weak CC (e.g., placing a premium on the extraction of detail at the expense of gestalt) (Happe et al. 2001), poor ToM (i.e., the inability to think and reason about mental states) (Baron-Cohen and Hammer 1997), and impaired executive functions (EF). The identification of phenotypic cognitive markers for reading disability and language disorders has been productive (Gayan et al. 1999; Barry et al. 2007); however, given significant variability in the expression of ASD, unambiguous phenotypic candidates have not been identified.

Potential variables of the endophenotype may be revealed through the BAP (Hughes et al. 1999; Wong et al. 2006). Social elements include the tendency to be withdrawn (Murphy et al. 2000), with fathers preferring solitary activities that are detailed and factual (Briskman et al. 2001). The BAP includes traits that may be advantageous in science and math (DeLong 2004). Wheelwright and Baron-Cohen (2001) have reported fathers/grandfathers of probands over-represented in engineering, accounting, and science.

Exploring patterns of psychopathology within the family system of ASD probands will further guide efforts to identify endophenotypic variables. Relatives of ASD probands have higher rates of major depression and social phobia (Piven and Palmer 1999), and increased rates of depression are not confined to post-birth (Lainhart 1999). Lauritsen et al. (2005) reported the relative risk of autism was about twice as high if the mother had been diagnosed with a psychiatric disorder.

The purpose of this study was to first examine the differences between cognition, parental occupational variables, and psychopathology in first-degree maternal and paternal biological relatives in ASD probands compared to dyslexia probands. The goal of this analysis was to identify possible endophenotypic variables once an ASD diagnosis was made based on clinical criteria. Learning Disability (LD) (i.e., dyslexia) probands were chosen as a comparison population given that they also represent a developmental disorder with written language-based deficits, and we anticipated oral language variables that emerged might be specific to ASD.

With respect to between group differences, it was hypothesized that (1) ASD probands would perform more poorly on tests of EF; (2) ASD parents would have more engineering/science occupations, and/or (3) more familial histories of ASD, language disorders, and/or mood disorders (especially in mothers). Within the ASD group, it was further hypothesized that different cognitive profiles would emerge for those children whose parents had science/engineering degrees and/or familial histories of ASD, language disorders, and/or mood disorders.

Method

Participants

Participants included 24 ASD probands (19 Males; Mean Age = 7.83 years): Autistic Disorder ($n = 5$), Asperger Syndrome ($n = 7$) and Pervasive Developmental Disorder, Not Otherwise Specified (PDD, NOS) ($n = 12$); and 49 children with LD (37 Males; Mean Age = 9.16 years) who presented for neuropsychological evaluation at Henry Ford Health System. ASD were diagnosed with the Diagnostic and Statistical Manual of Mental Disorders (*DSM-IV-TR)* (American Psychiatric Association 2000) and the Childhood Autism Rating Scale (CARS) (Schopler et al. 1988) or Autism Diagnostic Interview-Revised (ADI-R) (Lord et al. 1994). LD diagnosis was based on *DSM-IV-TR* (2000) criteria for Reading Disorder and performance on a test of phonological decoding (<18th %ile) (Simos et al. 2000). All ethical and federal guidelines regarding human subjects were followed.

Procedures

A comprehensive interview was conducted with parents, and the dependent demographic variable included occupations. Twelve occupational designations were generated from a standard Dictionary of Occupational Titles. Dependent variables related to psychopathology in first-degree biological maternal and paternal relatives included histories of (1) mood disorder, (2) thought disorder/psychosis, (3) anxiety disorder, (4) pervasive developmental disorder, (5) nonverbal and verbal learning disorder and/or attention deficit hyperactivity disorder (NLD/LD/ADHD), (6) speech and language disorder, (7) epilepsy, and (8) mental retardation. Reports of mental illness in parents were included if they preceded the diagnosis and were not secondary to having a child with an ASD. A first-degree maternal or paternal biological relative is defined as a relative who is one meioses away from the parent (e.g., probands grandparent, aunt or uncle).

Each subject completed the NEPSY, a developmental neuropsychological battery for children ages 3 through 12

(Korkman et al. 1998). The Core battery includes Attention/Executive, Language, Sensorimotor, Visual-Spatial, and Memory and Learning domains. The subtest scaled scores were chosen as the dependent variables (mean 10 ± 3). The NEPSY has adequate psychometric properties with average subtest reliabilities at age 5–12 generally ranging from 0.71 to 0.91 (Korkman et al. 1998).

Data Analysis

Between group differences on the NEPSY were analyzed using analysis of covariance with age as a covariate. Group differences for parental occupations and histories of psychopathology were examined with a chi statistic. Within group analysis was examined with a *t* statistic. Effect sizes were examined with Eta^2.

Results

ASD and LD groups did not differ significantly on gender $\chi^2(2, N = 73) = .12$, $p = .73$ or mean Full Scale IQ $t(71) = .34$, $p = .73$, with both groups performing in the Average range (ASD FSIQ = 90.5 (23.8); LD FSIQ = 92.2 (16.9)). The groups differed significantly on age $t(71) = 2.5$, $p = .02$, with LD probands older (age = 9.2 (1.8)) than ASD probands (age = 7.8 (2.3)). The age range for both groups was 5–12 years of age.

No significant group differences were found between occupations of the mothers $\chi^2(2, N = 64) = 11.41$, $p = .41$ or fathers $\chi^2(2, N = 61) = 8.70$, $p = .56$.

With respect to reported histories of psychopathology, there was a significantly higher rate of mood $\chi^2(2, N = 73) = 4.23$, $p = .04$ and anxiety disorders $\chi^2(2, N = 73) = 7.11$, $p = .008$ on the maternal side in ASD probands, but no additional group differences on the maternal side. There was a significantly higher rate of NLD/LD/ADHD $\chi^2(2, N = 73) = 3.97$, $p = .05$ on the paternal side in ASD probands, although no other group differences were noted (see Table 1).

ASD probands performed significantly lower than LD probands on the Tower Test $F(1, 69) = 3.84$, $p = .05$, while LD probands performed significantly lower than ASD probands on Memory for Names $F(1, 69) = 5.92$, $p = .02$, although the effect sizes were small. The Tower Test is a test of strategic planning and problem solving. There were no additional clinically significant cognitive differences.

Within ASD probands with mood disorders on the maternal side, significantly higher visuospatial functioning was noted on Design Copy $t(23) = 2.21$, $p = .05$ and Arrows $t(23) = 2.54$, $p = .03$ subtests (see Table 2). No additional significant within group differences were found on NEPSY subtests when examining rates of anxiety or NLD/LD/ADHD on maternal and paternal sides, respectively. All ASD probands revealed this profile, with no significant differences noted between individuals with Autistic Disorder, Asperger's, or PDD,NOS on Design Copy $F(1, 22) = .22$, $p = .81$ or Arrows $F(1, 22) = .39$, $p = .70$ (see Figs. 1 and 2).

Discussion

The purpose of this study was to examine the relationship between cognition, parental occupational variables, and reported familial histories of psychopathology in ASD probands to identify possible endophenotypic variables or 'subtypes' once the diagnosis was made based on clinical

Table 1 Number of parents who reported a positive family history of various forms of psychopathology in first-degree biological maternal and paternal relatives in the ASD and LD groups

	Maternal side of ASD ($N = 24$)	Maternal side LD ($N = 40$)	χ^2	Paternal side of ASD ($N = 23$)	Paternal side of LD ($N = 38$)	χ^2
Mood disorder	9	6	.04*	1	0	.2
Thought disorder	1	1	.71	1	1	.72
Anxiety disorder	4	0	.01**	0	0	
ASD	1	0	.19	1	1	.72
NLD/ADHD or LD/ADHD	3	8	.44	9	6	.05*
Speech/language	1	0	.19	1	0	.2
Epilepsy	2	1	.29	0	0	
Mental retardation	1	0	.19	0	0	

Note. ASD, Autism Spectrum Disorder; NLD, Nonverbal Learning Disorder; ADHD, Attention-Deficit Hyperactivity Disorder

* $p < .05$

** $p < .01$

Table 2 Mean average scores, standard deviations, *t* scores, & *p* values for the executive function, language, visual-spatial, & memory variables within ASD group

Cognitive domains	ASD with maternal mood disorder ($N = 9$) *M* (SD)	ASD without maternal mood disorder ($N = 14$) *M* (SD)	*t* Statistic	*p*
Executive				
Tower	9.3 (3.7)	7.1 (2.4)	1.8	.09
Auditory attention	8.4 (3.6)	7.7 (2.6)	.56	.58
Visual attention	8.3 (3.6)	9.4 (3.3)	.71	.49
Attention task	8.8 (3.5)	11.3 (9.8)	.73	.47
Response test	8.3 (3.0)	9.0 (6.3)	.26	.78
Language				
Phonological processing	7.7 (4.1)	7.9 (2.7)	.135	.89
Naming	7.3 (3.2)	7.4 (3.4)	.07	.95
Comprehension	6.6 (5.0)	6.5 (4.2)	.03	.98
Sensorimotor				
Imitation hand positions	7.9 (2.4)	6.6 (3.1)	1.1	.29
Visuomotor precision	7.4 (2.6)	5.5 (2.9)	1.6	.12
Visuospatial				
Design copy	13.0 (3.7)	8.1 (4.1)	2.21*	.05
Arrows	11.6 (2.6)	7.2 (3.3)	2.54*	.03
Memory				
Faces	7.8 (2.3)	9.7 (3.9)	1.03	.32
Names	9.8 (3.8)	9.1 (4.5)	.30	.77
Narrative memory	8.4 (4.8)	7.3 (4.1)	.46	.65

Note. ASD, Autism Spectrum Disorder

* $p < .05$

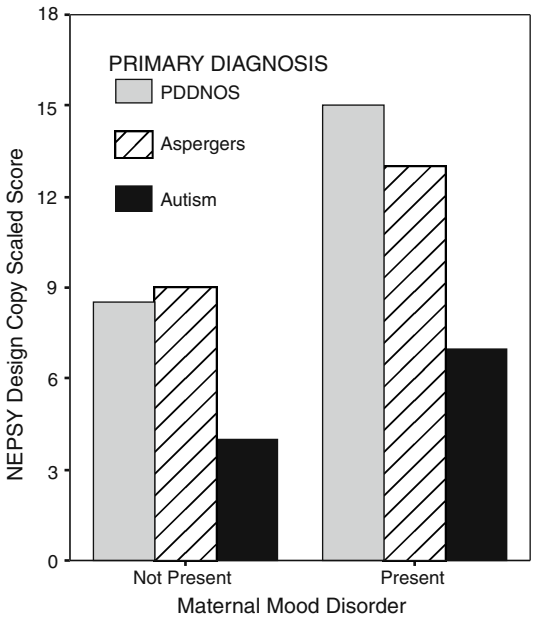

Fig. 1 Design Copy Scaled Scores in autism, Asperger's, and PDD,NOS probands for which a history of depression is reported in the mother or first-degree biological relative on the maternal side

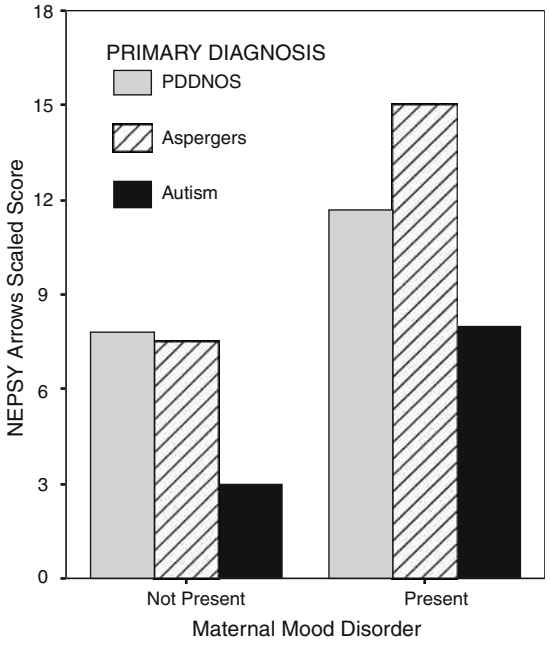

Fig. 2 Arrows Scaled Scores in autism, Asperger's, and PDD, lNOS probands for which a history of depression is reported in the mother or first-degree biological relative on the maternal side

criteria. Illuminating endophenotypic variables may assist with the identification of the genetic determinants of ASD.

There were no occupational differences between the parents of ASD or LD probands. This is inconsistent with reports by Wheelwright and Baron-Cohen (2001) who reported an over-representation of occupations of engineering, accounting and science in fathers and grandfathers of ASD probands. Replicating recent findings, higher rates of mood and anxiety disorders in first-degree maternal relatives were noted, and when in the mother, this was prior to the birth of ASD probands (DeLong 2004; Lainhart 1999; Micali et al. 2004; Piven and Palmer 1999; Lauritsten et al. 2005). To our knowledge, this is the first report of significantly higher rates of NLD/LD/ADHD in first-degree paternal relatives of ASD probands. This was an unexpected finding, and given that the NLD/LD/ADHD reports were collapsed, it is difficult to interpret whether the higher rates were related to NLD/LD or ADHD.

Consistent with the EF theory, ASD probands performed more poorly on an executive measure of strategic planning and problem solving. However, effect sizes were small suggesting that this function does not unambiguously characterize the phenotype of ASD.

Interestingly, significantly higher visuospatial scores were noted in ASD probands for which there was a reported history of mood disorder in a first-degree maternal relative, possibly suggesting an autistic spectrum subtype. Maternal mood disorder may serve a neuroprotective function for an autistic subtype in which children have preserved or accelerated visuospatial abilities, although future research is necessary to elucidate this complex relationship. This finding might be analogous to the genetic phenomena of imprinting, in which the manifestation of an inherited disorder is altered dependent upon maternal or paternal transmission (Carey and McMahon 1999). Our finding is consistent with a recent study in which maternal recurrent mood disorders were associated with elevated cognitive and adaptive functioning in ASD probands (Cohen and Tsiouris 2006).

Average to above average performance on tests tapping perceptual-motor and nonmotor visuospatial skill is consistent with prior reports of spatial skills as a strength in ASD (Caron et al. 2004; Edgin and Pennington 2005; Shah and Frith 1993). Caron et al. (2006) have suggested that the typical to superior performance of ASD probands on visuospatial tasks is inconsistent with the global-deficit-driven Weak CC hypothesis and deficits in magnocellular brain regions. The current findings imply two possibilities. First, typical or superior performance on visuospatial tasks may be most evident in a subgroup of ASD probands for which there is a family history of maternal depression. Second, while previous research has suggested that NLD may be a cognitive profile in Asperger Syndrome (Klin et al. 1995), these results suggest preserved or advanced skills, in at least a subgroup of Asperger's. This is consistent with a recent investigation by Edgin and Pennington (2005) in which children with high functioning autism (HFA) and Asperger Syndrome did not differ on the Embedded Figures Test, learning a spatial location, or on global/local processing tasks.

This study has a number of limitations. First, the small sample size limits generalizability. The relative rates of NLD/LD/ADHD on the paternal side of the family in ASD probands requires further investigation. Finally, it will be critical to examine whether visuospatial skills are preserved or enhanced in other developmental disorders when psychopathology is examined to determine whether this is a specific profile of ASD.

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