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Matching Procedures in Autism Research: Evidence from Meta-Analytic Studies

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In this paper, we summarize some of our findings from a series of three meta-analyses and discuss their implications for autism research. In the first meta-analysis, we examined studies addressing the theory of mind hypothesis in autism. This analysis revealed that theory of mind disabilities are not unique to autism, although what may be unique is the severity of the dysfunction in this group. Variables such as the chronological and mental age of the participants, and the matching procedures that the researchers employed, were found to be significant moderator variables. In the next two meta-analyses, data regarding siblings and parents of individuals with autism were analyzed. Type of comparison group (e.g., siblings or parents of individuals with Down syndrome or learning disabilities) and type of outcome measure (cognitive, psychiatric, language) were found to be important moderator variables. Furthermore, method of assessing the psychiatric difficulties (e.g., self-report, clinical measures) was found to be a moderator variable in parents' meta-analysis. Suggestions for future research are discussed, highlighting variables such as type of comparison group, matching procedures, chronological and mental ages, gender, and birth order.

KEY WORDS: Autism; siblings; parents; theory of mind; broad phenotype; psychiatric status; cognition.

INTRODUCTION

Once the diagnostic entity of autism was established (American Psychiatric Association, 1980), research in the past three decades was focused on two main issues. One was an attempt to pinpoint the underlying core deficit or deficits of the syndrome, and the second was a search for etiology. In these research endeavors, the comparison groups to which individuals with autism and their family members are compared are crucial for understanding the disorder and its underlying characteristics. In a series of meta-analyses, we examined the contribution of various comparison groups and methodological variables in several domains of autism research.

In the current paper, we present and discuss some of our findings, referring to the two issues of the core deficit and the search for etiology. First, we present evidence from our meta-analysis on the theory of mind hypothesis in autism, concerning methodological findings, and suggest implications for future research. We then present findings from two meta-analyses exploring methodological aspects in behavioral genetic studies, currently one of the leading research domains in the search for etiology.

THE SEARCH FOR A CORE DEFICIT

In the search for a core deficit in autism, various theories of autism emphasize one or more developmental themes as primary. In these hypotheses, developmental links are mapped from the primary deficits to the clinical features characteristic of the disorder, including impairments and special abilities, which are apparent in individuals with autism. When investigating

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the different theories, researchers conduct various studies in which performance patterns of individuals with autism are compared with those of individuals with diagnoses other than autism and with typically developing individuals.

The comparison of the developmental difficulties presented by individuals with autism to that of typical developing persons is insufficient for our understanding of the core deficits of autism. Comparisons of children with autism to other groups of children with atypical development are crucial for our attempt to answer at least two important questions. One, does the developmental course presented by children with autism present a deviancy or delay? That is, are individuals with autism able to gain the developmental milestones required at a later age than other individuals or does their pattern of behavior continue to show altered responses than that expected of other persons, even of the same mental age? In order to answer this question, children with autism need to be compared to both typically developing children of a comparable mental age and to children with various developmental delays, matched on chronological and mental ages. For example, whereas children with autism, especially high-functioning children, are often able to reflect on and verbalize their knowledge of emotions and the circumstances that give rise to them, they never achieve the same level of reflection and spontaneity of understanding that is found among individuals with typical development or with diagnoses other than autism (e.g., Capps, Yirmiya, & Sigman, 1992; Pilowsky, Yirmiya, Arbelle, & Moses, 2000; Sigman & Ruskin, 1999).

The second and related issue that needs to be addressed in the search for a core deficit refers to the conditions that must be met for any one symptom or group of symptoms to be defined as a core deficit. The three basic requirements are universality (that is, that the deficit is manifested in all or almost all individuals with autism), specificity (that is, that the disorder involves a domain-specific deficit in this particular area), and uniqueness (that is, that the deficit is not manifested by most individuals with other clinical diagnoses) (Sigman, 1994, 1996; Wagner, Graniban, & Cichetti, 1990; Zelazo, Burack, Benedetto, & Frye, 1996; Zelazo, Burack, Boseovski, Jacques, & Frye, 2001). In order to address these issues, researchers must carefully examine the characteristics of the groups employed in their studies. The criterion of universality can only be answered when different groups of individuals with autism are examined and even compared to each other. The uniqueness issue requires examination of different clinical groups that may present similar difficulties (e.g., developmental delays, attention difficulties) to those of individuals with autism and yet will be shown to perform differently than these individuals.

We examine the implications of different comparison groups for findings with regard to one of the current leading hypotheses concerning the core deficit involved in autism. According to the theory of mind (ToM) hypothesis, a neurologically based deficit in the understanding of minds lies at the origin of the specific social and communication impairments in autism. This hypothesis implies a unique developmental deviance in theory of mind acquisition among persons with autism (Baron-Cohen, Leslie, & Frith, 1985; Frith & Happe, 1999; Hill & Frith, 2003).

In a series of three meta-analyses (Yirmiya, Erel, Shaked, & Solomonica-Levi, 1998), we attempted to examine the issues of universality and uniqueness in depth, with a focus on the theory of mind hypothesis. These analyses included three data sets of studies regarding theory of mind abilities—all studies in which individuals with autism were compared to typically developing individuals, all studies in which individuals with autism were compared to individuals with mental retardation (MR), and all studies in which individuals with MR were compared to typically developing individuals.

In addition to the expected differences in theory of mind abilities between individuals with autism as compared with both typically developing individuals and with individuals with MR, the meta-analyses also revealed significant differences in theory of mind abilities between individuals with MR and typically developing persons. Thus, the ToM deficit cannot be identified as unique to autism because it is manifested by individuals with MR as well. However, the severity of the impairment rather than the impairment itself may be considered as unique.

The advantages and disadvantages of each of the comparison groups were apparent in the various analyses. One, the etiology of the individuals with MR who were included in the comparison groups impacted the findings. All the comparisons between individuals with autism and individuals with MR yielded significant differences. Yet, a larger effect size was revealed for comparisons between persons with autism and persons with Down syndrome than for those involving persons with autism and persons with MR of unknown etiology. Individuals with Down syndrome tend to display a unique profile, presenting specific strengths in attentional, social, and emotional abilities (Beeghly, Weiss-Perry, & Cicchetti, 1990; Mundy, Sigman, Kasari, & Yirmiya, 1988) that may be associated with higher abilities in theory of mind tasks. Accordingly, they may be

a less than optimal comparison group for investigating the unique difficulties of individuals with autism, in this as in other domains.

In our meta-analysis of theory of mind abilities, other relevant moderator variables concerning the construction of comparison groups were highlighted. Specifically, we found that the variables of chronological and mental age in all three groups impacted the results. Greater effect sizes, indicating a larger difference between children with autism and children from other comparison groups, were found for comparisons involving older and/or more cognitively able compared to younger and/or less cognitively able comparison individuals. Furthermore, larger effect sizes were yielded when participants with autism were matched on a group basis, rather than on a one-to-one basis, with the comparison participants. Thus, smaller differences emerge when participants are matched one-to-one on chronological and/or mental age than when researchers report matching based on nonsignificant group differences regarding the mean chronological and mental age of their groups. This again highlights the importance of stringent construction of matching procedures in order to achieve the most informative results. These findings emphasize the notion that the specific characteristics of the participating groups affect the findings and the subsequent conclusions.

FAMILIAL DATA IN BEHAVIOR GENETIC RESEARCH

We now turn to the second major domain of research in autism, that which focuses on the question of etiology. In this domain, a central line of research explores behavior genetic manifestations in family members of individuals with autism. The assumption underlying this line of research is that autism is a disorder in which genetic factors play a major role and that family members of individuals with autism may manifest characteristics that are not severe enough to be diagnosed as autism or even pervasive developmental disorders, but nonetheless reveal similar patterns of difficulties as those presented by individuals with autism (e.g., communication difficulties, social problems, and learning disabilities). This type of research may both aid the search for a genetic component in autism and also provide data relevant for the core deficit debate. Thus, in this type of research, family members of individuals with autism are examined for certain characteristics such as psychiatric problems or other characteristics that are now defined as "the broad phenotype of autism" (Piven, 2001; Szatmari *et al.,* 2000).

In this line of research, the question of the comparison groups to which family members of individuals with autism are compared is again crucial for the findings and their implications. As in the search for the core deficit, the identification of areas of difficulty among family members of individuals with autism is insufficient for conclusions regarding specific genetic components, and researchers should identify those difficulties that are both universal and unique to these families.

In order to summarize current knowledge concerning familial characteristics of individuals with autism in general and to examine the relevance of the characteristics of the comparison groups employed in such research, we conducted two meta-analyses. In the first, we examined all studies in which siblings of children with autism were compared with siblings of typically developing children and with siblings of children with diagnoses other than autism (Yirmiya, Shaked, & Erel, 2001). In the second meta-analysis, we examined various outcomes in the realm of psychiatric difficulties among parents of individuals with autism as compared to parents of typically developing individuals and of individuals with other diagnoses (Yirmiya & Shaked, in press).

In the studies that were included in the meta-analyses, different comparison groups were employed when different characteristics of family members were examined. The different comparison groups each "control" for different aspects associated with having a sibling or a child with autism. The comparison of siblings or parents of individuals with autism to siblings or parents of typically developing individuals is not informative about the extent to which the origin of the various characteristics are genetic or environmental in that they may be a sequelae of being a sibling or a parent of a child with autism. Furthermore, the examination of a comparison group of family members of persons with Down syndrome, for example, may include environmental implications of growing up with, or parenting a child with, Down syndrome. Therefore, this comparison group "controls" for at least some of the environmental effects of living with a child with special needs and thus may affect the siblings' or parents' coping abilities and well-being. However, because the majority of cases with Down syndrome do not arise from a genetic liability (Piven, Palmer, Jacobi, Childress, & Arndt, 1997), this comparison group is similar to that of siblings or parents of typically developing individuals when examined in regards to genetic liability.

Conversely, learning disabilities have a sound genetic basis (Wadsworth, DeFries, Fulker, & Plomin,

1995), and therefore a comparison of family members of individuals with autism and those of individuals with learning disabilities may help in the search for a specific genetic phenotype revealed in families of persons with autism, a phenotype that differs from that associated with learning disabilities. However, the "control" for the environmental effects is less stringent in these cases, as individuals with learning disabilities usually do not display mental retardation and in many ways are easier to care for, and live with, than individuals with autism. Thus, no one comparison group is optimal, and researchers must closely examine the advantages and disadvantages of their comparison group/s.

Meta-Analysis of Behavioral Genetic Studies of Siblings

In our search for sibling studies, we found that most researchers typically compared siblings of individuals with autism to siblings of individuals with Down syndrome or of typically developing individuals. In contrast, siblings of individuals with MR of unknown etiology, learning disabilities, psychiatric syndromes other than autism, or other syndromes were studied less often, thus leaving unanswered many of the important questions concerning the specificity of sibling characteristics in families who have a child with autism and the ability to relate these characteristics to genetic factors.

In our analyses, we separately examined the outcomes of a diagnosis of autism, a diagnosis of broad phenotype (e.g., PDD-NOS), psychiatric difficulties, and cognitive abilities. Our analysis of comparisons in which the broad phenotype of autism was examined in siblings of children with autism and in siblings of other children revealed a difference only between siblings of children with autism and siblings of children with Down syndrome. Likewise, comparisons between siblings of individuals with autism and siblings of other individuals with regard to the outcome measure of psychiatric difficulties revealed differences only for the comparison between siblings of individuals with autism and siblings of individuals with Down syndrome. These findings highlight the relevance of the genetic liability of the comparison group (or lack of it) and raise questions as to the current definitions of the broad phenotype and its possible uniqueness in families of children with autism.

Inconsistent findings emerged when the cognitive abilities of the siblings were assessed. The siblings of individuals with learning disabilities displayed higher cognitive abilities than siblings of individuals with autism. In contrast, no significant differences emerged between siblings of individuals with autism and siblings of typically developing individuals or of individuals with Down syndrome. In comparisons involving siblings of individuals with autism and siblings of individuals with MR of unknown etiology, the evidence was mixed regarding level of cognitive abilities between the groups because some researchers found higher cognitive abilities in siblings of individuals with MR whereas others found higher cognitive abilities in siblings of individuals with autism.

Comparison groups should be compatible with the specific outcome measure on which family members of individuals with autism are examined. For example, in assessing the rate of autism or of other psychiatric disorders, comparison groups of individuals with various psychiatric disorders who may be vulnerable to both a genetic risk and to environmental stressors are appropriate if one is interested in the question of whether family members of children with autism are more affected. Yet, various comparison groups of individuals with learning disabilities, with and without developmental delays, may be more suited for the assessment of cognitive abilities when one is interested in the cognitive profile of family members of individuals with autism.

The ages of the siblings who were examined is also relevant because the various outcomes studied, including cognitive abilities and psychiatric difficulties, are subject to developmental variances. Examination of siblings of around the same chronological age in the two study groups will enable researchers to focus on those developmental milestones relevant to that age and thus may provide more precise data as to the strengths and weaknesses in these groups of siblings. For example, although measures of theory of mind can be measured at all ages, the examination of it at about the age in which it develops, (i.e., around the age of 4 years) is necessary to answer the question of whether theory of mind development is, or is not, developmentally hindered in siblings of children with autism (Burack, Charman, Yirmiya, & Zelazo, 2001). Likewise, when taking into account the possibility of environmental effects, the position of the siblings in comparison to the sibling with autism or to the sibling with disorders other than autism should also be considered. Currently, the majority of studies conducted with siblings of children with autism include samples of heterogeneous ages and birth order in the family (Yirmiya, Shaked, & Erel, 2001) in which specific questions regarding the developmental trajectories of siblings remain unanswered.

Meta-Analysis of Psychiatric Difficulties of Parents

Our next meta-analysis was focused solely on the outcome measures of psychiatric difficulties in parents. In analyzing the moderating effects of different comparison groups, we found that parents of children with autism present more psychiatric difficulties as compared to parents of typically developing children and to parents of children with Down syndrome. Conversely, when the comparisons included a group with a genetic liability (i.e., parents of individuals with learning disabilities or with psychiatric disorders), parents of individuals with autism presented less psychiatric difficulties.

Interactions were also found between the specific outcome measure examined and the specific comparison group. For example, for the outcome of depression, differences emerged only for comparison groups without a known genetic liability, and nonsignificant differences were found for comparison groups that carry a genetic liability. Conversely, the outcome measure of bipolar disorder revealed nonsignificant results for the comparison groups of parents of individuals with typical development, with Down syndrome, or with learning disabilities.

These results highlight the importance of genetic risk factors in autism in general and in relation with various psychiatric difficulties in particular. The issues of genetic versus environmental effects are clearly far from resolved at this time. Advances in the understanding of these issues is dependent on carefully choosing comparison groups to best reveal the specific characteristics under examination in each study.

In addition to matching procedures, other methodological issues were revealed. For example, the issue of gender in studying family members is necessary in the case of a disorder such as autism in which the male/female ratio is high and in which females tend to be more severely impaired cognitively (Leboyer, Plumet, Goldblum, Perez-Diaz, & Marchaland, 1995). Although such a fine grain level of analyses requires large samples, researchers should examine this issue carefully and provide separate analyses for comparisons of mothers, fathers, brothers, and sisters of female and male probands with autism.

CONCLUSIONS

Autism is a complex syndrome with many possible causative pathways. Researchers studying individuals with autism and their siblings and parents should therefore account for differential characteristics of the probands with autism and their families. Probands with autism should be differentiated according to characteristics such as gender, level of functioning, and clinical symptomatology (e.g., probands whose developmental trajectory includes regressions versus those without regressions; Lainhart, Ozonoff, Coon, Krasny, Dinh, Nice, & McMahon, 2002) and family members differentiated according to important characteristics such as age and gender. More in-depth understanding of the effect of these characteristics together with a careful evaluation of the advantages and disadvantages of various comparison groups will hopefully assist in resolving the enigma of autism.

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