

Why Do Only Some Institutionalized Children Become Indiscriminately Friendly? Insights From the Study of Williams Syndrome

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ABSTRACT—*Why do some institutionalized children develop indiscriminate behavior (IB) while others do not? Considering children with Williams syndrome (WS) may provide an answer because IB has been observed routinely among individuals with this rare genetic neurodevelopmental disorder. By conceiving WS as a natural genetic model that mimics the indiscriminate phenotype and, more importantly, is associated with the deletion of genes in a specific region, we propose an integrative conceptual framework that underscores the dynamic developmental interplay between genes, endophenotypes, and environment. In this article, we consider the etiology of IB among institutionalized children, which emphasizes environmental factors, followed by the effect of such behavior on WS children's hypersociability, which highlights the crosstalk between genes and neuropsychological features in programming their distinctive social-emotional/behavioral phenotype. We propose new hypotheses regarding the etiopathogeny*

of IBs in institutionalized children, particularly the prediction of specific gene-X-environment interactions.

KEYWORDS—*indiscriminate behavior; institutionalized children; Williams syndrome*

For most infants growing up under adequate rearing conditions, a developmental shift occurs in the last quarter of the first year from a general, positive social orientation toward others to a more focused, discriminating preference for particular significant others. In contrast, formerly and currently institutionalized children can show persistent indiscriminate behavior (IB), approaching unfamiliar adults without reticence, wandering away from their caregivers without checking back, and behaving affectionately toward familiar and unfamiliar adults (Bruce, Tarullo, & Gunnar, 2009; Oliveira et al., 2012; Rutter et al., 2007; Smyke, Dumitrescu, & Zeanah, 2002).

In the last four decades, several research teams have chronicled such atypical behaviors in institutionalized and formerly institutionalized children, often guided by insights from attachment theory. These teams consistently report that, in contrast with children living with their families, those living in institutions (and thus being cared for in a traditional—and very neglectful—manner) often display overfriendly attention and comfort seeking and affectionate behavior toward unfamiliar people (Smyke et al., 2002). More recent reports indicate that even after several years of placement in adoptive families, a significant number of children who spent their early years in depriving orphanages continue to show mild to high levels of IB (Rutter et al., 2007). Furthermore, the presence of IB does not seem to be restricted to formerly and currently institutionalized children; significant levels have been reported in high-risk families, where neglect is also prevalent (Lyons-Ruth, Bureau, Riley, & Atlas-Corbett, 2009).

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The authors acknowledge the support Carla Martins in the preparation of the manuscript. This review was supported by grants from Bial Foundation (ref.13/06) and from the Portuguese Foundation for Science and Technology—PTDC/PSI-PCL/116897/2010; PTDC/PSI PCL/115316/2009; PTDC/PSI-PCL/101506/2008.

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Child Development Perspectives © 2013 The Society for Research in Child Development
DOI: 10.1111/cdep.12036

Dispatch: 29.5.13	Journal: CDEP	CE: Priya C.
Author Received	No. of pages: 6	PE: Karpagavalli
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Indiscriminate behavior was originally attributed to the low quality of care (e.g., high child-caregiver ratios, frequent changes in shifts) that is characteristic of most institutions (Tizard & Rees, 1975). But quality of care may not fully account for the emergence and maintenance of IB over time. After all, IB persisted in late-adopted but not early-adopted children, according to a longitudinal adoption study in which the former were institutionalized for at least 8 months, compared with 4 months or less for the latter (Chisholm, 1998). The combined and perhaps interacting effects of *timing* and *dose* of exposure to limited-quality care may be especially influential, suggesting that early exposure to severely depriving conditions may biologically program enduring IB (Rutter & O'Connor, 2004). To understand the nature and developmental course of IB, we must consider (a) the quality of the environment in which the child is raised (i.e., from harmful to protective), (b) when it is experienced (i.e., the first year and/or thereafter), and (c) how long it lasts.

Although quality of care and its timing and dosage appear critical to understanding the maintenance of IB, two recent findings challenge a traditional attachment-theory interpretation of IB. First, IB may be evident even when children are classified as securely attached to a primary caregiver (Rutter et al., 2007). Second, improvements in quality of care that promote secure attachment (van den Dries, Juffer, van Ijzendoorn, & Bakermans-Kranenburg, 2009) are not consistently associated with reductions in IB (Rutter et al., 2007). Consequently, some scholars suggest that the development of IB be distinguished from the development of insecure attachments (Bakermans-Kranenburg et al., 2011; Zeanah & Gleason, 2010). But what needs to be distinguished may be the *establishment or formation* of a focused attachment and the *quality or security* of those attachments that become established. A system for measuring the degree of attachment formation—rather than whether an attachment is secure or insecure—based on behavior in the strange situation supports this claim (Zeanah, Smyke, Koga, Carlson, & Group T. B. E. I. P. C., 2005). Notably, most—92 of 95—institutionalized children studied did not show attachment behavior reflective of typical attachment strategies, but *all* community children did, clearly indicating that the former did not even qualify to have the quality of their focused attachment evaluated. More recently, attachment-related behaviors toward the adoptive parents were unrelated to the presence of disinhibited social behavior in a sample of adopted children, thereby offering additional support for the need to distinguish these two types of behaviors (Bruce et al., 2009).

Thus, two important points regarding IB emerge. First, a sensitive period may exist during which rearing conditions biologically program enduring IB so that such behavior persists well after adoption in some previously institutionalized children (Rutter et al., 2007). Second, the formation of a focused attachment needs to be distinguished from its quality once established. In addition, the degree of phenotypic expression of

IB, reflected in its frequency and intensity, needs to be considered; research has been unable to fully explain this observed variability in terms of the environment (e.g., quality of care). Interestingly, children with Williams syndrome (WS), a rare genetic disorder, also display indiscriminate friendliness, suggesting that we must understand the interaction between genes and environment (GXE) to understand variation in IB among institutionalized children.

INSIGHTS FROM WILLIAMS SYNDROME

Williams syndrome is caused by a deletion on chromosome 7 (region 7q11.23), and is well known for its distinctive pattern of physical, medical, cognitive, and socioemotional features (Mervis & Klein-Tasman, 2000; Sampaio et al., 2010). Particularly interesting for our argument, children with WS are excessively social, overly friendly, and disinhibited in social contexts (Capitão, Sampaio, Fernández, et al., 2011), phenotypic characteristics that seem to make them similar to some institutionally reared children.

Despite such behavioral similarities, while many children reared in institutions show a pervasive tendency to exhibit IB, young children with WS tend to discriminate their caregivers from strangers and develop secure attachment relationships, according to preliminary evidence (Plesa-Skwerer, Lindeke, Ogrodnik, Ciciolla, & Tager-Flusberg, 2008). Fundamentally, the fact that WS children discriminate between mother and stranger, together with their well-known hypersociability, substantiates the proposal that the presence of aberrant social behavior must be distinguished from the absence of a focused attachment (Zeanah & Gleason, 2010).

Although these aspects of social functioning are distinct, they are closely linked. More specifically, the establishment of a focused attachment relationship may function as a braking system, which, once activated under distressing situations, down regulates and even eliminates what could also be regarded as indiscriminate social behavior in WS children. When focused attachments do not develop, however, as in the case of many institutionalized children, early indiscriminate social affiliation persists (Bakermans-Kranenburg et al., 2011).

The *seemingly* similar social phenotypes observed in institutionalized and some WS children may have somewhat different origins; nevertheless, they may share at least one causal factor—genetics—that could account for *some* of the *variation* seen in institutionalized children with respect to IB. Institutionalized children, contrary to the significant deletion (approximately 20 genes) observed in WS, may display minor genetic alterations, namely single nucleotide polymorphisms within the Williams syndrome critical region (WSCR), particularly in genes that are expressed within the central nervous system (CNS) and that have been shown to be involved in socially IB. Single nucleotide polymorphisms are common genetic alterations occurring in the general population and

1 have been associated with increased vulnerability to several
 2 conditions, including ones affecting the CNS (Allen-Brady
 3 et al., 2009; Harold et al., 2009). Furthermore, these polymor-
 4 phic variants could modulate the degree of impact of early
 5 adverse rearing experiences, in turn leading to distinct levels
 6 of expression of altered social behaviors. In fact, one study
 7 chronicled the role of genetic polymorphisms in moderating
 8 the differential impact of caregiving quality on indiscriminate
 9 social behavior (Drury et al., 2012).

11 The Neurogenetics of IB

12 While the social phenotype observed in WS is typically
 13 accounted for in terms of genetic abnormalities, pathogenic care
 14 is regarded as the necessary condition for the diagnosis of IB in
 15 institutionalized children. However, contrary to what happens
 16 with emotionally withdrawn or inhibited children, changes in
 17 quality of care do not result in significant decreases in IB among
 18 institutionalized children displaying such behavior (Zeanah
 19 et al., 2005). This, coupled with the fact that not all children
 20 exposed to adverse rearing conditions in institutions develop IB,
 21 clearly indicates that low-quality care alone cannot explain the
 22 IB observed in so many such children, especially when it
 23 persists for so long in so many children even after they leave the
 24 institution.

25 The study of WS children may illuminate the role of genetics
 26 in enduring IB (without any WS diagnosis). Above and beyond
 27 the influence of timing and low-quality care, we propose a GXE
 28 hypothesis whereby genetic *and* environmental factors may be
 29 necessary for institutionalized children to develop enduring
 30 indiscriminate tendencies.

31 The WS genotype is characterized by a deletion on chromo-
 32 some 7, which includes about 20 genes. Besides the involve-
 33 ment of some of these genes in certain WS characteristics,
 34 such as cardiac abnormalities, less is known about the role of
 35 alterations within particular genes of this critical region
 36 (WSCR) vis-à-vis social behavior (Doyle, Bellugi, Korenberg,
 37 & Graham, 2004). Nevertheless, we propose that WS may
 38 serve as a valuable genetic model for understanding the indis-
 39 criminate social behavior of some institutionalized children.
 40 Indirect support for this claim comes from studies with individ-
 41 uals with partial deletions in the WSCR who differ from the
 42 typical WS phenotypical manifestations (Karmiloff-Smith et al.,
 43 2012).

44 Studies with rodents have been done to determine the involve-
 45 ment of genes in key aspects of WS phenotype. From those stud-
 46 ies, STX1, GTF2IRD1, LIMK-1, CYLN2, and FZD9 emerged as
 47 potential candidate genes given their expression within the CNS
 48 and their likely association with relevant aspects of the WS
 49 social behavior. Indeed, Stx1a-knockout animals—those lacking
 50 the expression of the Stx1a gene—are impaired in the latent in-
 51 hibition test (Fujiwara, Snada, Kofuji, Yoshikawa, & Akagawa,
 52 2010), which is closely related to attention deficits and to the
 53 control of behavior by context (Lubow, 2005). In humans, these

processes are seen when an infant or child is confronted with an
 unfamiliar situation or individual, and are usually referred to
 under the rubric of behavioral inhibition (Fox, Henderson,
 Marshall, Nichols, & Ghera, 2005).

Furthermore, Gtf2ird1-targeted mice are less anxious, less
 aggressive toward unfamiliar objects, and more engaged in
 social contact than wild-type animals; additionally, the former
 manifest impaired fear conditioning (Young et al., 2008). One of
 the functions of behavioral inhibition is to increase vigilance
 and attention to environmental cues of danger or threat (LeDoux,
 2000). Both WS children and institutionalized children with IB
 are usually less attentive to potentially threatening stimuli. The
 two genes in question—Stx1a and Gtf2ird1—conceivably con-
 tribute to the increased interest in social interactions and readi-
 ness to approach strangers that are common to WS children and
 some institutionalized children.

Finally, knockout mice for Limk-1 are impaired in fear condi-
 tioning and spatial learning (Meng et al., 2002), whereas Cyln2
 and Fzd9 knockout mice are delayed neurodevelopmentally and
 are impaired in learning and memory (Zhao et al., 2005). These
 deficits may be associated with a decreased ability to implement
 specific cognitive strategies, including emotional processing
 modulation as well as attention focusing and shifting (Fox et al.,
 2005), and these may influence social functioning.

These characteristics of behavioral disinhibition, developmen-
 tal delay, and attention problems, learning and memory impair-
 ments, and abnormal emotional regulation are evocative of fea-
 tures observed in institutionalized children (Croft et al.,
 2007; Kreppner et al., 2007) *and* children with WS. Altered
 brain structure and functioning have been proposed as possible
 explanatory mechanisms. Specifically, the neural bases of
 behavioral inhibition and memory/learning abilities, which are
 important forces shaping social behavior, call attention to pre-
 frontal-striatal-amygdalar circuits and hippocampal formation,
 respectively.

In this research, we chronicled the structural and functional
 role of hippocampal formation, prefrontal cortex, and amygda-
 lar region in WS. Specifically, memory, behavioral inhibition,
 and fear conditioning are functionally dependent on the integ-
 rity of such frontostriatal circuits. Abnormal structure and
 function of these brain regions are evident in WS (Capitão,
 Sampaio A., Sampaio C., et al., 2011; Meyer-Lindenberg et al.,
 2005; Sampaio et al., 2010) and thus could also underlie
 social IB in institutionalized children. Consistent with this
 hypothesis, one study documented abnormalities in these brain
 circuitries as a result of early institutionalization (Tottenham
 et al., 2009).

These neurogenetic findings underscore the genetic basis of
 behavioral alterations observed in WS, similar to those
 displayed by some institutionalized children. Therefore, WS and
 some institutionalized children might share neurofunctional
 mechanisms, making STX1, GTF2IRD1, LIMK-1, CYLN2, and
 FZD9 genes relevant to the understanding of the etiology of IB.

Consequently, association studies using single nucleotide polymorphism should be the first approach for understanding the contribution of genes within WSCR for IB among institutionalized children. Such studies would test the hypothesis that these genes—singularly or collectively—distinguish institutionalized children who do or do not display IB and who are or are not responsive to environmental improvements, such as adoption, in terms of the persistence of IB.

Other genes beyond WSCR may be associated with variation in IB among institutionalized children. Genes in the oxytocin family seem to be important biomarkers for social and affiliative behaviors (Insel & Young, 2001), partly by reducing fear of social unfaithfulness, inhibiting avoidance behavior (Lim & Young, 2006), and modulating amygdala functioning (Hurlemann et al., 2010). Thus, oxytocin genes may be important for understanding the indiscriminate-behavioral functioning of some institutionalized children.

Integrative, Multi-Level Conceptual Model for Understanding IB

Taking these arguments into consideration, we advance an integrative conceptual model that underscores the dynamic developmental interplay between different levels of analysis—genes, endophenotypes, and environment—in explaining the etiology and maintenance of IB. Our model presumes that IB is associated with variations in candidate genes of chromosome 7, especially within the WSCR, that, in particular environments, will account for the endophenotypic and/or behavioral variability. Specifically, inhibitory control, memory, and learning are viewed as endophenotypes closely related to those genes and dependent upon specific neurofunctional substrates. Although these processes may be necessary to develop IB, they are insufficient in light of an integrative model of its emergence and maintenance over time. Therefore, the environment has to be included, particularly if we consider evidence underscoring the significance of timing, dosage, and low-quality care in the maintenance of IB.

In our model, the rearing conditions are the most relevant aspect of the quality of the environment and range from highly sensitive and nurturing to negligent and disturbed. The model is developmentally and temporally informed, especially by attachment theory (Bowlby, 1969), calling attention to the first year of life as a sensitive period for the emergence—or lack—of discriminate social behavior and the establishment of selective—and discriminating—attachment relationships. Children with a specific genetic makeup (*polymorphism variations within WSCR*) who are extensively exposed to low-quality institutional care, especially in the first year of life when selective and discriminating affectional attachment bonds are developing, will be at greatest risk of displaying IB, which endures over time.

In our model, IB is conceptualized dimensionally, ranging along a spectrum from absent to mild to very severe and

pervasive. Ultimately, the model depends on the strength of the connections between the different levels of analysis—genes, endophenotypes, and environment—that determines the pattern of behavioral expression. In other words, we predict the GXE interaction will account for noteworthy variation in IB among institutionalized children, and this phenotype may reflect the fact that different polymorphisms are differentially regulated by adverse experience in the institution, thereby affecting downstream neural processes that serve as the proximal mechanisms instantiating IB. This conceptualization supports a move from categorical considerations of presence versus absence of IB to a dimensional framework, ranging from no such behavior to such behavior occurring only in nonstressful contexts, to its very intense display in both stressful and nonstressful situations. Despite the complexity of the model, other players, namely oxytocin, will no doubt prove influential in shaping IB.

CONCLUSION

The conundrum we seek to illuminate is why some institutionalized children manifest persistent indiscriminate social behavior. The hypothesis that low-quality care during a sensitive period results in insecure attachment is insufficient—even if necessary—to account for why IB endures among some children raised in institutions. The study of WS offers insights into the genetics—and thereby neuropsychology—of hypersociability, which may help us understand the persistence of IB in institutionalized children. Specifically, we propose that children will be most likely to manifest indiscriminate social behavior (particularly IB that endures following adoption into emotionally supportive family environments) when they carry specific polymorphisms within the WSCR *and* experience in their first year the low quality of care typical of many institutions.

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