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Using biological factors to individualize interventions for youth with conduct problems: Current state and ethical issues

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ABSTRACT

A growing body of evidence suggests that biological factors such as genes, hormone levels, brain structure, and brain functioning influence the development and trajectory of conduct problems in youth. In addition, biological factors affect how individuals respond to the environment, including how individuals respond to programs designed to prevent or treat conduct problems. Programs designed to reduce behavior problems in youth would have the greatest impact if they were targeted toward youth who need it the most (e.g., who are mostly likely to demonstrate persistent behavior problems) as well as youth who may benefit the most from the program. Biological information may improve our ability to make decisions about which type or level of intervention is best for a particular child, thus maximizing overall effectiveness, but it also raises a number of ethical concerns. These include the idea that we may be providing fewer services to some youth based on biological factors, and that information about biological risk could potentially lead to discrimination or labeling. In this article, I discuss the risks and benefits of using biological information to individualize interventions for youth with conduct problems.

1. Introduction

Children with early-onset conduct problems exhibit greater risk for externalizing behavior problems in adulthood than those with late-onset conduct problems, including higher rates of antisocial behavior, alcohol, and substance use disorders (Jaffee, Strait, & Odgers, 2012). Furthermore, a substantial body of research has documented that disruptive behavior problems often co-occur with poor academic functioning (Bradshaw, Buckley, & Ialongo, 2008). Behavior problems in childhood are associated with academic failures in middle and high school and have been found to significantly and strongly diminish the probability of receiving a high school degree (McLeod & Kaiser, 2004), which in turn affects students' occupational and life adjustment. Aggressive children are more likely than their non-aggressive peers to experience social rejection, which increases the likelihood that they will affiliate with deviant peers in adolescence and increases their involvement in delinquency, violence, and substance abuse through high school and young adulthood (Dodge, Greenberg, Malone, and Conduct Problems Prevention Research Group, 2008).

A number of programs have been developed to prevent the development of behavior problems in at-risk youth. However, these programs are often complex and expensive and the average effects are often modest (McCart, Priester, Davies, & Azen, 2006). One reason for modest effects is that the programs are not uniformly effective (Lochman et al., 2015). Whereas a particular intervention may work for some youth, others may show no improvement in response to the intervention, or may even continue to develop more severe conduct problems. Thus, interventionists face a number of challenges. First, interventionists must determine which youth are most in need of interventions. For example, some youth may "phase out" of behavior problems with minimal intervention whereas others, in the absence of intervention, may develop more severe behavioral problems (Monahan, Steinberg, Cauffman, & Mulvey, 2009). These youth may appear similar in their behavioral symptoms at a single point in time, yet may develop very different trajectories (Moffitt, 1993). Distinguishing youth who are on a trajectory for persistent behavior problems and targeting these youth with intervention programs would greatly improve our ability to reap the most benefit from limited resources.

A second challenge for interventionists is to determine which type of intervention might work best for a particular child. There is significant heterogeneity in youth with externalizing problems, and research suggests that different factors may lead to behavioral problems in different individuals (Connell & Frye, 2006; Frick, 2012). Whereas some youth may have difficulty with self-regulation and attention, other youth may have deficits related to emotional responding (Pardini & Fite, 2010). These individual differences are likely to affect how youth respond to interventions, making some interventions more or less effective for specific subgroups of youth. Thus, in order to improve the effectiveness of interventions, it seems essential to understand the

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factors that affect intervention responses, and to use this information either in the selection of youth for intervention programs, or to tailor programs to specific youth based on this information.

In this paper, I focus on the idea that biological factors represent a significant source of variation between individuals, and thus may be useful, in combination with other psychosocial factors, in 1) determining which youth might be most in need of interventions, and 2) determining which intervention might work best for a particular child. In other words, biological information may help us to identify individuals who are most in need of intervention efforts, and who may benefit the most. Considering biological information, as well as existing measures of psychosocial variables, may improve our ability to get the most benefit from our intervention efforts.

A real-world example of the importance of considering biological factors was demonstrated in a recent study by Albert et al. (2015). The researchers conducted a genetic analysis of the Fast-Track randomized control trial, which was a 10-year multilevel intervention program delivering services to high-risk children and their families through direct contact and via school-based programming. Albert et al. (2015) found that for carriers of a particular gene variant, the intervention made a very large difference – 18% of treated children demonstrated externalizing psychopathology at adult follow-up compared to 75% of control children with the same variant. In contrast, for non-carriers, the intervention had no effect. A formal economic evaluation of Fast Track estimated the total cost of the 10-year intervention at $58,000 per child (Foster & Jones, 2006). Thus, targeting such resources at the children most likely to benefit, *and who additionally would fare worse in the absence of intervention*, would result in significantly better outcomes overall. Furthermore, improving our understanding of why non-carrier youth did not respond, and focusing efforts on developing interventions that *would* benefit those youth would also be a more effective use of resources.

Although using biological information to "individualize" intervention programs may produce benefits in terms of improved intervention efficacy, there are also costs to consider in terms of ethical issues concerning stigma, discrimination, privacy, and equity of service provisions. In this paper I will also discuss these issues and propose potential solutions to minimize the potential negative effects of using such information.

2. Biological research on conduct problems in youth

A significant body of research demonstrates that biological factors influence the development of conduct problems in youth. It is now widely accepted that youth outcomes are the product of both the environment in which the child develops and genetic factors that influence the individual characteristics of the child (e.g., the child's temperament, intelligence quotient (IQ), etc.) and how the child responds to his or her environment. Twin studies, adoptive studies, and studies in twins reared apart have provided substantial evidence for genetic influences on antisocial and aggressive behavior (Kendler, Aggen, & Patrick, 2013; Popma & Raine, 2006); although published estimates of heritability vary among studies, the genetic contribution is thought to be 40–50% (Moffitt, 2005; Salvatore & Dick, in press).

Studies assessing the whole genome have identified a number of promising genomic regions, but these remain to be replicated (Salvatore & Dick, in press). Furthermore, a small number of candidate genes have been associated with conduct disorder. Although, it is important to keep in mind that the contribution of any single gene to any complex behavior such as conduct problems is likely to be very small, genetic information is relatively easy and inexpensive to collect, and can potentially serve as a proxy for other types of information, such as information about brain functioning acquired using magnetic resonance imaging (MRI). As outlined by Hariri (2009), functional genetic polymorphisms may efficiently represent emergent variability in the biological cascade from molecular signaling pathways, to brain circuit functioning, to individual differences in personality. For example, numerous studies have demonstrated links between specific genetic polymorphisms and levels of activity in specific brain regions (Buckholtz et al., 2008; Forbes et al., 2007; Hariri et al., 2002). Thus, in the absence of the capability to do brain imaging, genetic information, or information about combinations of genes, may be useful.

A number of studies have examined differences in the stress response system in youth with conduct problems. The stress response system includes the hypothalamic-pituitary-adrenal axis and the autonomic nervous system. The hypothalamic-pituitary-adrenal axis releases the hormone cortisol in response to stress, which serves to mobilize the body's resources. Several studies have found that youth with conduct problems demonstrate lower levels of baseline cortisol (Loney, Butler, Lima, Counts, & Eckel, 2006; Oosterlaan, Geurts, Dirk, & Sergeant, 2005) and reduced cortisol reactivity to stress (Northover, Thapar, Langley, Fairchild, & van Goozen, 2016; Stadler et al., 2011; van Goozen et al., 1998; van Goozen, Matthys, Cohen-Kettenis, Buitelaar, & van Engeland, 2000). Blunted cortisol reactivity may reflect fearlessness and reduced inhibition of antisocial behavior (van Goozen, Fairchild, Snoek, & Harold, 2007).

The autonomic nervous system consists of the sympathetic nervous system, which drives the fast-acting "fight-or-flight" response, and the parasympathetic nervous system, which acts in a regulatory capacity to restore homeostasis, or a stable internal environment. The functioning of these systems is commonly measured through physiological recordings of heart rate and skin conductance. Conduct problems in youth have often been associated with low resting heart rate (Baker et al., 2009; Gao, Huang, & Li, 2017) and reduced skin conductance levels and reactivity (Herpertz et al., 2008; Lorber, 2004; Posthumus, Böcker, Raaijmakers, Van Engeland, & Matthys, 2009).

Findings related to parasympathetic nervous system activity, often measured via respiratory sinus arrhythmia (RSA), or variability in heart rate in synchrony with respiration, have been more mixed. Beauchaine, Hong, and Marsh (2008) found that boys scoring higher in aggression had lower baseline levels of RSA. However, other studies have found that externalizing problems were positively associated with RSA (Dietrich et al., 2007; Gao et al., 2017). Other studies have not found aggression in youth to be associated with RSA (Aults, Cooper, Pauletti, Jones, & Perry, 2015; Calkins, Graziano, & Keane, 2007; Hinnant & El-Sheikh, 2009). Higher RSA is thought to reflect physiological flexibility and the ability to adapt to environmental stressors and regulate emotion (Fabes & Eisenberg, 1997); thus it is generally considered adaptive (Beauchaine, 2001; Porges, Doussard-Roosevelt, & Maiti, 1994). However, excessive RSA reactivity has been linked with social maladjustment and anxiety in some studies (e.g., Gazelle & Druhen, 2009), and it has been argued that heightened parasympathetic relative to sympathetic activity may indicate a passive coping response to stress, which may contribute to underarousal and antisocial behavior (Gao et al., 2017).

Finally, both structural and functional neuroimaging studies have found evidence of differences in brain structure in functioning in youth with conduct problems. Conduct disorder is associated with structural differences (primarily reductions) in the temporal lobe, prefrontal cortex, and insula (Fairchild et al., 2011; Huebner et al., 2008; Kruesi, Casanova, Mannheim, & Johnson-Bilder, 2004; Sarkar et al., 2015; Sterzer, Stadler, Poustka, & Kleinschmidt, 2007). Recently, Noordermeer, Luman, and Oosterlaan (2016) conducted a meta-analysis of 29 structural and functional neuroimaging studies in youth with oppositional defiant disorder and/or conduct disorder. For youth with these disorders who did not have comorbid Attention Deficit Hyperactivity Disorder (ADHD), reduced structure and/or functioning was observed in the amygdala, insula, striatum, and anterior cingulate. They reported that there is strong evidence that abnormalities in the amygdala are specific to oppositional defiant disorder and conduct disorder compared to ADHD.

Matthys, Vanderschuren, and Schutter (2013) have suggested that the biological differences identified in youth with conduct problems represent deficits in three interrelated mental domains: punishment processing, reward processing, and cognitive control. They suggest that reduced cortisol reactivity to stress, amygdala hyporeactivity to negative stimuli, and low serotonin and noradrenaline neurotransmission suggest low punishment sensitivity, which may impair the ability to form associations between behavior and impending punishment. Low heart rate and sympathetic nervous system, in addition to reduced activity in the orbitofrontal cortex to reward result in a hyposensitivity to reward that may drive sensation-seeking behavior. Finally, they suggest that impairments in executive functions and impairments in regions of the paralimbic system may result in impaired cognitive control over emotional behavior.

Importantly, not all youth with conduct problems will exhibit all of the biological abnormalities or differences described above. Whereas some youth may have deficits related to systems important for punishment processing that underlie their antisocial behavior, others may have deficits primarily in reward-related systems. Furthermore, not all youth with specific biological features have or will develop conduct problems. Fanti (in press) recently reviewed literature on the role of different physiological systems in understanding heterogeneity in conduct disorder. He found that conduct disorder is manifested in diverse ways physiologically, and that different subgroups of youth with conduct disorder can score in opposite extremes on physiological measures. This heterogeneity cannot easily be accounted for using existing methods for subtyping youth based on behavioral or symptom-level assessments. Fanti (in press) suggests that future work should use physiological measures as grouping or clustering variables rather than creating groups based on co-occurring psychopathologies or traits.

It is likely that these different biological risk factors underlie heterogeneity in how youth respond to the environment, including producing variability in how they respond to interventions. The next section outlines some of the ways in which biological factors have been found to influence responding to the environment, particularly in ways that may influence intervention responsiveness.

3. Biological factors influence responding to the environment

In addition to research demonstrating the relationships between biological factors and antisocial behavior, there is a growing body of work focusing on biosocial interactions. The relationship between biological and environmental factors is reciprocal. Biological factors can influence how individuals respond to the environment (e.g., individuals with a greater biological predisposition to anxiety are likely to respond to anxiety-inducing situations differently than those without such predisposition), and environmental factors are capable of changing biology (e.g., prolonged exposure to stress results in altered functioning of the stress response system and even altered gene expression (Weaver, Meaney, & Szyf, 2006)). In many cases, biosocial studies demonstrate that the presence of both a biological risk factor and a social risk factor are associated with higher levels of antisocial behavior (e.g., Caspi et al., 2002). However, some studies suggest that existing biological factors may influence responding to different types of environments.

For example, studies have found that biological factors can influence whether the experience of peer rejection is associated with externalizing behavior. Janssens et al. (2015) found that for adolescents experiencing high rates of peer rejection, those who were carriers of a particular variant of the dopamine transporter gene demonstrated more rule-breaking behavior than non-carriers. Similarly, Gregson, Tu, and Erath (2014) found that negative peer experiences were positively associated with externalizing behaviors only among preadolescents who exhibited lower skin conductance reactivity. They suggest that lower sympathetic nervous system functioning may reflect fearlessness, which may potentiate retaliatory responses to negative peer experiences and may reflect weaker inhibitory self-control efforts that could otherwise help to facilitate more benign interpretations or reappraisals of stressful peer situations. Furthermore, they suggest that lower sympathetic nervous system functioning may indicate a lack of awareness or engagement with peer stress experiences, limiting the ability of preadolescents to learn from problem situations involving peers or to develop skills that help them avoid escalating conflicts with peers in the future. Finally, Rudolph, Troop-Gordon, and Granger (2010) found that peer victimization was associated with aggression among children with higher levels of cortisol and alpha-amylase (an enzyme found in saliva associated with sympathetic nervous system activity), but not among children with lower levels.

Although most studies to date have examined how *negative* environmental factors interact with biological factors to predispose for antisocial behavior, biological factors will also influence responding to positive, enriching environments. Recently, a number of research have begun exploring the idea that some youth are more sensitive to environmental influences regardless of whether the environment is negative or positive (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007). Thus, the children who are most at risk for adverse developmental outcomes may also be the ones who would benefit the most from intervention programs and additional services. This model, the differential susceptibility model, suggests that sensitive/susceptible children are especially responsive to the environment both "for better *and* for worse." The next section reviews studies that have examined how biological factors may influence responding to treatment and intervention studies.

4. The use of biological information in treatment and interventions

Intervention during childhood has the potential to prevent a cascade of negative outcomes in youth who may be showing early signs of aggressive behavior (Dodge, 2009). Evidence of this has made strategies for investing in youth a policy priority in the United States and globally (Barnett & Masse, 2007; Heckman, 2006). Such programming may afford an opportunity to shift the developmental trajectory of aggressive behavior, and in turn prevent subsequent negative outcomes such as school failure, substance use, and legal problems.

As mentioned in the introduction, intervention programs are often complex and expensive and the average effects are often modest (McCart et al., 2006). One reason for modest effects is that the programs are not uniformly effective and do not work for all individuals whom they reach. A common presumption as to why interventions are less effective than anticipated is that they may be poorly implemented. Although this is an important concern, emerging research suggests that the individual characteristics of the youth participating in the intervention may be important in determining "what works for whom" (Albert et al., 2015; Bakermans-Kranenburg, Van, Pijlman, Mesman, & Juffer, 2008; Beauchaine et al., 2015; Glenn, Lochman, Dishion, Powell, Boxmeyer, Kassing, et al., in press; Glenn, Lochman, Dishion, Powell, Boxmeyer, and Qu, 2018; Stadler et al., 2008).

Despite the fact that approximately half of the variance in conduct problems is likely attributable to genetic factors (for a meta-analysis, see Burt, 2009), and that numerous biological factors have been associated with conduct problems (Matthys et al., 2013), biological factors are rarely taken into account when considering which youth may be most in need of treatment or intervention, or in trying to determine what form of intervention might work best for a particular child. This is likely for several reasons. First, gathering biological information can be expensive, although when weighed against the potential benefits of targeting the right children with the right intervention, this expense may become less of an issue. Secondly, for the most part, we have not developed an adequate knowledge base for actually understanding the influence of most biological factors, and thus it is not yet clear how specific factors could be incorporated into decisions about existing interventions. However, a few studies have begun to look at how biological factors may moderate intervention responsiveness, which represents a first step in improving our understanding of what works for whom.

4.1. Biological factors that affect intervention responsiveness

First, genetic factors have been found to influence intervention response. Studies have found that genes associated with dopamine (Bakermans-Kranenburg et al., 2008; Brody et al., 2014), serotonin (Brody, Beach, Philibert, Chen, & Murry, 2009), and glucocorticoids (Albert et al., 2015) moderate responses to interventions designed to reduce behavior problems and negative outcomes in youth. For example, as mentioned in the introduction, Albert et al. (2015) examined how a genetic variant influence responsiveness to the 10-year Fast Track intervention, which was designed for high-risk children with early-starting conduct problems. Among European-American participants, individuals with a risk allele, or gene variant, of the glucocorticoid receptor gene *NR3C1* were both (1) especially likely to develop externalizing problems if they did not receive the Fast Track intervention; and (2) especially likely to benefit in terms of reduced likelihood of developing externalizing problems if they received the intervention. For individuals without the risk allele, the intervention did not have any effect.

Recently, a genetic factor was found to moderate responsiveness to the Coping Power intervention (Glenn, Lochman, Dishion, Powell, Boxmeyer, and Qu, 2018). Coping Power is one of the relatively few rigorously-tested school based programs currently available to address behavior problems among at-risk children (Lochman & Wells, 2002, 2003, 2004). This multi-component program is designed for youth who display high levels of aggressive behaviors and are therefore at risk for later problem behaviors (i.e., school failure, substance use and abuse, and delinquency). When implemented in the traditional format, it involves group sessions that take place at the students' schools, separate group sessions for parents, and supports to teachers. Because of concerns about potential iatrogenic effects secondary to aggregation of high-risk youth, a version of the program was developed in which children met individually with the interventionist rather than in group settings. Glenn, Lochman, Dishion, Powell, Boxmeyer, Kassing, et al. (in press), Glenn, Lochman, Dishion, Powell, Boxmeyer, and Qu (2018) found that a variant of the oxytocin receptor gene interacted with intervention delivery format in predicting responsiveness to the intervention. For youth with one variant of the gene, reductions in externalizing behavior were observed regardless of intervention format. However, youth with the alternate variant of the gene who received the group-based intervention showed little improvement over the course of the intervention, and a worsening of symptoms during the follow up year. In contrast, those with this variant who received the individual format of the intervention demonstrated reductions in externalizing problems. This study suggests that genetic factors may be informative when making decisions about which form of an intervention may work best for a particular child. In this case, the oxytocin receptor gene has been associated with social behavior, and may influence susceptibility to social reinforcement and deviant peer influences – factors that may affect responsiveness to group-based interventions more than individual-based interventions.

Other biological factors have also been found to be associated with intervention responsiveness. Stadler et al. (2008) found that heart rate was significantly lower in children with disruptive behavior disorders who did not benefit from an intensive day-care treatment and parent training. Importantly, they found that heart rate was a significant predictor for therapy success whereas other risk factors (initial levels of aggression, delinquent behavior, attention problems, externalizing or internalizing behavior, cognitive functioning, age of the child) did not affect therapy success.

Similarly, Beauchaine et al. (2015) found that nonspecific fluctuations in skin conductance, which index sympathetic nervous system activity, predicted treatment responses to the Incredible Years intervention in preschool children with ADHD. The Incredible Years intervention involves both parent and child training (20 weekly 2-h sessions). Youth with fewer nonspecific fluctuations showed poorer treatment response on 4 of 7 externalizing outcomes. Furthermore, the intervention was associated with longitudinal increases in electrodermal activity from pre- to post-treatment. This study emphasizes the importance of understanding the mechanisms by which treatments have an effect. If we can identify which biological factors may be changed by intervention, we may be able to select youth who demonstrate particular deficits in these factors to receive this type of intervention.

Glenn, Lochman, Dishion, Powell, Boxmeyer, Kassing, et al., (in press) found that RSA and skin conductance level both moderated responsiveness to the Coping Power intervention. Youth with lower skin conductance levels (i.e., sympathetic nervous system functioning) at pre-intervention demonstrated greater reductions in teacher-rated proactive aggression from pre-intervention to a one-year follow-up than those with higher skin conductance levels; this effect was found regardless of intervention format (individual or group delivery). RSA interacted with intervention format to influence responsiveness in individuals with high initial levels of aggression. Compared to brain imaging, psychophysiological information is relatively inexpensive and easy to collect (e.g., it can be collected using portable devices), and thus represents one of the more feasible options for obtaining biological information.

A few studies have also examined how hormones may be associated with intervention responsiveness. In youth with disruptive behavior disorders, van de Wiel, van Goozen, Matthys, Snoek, and van Engeland (2004) found that those with high cortisol stress responsivity at pre-treatment showed more improvement in response to a structured intervention aimed to decrease aggressive behavior than those with a blunted cortisol stress response. Shenk et al. (2012) found that youth with disruptive behavior disorders with higher pre-treatment concentrations of testosterone, but not other hormones, were four times more likely to be considered non-responders to a multi-faceted psychological treatment.

Together, these studies indicate proof of concept that biological information may be useful in predicting which youth may benefit the most from intervention programs, as well as to identify youth who are unlikely to respond and thus may require a different form (e.g., change in format, change in focus, or change in intensity) of intervention that may be more effective. Much more research is needed to replicate existing findings in order to develop measures that would be considered reliable predictors. Additional research is also needed to examine the effects of multiple biological factors simultaneously so that we can gain a better understanding of which risk factors or combinations of risk factors demonstrate the strongest effects on intervention responding.

Finally, this work may also provide information that can be used to develop interventions for youth that are more tailored and targeted to the specific needs of the individual. For example, we know that interventions are capable of changing biological factors. Therefore, interventions known to improve specific biological risk factors could potentially delivered to youth who demonstrate those risk factors. Brotman et al. (2007) found that a 22-week family-based intervention in preschool children at risk for antisocial behavior was capable of increasing cortisol responses to a social challenge. Similarly, in a sample of 3- to 6-year-old foster children, Fisher, Stoolmiller, Gunnar, and Burraston (2007) found that a 12-month family-based therapeutic intervention was able to restore altered diurnal cortisol patterns to a level that became comparable to the patterns demonstrated by non-maltreated children. It is worth emphasizing that these studies involve psychosocial forms of treatment or intervention; it is not necessarily the case that biological deficits must be targeted with biologically based forms of treatment such as medication.

In related fields, such as substance use, genetic factors have proven to be useful in predicting responsiveness to medication. Johnson et al. (2011) recently found that ondansetron, a specific serotonin receptor agonist, was much more effective in improving abstinence in alcoholics in individuals with one variant of the serotonin transporter gene than another. These findings demonstrate the promise of a

pharmacogenetics approach in reducing the severity of alcohol consumption in individuals with specific genetic polymorphisms.

Opportunities to maximize the fit between children and programs have great potential for improving intervention impacts. Research is needed to uncover measurable characteristics of individuals that affect their likelihood to respond more or less positively to intervention. Answering the question of which individual characteristics matter holds the promise of enabling interventionists to tailor interventions to individuals, thereby improving the efficiency of program delivery and maximizing impact.

4.2. The use of biological information in determining which youth may be most in need of intervention

In addition to determining which interventions work for specific children, in the face of limited resources, it is equally important to determine which children may be most in need of interventions. Without any intervention, some youth may be at greater risk for escalating behavior problems, whereas others may "age out." Studies have suggested that among children who demonstrate high levels of conduct problems, less than 50% will continue to exhibit these problems into adolescence (Barker & Maughan, 2009; Moffitt, 1993; Nagin & Tremblay, 1999). Thus, not all youth may require intensive interventions. With limited resources available for intervention efforts, it is critical to be able to determine which youth are likely to have persistent behavior problems.

Biological factors may help to determine which youth are at greater risk for later behavior problems. Studies have found that genetic factors influence the trajectory of behavior problems (Dick, Latendresse, Lansford, et al., 2009; Fontaine, Rijsdijk, McCrory, & Viding, 2010; Latendresse et al., 2011). For example, Dick et al. (2009) found that youth who showed persistent elevated trajectories of externalizing behavior from age 12 to 22 were more likely to carry a specific variant of the GABRA2 gene. Moffitt, Lynam, and Silva (1994) found that poorer neuropsychological functioning in males at age 13 predicted a trajectory of persistent antisocial behavior from age 13 to 18. Although a number of other factors such as parenting, conflict in the home, and child temperament have been found to predict trajectories of antisocial behavior (Barker & Maughan, 2009), the additional consideration of biological factors may be able to improve our predictive ability.

A study by Brody et al. (2014) demonstrates how improved prediction of antisocial trajectories could benefit interventions. This study implemented the Strong African American Families intervention, a seven-week, family-based youth risk behavior prevention program for rural African Americans. For youth in the control condition who did not receive the intervention, Brody et al. (2014) found that male adolescents with a risk allele of a dopamine-related gene demonstrated significantly greater increases in substance use across 22 months than those in the control condition who did not carry the risk allele. The youth with the risk allele who were in the intervention condition demonstrated significantly lower rates of substance use than those in the control condition. This study demonstrates two things. First, is shows that in the absence of intervention (control condition only), some individuals are at much greater risk for substance use problems than others. These are the individuals who would presumably benefit most from intervention. Second, it shows that the intervention is successful in reducing maladaptive behavior in these youth. In contrast, the intervention does little to change the behavior of the youth without the risk allele who did not show increased substance use in the absence of intervention.

Thus, when developing intervention programs for youth who may be showing early signs of aggressive behavior, it is important to be able to determine which youth may be at greatest risk for a trajectory of persistent behavior problems, and who may require more intensive forms of intervention. Furthermore, if it is true that some youth may benefit greatly from interventions, it would be important to be able identify these individuals.

In sum, to achieve the best overall outcomes, it seems essential to understand the factors that affect intervention responses, and to use this information either in the selection of youth for intervention programs, or to tailor programs to specific youth based on this information. Programs that reduce behavior problems and improve social, emotional, and academic functioning would have the greatest impact if they are targeted toward youth with the most biological risk. However, there are a number of concerns that arise regarding the use of biological information that should be thoroughly considered.

5. Exemplar and ethical issues

The ideas discussed above have considerable implications for policy. However, it is important to keep in mind that to date, the available evidence is not strong enough to warrant the use of biological information in making decisions about interventions. Most of the studies discussed here have not been replicated, and it has yet to be determined how effect sizes for different types of factors (biological, psychosocial, demographic) compare in terms of predicting responsiveness or predicting trajectories of antisocial behavior. Another important point is that with the exception of single genetic polymorphisms, which likely have small effects, biological factors represent continuous dimensions. Applying such information in a practical setting would require normative data to be established, and recommendations to be made regarding appropriate thresholds for cut-off scores.

However, assuming that we do reach a point in which we have developed a method for predicting which youth are more likely to respond to interventions and which youth are not likely to respond, and that this method involves the use of biological information, there are a number of issues that may arise.

Distinguishing youth based on biological information carries with it ethical issues concerning stigma, discrimination, and equity of service provisions (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011). In the medical field, there is ongoing debate over the ethical means of incorporating genetic information into screening and treatment decisions (Dancey, Bedard, Onetto, & Hudson, 2012; Goldenberg & Sharp, 2012) and it has been suggested that this debate should be going on in the social and behavioral sciences as well (Albert et al., 2015).

In order to better understand the ethical issues that may arise, and the extent to which they may be problematic, here I will discuss a hypothetical scenario using the Coping Power intervention as an example. As described previously, this preventive intervention was designed for 4th grade youth who have been identified primarily by teachers as demonstrating aggressive behavior. Typically, the highest scorers in a given school will be selected for participation in the intervention. In other words, these youth all have similarly high rates of externalizing problems prior to the intervention. One can imagine that a battery of tests could be conducted on these youth. In addition to gathering further information about symptoms, family factors, and demographics, a number of tests could be conducted to collect biological information. This might include a cheek swab to test for specific genetic polymorphisms, measurement of heart rate and skin conductance levels, the collection of saliva samples for assessing hormone levels (the latter two could be conducted at rest and/or in response to a specific type of stressor), and a series of neurocognitive tests that measure processes such as inhibitory control, working memory, and other executive functions.

This information could be weighted according to results from research examining the relative influence of these variables in predicting Coping Power outcomes and used to categorize youth into different groups. If we want to obtain the most benefit from limited resources, we could imagine dividing youth into three groups:

> *Group 1*: Youth who are likely to benefit from Coping Power and who would likely to persist in antisocial behavior problems in the absence of intervention. These youth would receive the standard Coping Power intervention.

Group 2: Youth who are less likely to persist with antisocial behavior regardless of whether they receive an intervention or not (e.g., similar to the adolescent-limited taxon desribed by Moffitt, 1993). These youth could receive a modified version of Coping Power that is less intensive. For example, briefer versions of Coping Power (24 rather than 34 child sessions, and 10 rather than 16 parent sessions) have been found to produce significant reductions in teacher ratings of children's externalizing behaviors at long-term follow-ups (Lochman et al., 2014). Recently a hybrid version of Coping Power that includes both face-to-face (12 child sessions and 7 parent sessions) and internet components has been developed which can also be administered more efficiently (Lochman et al., 2017).

Group 3: Youth who are less likely to benefit from Coping Power and who would be likely to persist in antisocial behavior problems in the absence of intervention. These youth should be the target of modified or alternative interventions that may ultimately prove to be more effective for these youth. This might involve increasing the duration or intensity (e.g., frequency of sessions) of the intervention, adding components, changing the format (e.g., individual versus group-based format of Coping Power, described above), or providing more focus on a particular area. For example, if research suggests that these youth often have blunted cortisol reactivity, then selecting interventions or adding components of interventions that are known to increase cortisol reactivity may be promising. In other words, the more we are able to understand about how interventions work, and the more we know about the individuals for whom interventions do not work, the better we will be able to match youth to interventions in a sophisticated way.

There are a few issues that arise from implementing such a procedure. Some may argue that providing different levels of services to different individuals based on biological factors violates our sense of fairness and equality. However, if we are able to reliably identify individuals who very likely will not benefit from a particular intervention, then it would seem questionable to provide publically funded services that are unlikely to be effective simply so that everyone is "treated" in the same way (Belsky & van Ijzendoorn, 2015). It seems that by continually modifying and improving the above procedure, including furthering our research on finding programs that work for "non-responders" we will be able to achieve the best outcomes for all youth, and this would result in more equity overall.

There are also concerns about the collection and use of biological information, including the potential that it could be used to discriminate against particular youth. First, biological information collected from the child should be kept private and only used by interventionists; however, it is possible that collecting biological information from youth could result in this information being used in inappropriate ways. It could be argued that the types of information collected for this purpose may be less "revealing" than information collected for some medical purposes (e.g., genes that confer high risk for a disease). As stated previously, each biological factor is likely to contribute to only a small portion of variance in antisocial behavior, and thus it may be less likely to be used for malicious purposes. Data collected from youth would be multifaceted, and the procedure for determining categories would be based on the combination of this data (biological and non-biological). We, as a society, will need to decide whether the potential benefits of incorporating this information into existing methods of prevention and intervention are worth the risks to individual privacy.

Another concern is that by categorizing youth there could be negative effects related to labeling. In particular, if parents or teachers perceive that a child has been categorized as a "non-responder" they may change how they interact with the child. Thus, it will be important to have procedures for explaining the goal of selecting a particular intervention for a specific child. When explaining the procedure to parents, it would be important to emphasize that biological factors, even genes, are not fixed and immutable. Research suggests that these factors are modifiable through intervention.

When considering the perspective of parents/caregivers, one can imagine how the results of the initial testing might be explained. For *Group 1*, parents would be told that we have an effective intervention that is known to work well for individuals who have similar characteristics to their child. For *Group 2*, parents would be told that youth who have similar characteristics to their child typically do not go on to develop severe behavioral problems, but we are offering some support in the form of an abbreviated intervention. Finally, for *Group 3*, parents would be told that we are providing an alternate form of intervention that may prove to work better for their child than the traditional intervention. Although outcomes in this case may be less certain, it would hopefully suggest to the parent that efforts are being made to reach the best possible outcome.

Lastly, there are issues related to miscategorization of individuals. In the face of changing environments, interventionists will never be able to predict without error. However, the more research that is conducted in this area, the more we can improve our methods of predicting. It could be argued that even a rudimentary calculation based on a few factors could result in overall intervention effects that exceed current effect sizes.

6. Conclusions

Currently, the average effects of preventive or therapeutic interventions are modest, with small effect sizes. This may partly be due to failure to consider heterogeneity in youth who demonstrate early signs of aggressive behavior. Intervention effects may be much larger for some individuals, who may be more susceptible to the influence of the environment (positive or negative). Weak intervention effects may be taken as a sign that there is little we can do to prevent poor outcomes in at-risk youth, resulting in policymakers being less inclined to support efforts to fund large-scale intervention efforts given concerns that impact might be limited and/or not cost effective (Belsky & van Ijzendoorn, 2015). Being aware of individual differences in biology creates more realistic expectations of intervention efficacy, and may highlight the fact that interventions may be highly effective in subgroups of youth who are more sensitive to environmental influences. Previously unobserved differences in children's likelihood of responding to an intervention may be revealed through examining biological moderators of interventions. Efforts are needed to further our understanding of how biological factors affect intervention responsiveness, as well as how interventions may alter biological factors. We should also engage in more discourse about how we as a society want to deal with ethical issues that arise from using biological information to individualize interventions. Individualizing interventions may mean that some youth would receive more intensive or longer interventions than others. Collecting biological data also increases the risk that such data could be misused, and that individuals could face discrimination or stigma. Finally, as with the use of demographic or psychosocial information, genetic or other biological information may not always result in an accurate prediction of which type of intervention would work best for the child. Addressing these issues will require clear communication from researchers to both parents/caregivers and the general public about the risks and benefits of incorporating biological measures into intervention programs.

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