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Genotype and Neuropsychological Response Inhibition as Resilience Promoters for ADHD, ODD, and CD under Conditions of Psychosocial Adversity

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Abstract

Whereas child personality, IQ, and family factors have been identified as enabling a resilient response to psychosocial adversity, more direct biological resilience factors have been less well delineated. This is particularly so for child ADHD, which has received less attention from a resilience perspective than have associated externalizing disorders. Children from two independent samples were classified as resilient if they avoided developing ADHD, ODD, or CD in the face of family adversity. Two protective factors were examined for their potential relevance to prefrontal brain development: neuropsychological response inhibition, as assessed by the Stop task, and a composite catecholamine genotype risk score. Resilient children were characterized in both samples by more effective response inhibition, although the effect in the second sample was very small. Genotype was measured in Sample 1, and a composite high risk genotype index was developed by summing presence of risk across markers on three genes expressed in prefrontal cortex: dopamine transporter, dopamine D4 receptor, and noradrenergic alpha 2 receptor. Genotype was a reliable resilience indicator against development of ADHD and CD, but not ODD, in the face of psychosocial adversity. Results illustrate potential neurobiological protective factors related to development of prefrontal cortex that may enable children to avoid developing ADHD and CD in the presence of psychosocial adversity.

Resilient adaptation can be conceptualized in different ways, but as used here it refers to the avoidance of psychopathology, or adapting in a positive manner despite the experience of adversity that is associated with elevated risk for the symptomatic outcome (Luthar, Cicchetti, & Becker, 2000; Masten & Powell, 2003). As this special issue attests, resilient adaptation has long been studied but usually with a focus on psychological or psychosocial protective factors. In the case of ADHD, a small number of studies have looked at characteristics that make children with ADHD resilient to the worst later outcomes (Hechtman, 1991; Mikami & Hinshaw, 2003), but none to our knowledge have looked at biological or cognitive characteristics that may protect against ADHD itself in the face of adversity. Literature examining oppositional defiant disorder *per se* is also sparse, although more literature describes protective factors against externalizing behavior problems more generally in the face of adversity (Masten et al. 1999; Mendez, Fantuzzo, & Cicchetti, 2003; Ungar, 2004).

In the case of ADHD, ODD, and CD, considering biological or genetic sources of resilient adaptation requires recognition of the role of adversity in their development. Whereas psychosocial adversity has been long recognized as a contributor to conduct disorder in children (Masten et al., 1999; Rutter et al., 1975), it has recently also been identified as a contributor to exacerbation of symptoms of ADHD apart from conduct disorder (Biederman et al., 1995;

2002; Counts et al., 2005). Therefore, it is of considerable interest to understand why some children with a given adversity risk develop ADHD, and others do not. Examination of cognitive and genetic characteristics of the child requires a new perspective on what are usually thought of as risk factors for ADHD. Here, in the presence of adversity, protective genotype and strong cognitive control (operationalized as response inhibition) are posited as promoters of resilience for the child. Identifying in this way how genetic or cognitive mechanisms protect children exposed to adversity so they are able to avoid severe symptoms of ADHD, as well as ODD or CD, is a virtually unexamined arena.

Within a given syndrome domain, this type of work may clarify distinct pathways to the development of ADHD, as well as of conduct and oppositional behaviors. In the case of conduct problems, for example, distinctions can be made between routes related to low fear and temperamental risk (Blair et al., 2005), versus routes related to adversity and distress (see Nigg, 2006a for review). Consistent with that picture, genotype by environment (Cadoret et al., 1995) and genotype by trauma (Caspi et al., 2002) interactions have been suggested in the genesis of some cases of aggression, suggesting that genotype may protect against conduct problems in the presence of adversity. In the case of ADHD, recognition is growing that despite its high heritability, psychosocial factors also contribute to the disorder, presumably either by means of non-shared environment effects, or via gene-environment correlations (Johnston & Mash, 2001; Nigg, 2006b). Thus, genetic effects do not explain the genesis of the disorder, but rather provide for liability to it (Asherson et al., 2005). In some instances, adversity may activate the liability; conversely, genotype may protect against emergence of ADHD in high adversity families. Moreover, the cognitive markers that are associated with ADHD appear only to be associated in a subset of cases (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). Whether they may protect against effects of adversity also remains unexplored.

Along with illuminating heterogeneity within ADHD, this type of investigation can also speak to ADHD effects in relation to conduct and oppositional disorders, because these so frequently co-occur. Etiological similarities and overlaps between disorders in the externalizing spectrum are of considerable interest as the DSM-V is contemplated. Identifying the factors that enable children to resist these disorders in the face of marked adversity may provide clues to further inform their nosological relationship. If ADHD, ODD, and CD represent developmental continuities, driven by many of the same risk and protective factors (for discussion, see Lahey et al., 1999; Patterson et al., 2001), we might expect similar etiological and protective profiles across these disorders. In contrast, if these syndromes emanate from distinct developmental pathways, we would expect somewhat unique profiles of resilient elements when a child is faced with adversity.

To identify relevant neurobiological protective factors, therefore, we relied on current theories about ADHD as well as recent findings relating stress to brain function. The ADHD literature indicates that several cognitive abilities related to cognitive control are affected. One major exemplar in the neurocognitive realm involves a right-lateralized frontal-striatal neural network involved in rapid, on-line, response suppression or response control (sometimes called response inhibition). This ability is well replicated weakness in ADHD (Barkley, 1997; Crosbie & Schachar, 2001) as well as to a lesser extent in CD (Oosterlaan et al., 1998; Seguin et al., 2004). A now-extensive molecular genetic literature implicates dopaminergic and noradrenergic genes in ADHD, including those expressed in prefrontal cortex (Faraone et al., 2005).

With regard to stress and brain function, animal studies by Arnsten and colleagues (e.g., Arnsten & Goldman-Rakic, 1998; for review see Arnsten, 2001) have suggested that stress particularly affects prefrontal brain function, more than other brain regions, apparently due to effects on receptor sites related to dopamine and norepinephrine. Thus it may be that chronic

adversity during childhood has effects that can be modulated by the integrity of cognitive and neurobiological systems in prefrontal cortex.

Considering these lines of work therefore, we sought to probe a response suppression component of cognitive control that involves areas of prefrontal cortex, and to capture elements of genotype relating to prefrontal cortex. Response inhibition is only one of the cognitive functions involving prefrontal cortex, (others include working memory), and different functions may involve different neurotransmitter systems. However, we chose response inhibition as a reasonable starting point for a resilience investigation in the cognitive domain. In the genetic realm, we therefore considered genes that were expressed in prefrontal cortex and associated empirically with ADHD and/or the cognitive abilities thought to be impaired in ADHD. This led us to examine dopaminergic and noradrenergic genes. Our exemplars were markers on the DRD4 receptor gene and dopamine transporter gene—both associated with ADHD in meta-analyses (Faraone et al., 2005). Our final exemplar was the noradrenergic alpha-2 receptor gene, which is associated with working memory in primates (Arnsten, 2001) and with ADHD in initial studies from our group (Park et al., 2005).

Adversity can be defined in numerous ways. In these studies, we combined two approaches. To define adversity, we follow in approximate form the classical adversity index first developed by Rutter et al (1975), which emphasized (a) family conflict, (b) low SES, and (c) presence of parent psychiatric disorders. We also added (d) stressful events, because of other literature indicating their importance (Velez et al., 1989).

We operationalized resilience as avoidance of clinical-range behavioral problems in the face of adversity. The symptomatology we focus on is in the areas of ADHD, ODD, and CD and their related behavioral domains. The definition we chose for a successful outcome was the avoidance of clinical threshold for any of these disorders under conditions assaulting that adaptation. This has been the usual criterion of interest both in large scale intervention studies (Swanson et al., 2001) and prevention trials (The Conduct Problems Prevention Research Group, 2002). If resilient characteristics can be identified that enable children to avoid these disorders under otherwise challenging circumstances, they may inform future intervention or prevention.

To define our adaptation groups we followed the conceptual framework of Zucker, Wong, Puttler, and Fitzgerald (2003) which cross-classifies presence/absence of damaged (e.g., symptomatic) outcome and presence/absence of family adversity. *Resilient* children were defined as those exposed to adversity who avoided developing a disorder (ADHD, CD, or ODD). *Vulnerable* children were those exposed to adversity who did develop a disorder. *Troubled* children developed disorder under low family adversity conditions; *unchallenged* children had low adversity and had no disorder.

Two samples were utilized to maximize the generalizability of our findings. The first sample, from the Michigan State ADHD study (Nigg et al., 2002), was used to evaluate the protective effects of (a) genotype and (b) effective response inhibition, in relation to ADHD and externalizing behavior problems in the face of adversity. The second sample, from the Michigan Longitudinal Study (Zucker et al., 2000), was used to replicate the protective effects of strong response inhibition in a longitudinal framework, at an older age, and in a higher-risk sample. Adversity was defined similarly in the two samples, and response inhibition was measured in the same manner, but the participants and samples differed substantially in demographics and age, thus enabling a strong test of the generalizability of our hypothesis about response inhibition.

Our primary hypotheses were that genotype (low risk in prefrontally expressed genes) and strong response inhibition would protect children against developing ADHD and related

externalizing problems in the face of high adversity. For a comparison, we examined the protective effects of IQ, a frequent target of resilience studies but one that we did not expect to protect against ADHD (although prior findings suggest that it is protective against CD; Masten et al. 1999).

Study 1: Genotype and Strong Response Inhibition as Protective Against Adversity

METHOD

Participants—A total of 206 boys and girls and 337 parents (206 mothers, 131 fathers) provided at least partial data on symptoms and adversity indices. Children were classified into three groups: ADHD-Combined Type (ADHD-C, $n=96$), ADHD-Primarily Inattentive Type (ADHD-PI, $n=38$), and non-ADHD (*Control*, $n=72$). A generally but not exclusively community-based recruitment strategy was followed, in which families with a child in 1st through 6th grade were recruited from invitation letters sent to parents of children in the local school districts and by public advertisements. A small percentage (10%) was recruited from a local pediatric clinic specializing in ADHD referrals and from a local support group for parents of children with ADHD. A standard multi-stage screening process then was used to select children and families into the study. At stage 1, rule outs were evaluated by telephone (physical handicap, mental retardation, autistic disorder, non-English-speaking, and prescription of long-acting psychoactive medication including anti-depressant, anti-psychotic, and anti-convulsant medications; stimulant medications were not a rule-out). At stage 2, parent and teacher normative rating scales were obtained (Achenbach Child Behavior Checklist or Teacher Report Form, Behavior Assessment Scale for Children, Conners Rating Scale, or a DSM-IV symptom checklist. To be considered possible ADHD, children had to (A) exceed the 90th percentile on at least one teacher rating and the 80th percentile on at least one parent rating of attention problems or ADHD symptoms OR (B) be previously diagnosed as ADHD (any type) by a physician or psychologist in the community who utilized teacher and parent ratings to arrive at their diagnosis. To be considered possible Control, they had to be below the 80th percentile on all parent and teacher ratings of attention problems or ADHD symptoms and never previously diagnosed with ADHD. At stage 3, the DISC-IV was completed and final group assignments were completed as described below.

Exclusion criteria: Families and children were excluded from the study if the target child had mental retardation, autistic disorder, Tourette syndrome, or bipolar disorder as assessed by structured clinical interview of the parent or identified in the clinical history, or if the child had a physical or neurological handicap as ascertained by parent report. All children and their parents were native English speakers and all children had a valid Full Scale IQ > 75 based on a 5-subtest short form of the Wechsler (1991) Intelligence Scale for Children, 3rd Edition. Adoptive and step-parents participated but did not complete diagnostic interviews.

Diagnostic assignment of index children: Child diagnosis was confirmed at Stage 3 of the multi-gate procedure, using a parent structured diagnostic interview (the DISC-IV, Shaffer et al., 1997) supplemented by an “or” algorithm following the DSM-IV field trials validity data (Lahey et al., 1994). Prior versions of the DISC have exhibited acceptable reliability and validity. The “or” algorithm was implemented as follows. If children met age of onset, duration, impairment, and cross-situational criteria, then diagnostic assignment was determined by counting as present any symptom endorsed by either the parent (on the DISC-IV) or the teacher (“sometimes” or “often”) on the DSM-IV symptom checklist (ADHD Rating Scale or SNAP-IV). In the ADHD sample, 57% were receiving medication treatment at the time of the study (all completed the stop task after an appropriate med washout).

Control children were negative for ADHD (all types) based on the above criteria, and had 4 or fewer symptoms in either domain by the “or” algorithm. The final control sample had 4% with Oppositional Defiant Disorder, 6% with separation anxiety disorder, 1.5% with a history of major depression, 1.4% with OCD, and 2% with transient tic disorders, all by the DISC-IV. Because we did not have strong hypotheses about ADHD subtype effects, power to examine those effects would be low, and because we did not find robust subtype effects for adversity previously (Counts et al., 2005), we did not examine ADHD subtypes separately here.

For this report, we also included those children who failed to meet criteria for either ADHD or control group due to being “borderline” cases (e.g., 5 symptoms of ADHD). This enabled us to have a full range of symptomatology in the sample for regression models.

Operational Definition of Adversity—Five candidate family adversity factors were evaluated in an approach based on but not identical to that of Biederman et al (1995): Low SES, maternal and paternal psychopathology, marital conflict, and stressful events. Family size correlated *negatively* with behavior problems in our relatively higher-functioning sample and so was excluded with no change in results. We included stressful events because they have been related to elevated risk for externalizing psychopathology in other reports (Velez et al., 1989). The following measures were used.

Socioeconomic status (SES): Parental education level, occupation, and salary were obtained from a family background form completed by the mother. The *Revised Duncan Socioeconomic Index (TSEI)* (Stevens & Featherman, 1981) then was employed to code SES. The higher of both custodial parents’ SES served as our SES score.

Parental psychopathology: Parental mental disorder was evaluated using *The Diagnostic Interview Schedule-IV* [DIS-IV; Robins, et al. (1995)] in most cases. (The screen version of the *Diagnostic Interview Schedule for DSM-III-R*, Bucholz, et al., 1996, was used for 13% of cases, prior to the DIS-IV computer version becoming available in 1998. Rates of diagnoses did not differ for the two interview formats and so were combined). The DIS is a computer assisted, structured interview administered by trained interviewers. Interviewers underwent 14 hours of training with an experienced trainer. Lifetime psychiatric disorders were assessed for Generalized Anxiety Disorder, Major Depressive Disorder, Post Traumatic Stress Disorder, Alcohol Dependence, Drug Dependence, Bipolar Disorder, Antisocial Personality Disorder, and ADHD. Total number of lifetime psychiatric disorders for each parent was recorded. Parent ADHD was omitted from that total. Instead it was a covariate to determine whether adversity measures were related to child problems over and above parental ADHD. All correlations between the adversity index described below and child behavioral outcomes remained significant when controlling for parent ADHD (all $p < .019$).

Marital Conflict: Children completed the *Child's Perception of Interparental Conflict Scale* (CPIC; Grych et al., 1992) in an interview format with a project staff member. Children were told that their answers would be confidential but were alerted through the assent process to the potential need to report any disclosures of harm or abuse. Parents agreed in the consent process not to seek access to their children’s individual answers to these questions. The CPIC consists of forty-eight questions regarding marital conflict in a “true, somewhat true, false” format assessing child’s perception of the frequency, intensity, resolution, and content of their parents’ arguments. The total score ($\alpha=.92$) served as the outcome measure.

Stressful Events: Stressful events were assessed with the final section of the *Parenting Stress Index-3rd edition* (Abidin, 1995). These 17 questions ask parents whether they experienced listed stressful events (e.g., death of a relative, loss of a job) in the past twelve months. One

point was given for each item endorsed; maternal and paternal scores were averaged to obtain a single estimate of events per family.

Adversity Index: An “Adversity Index” ranging from 0–5 was created in which one point was given for the presence of each of the following: Low SES (lowest quartile of possible scores on the Duncan SEI), maternal and paternal psychiatric disorder (more than one lifetime Axis I disorder not counting ADHD, placing 24% of mothers and 28% of fathers into the “high risk” category), high levels of marital conflict (CPIC total > 1.5 standard deviations above the mean of the control group or history of parental divorce, separation, or never married), and high occurrence of stressful events (>4.5 events, equivalent to 1.5 standard deviations above our control group mean and approximately the 50th percentile in normative data from Abidin, 1995). We defined the high adversity group as those with 1 or more adversity indicators positive. Although this could result in placing some families with relatively low absolute levels of adversity in the “high adversity” group, we reasoned that (a) even moderate stress or adversity could influence families and (b) this approach would maximize statistical power by creating approximately equal cell sizes (i.e., this level approximated a median split in the sample). Of the original sample of 206 children, 109 (52.9%) were classified as low adversity and 97 (47.1%) as high adversity.

Operational Definition of Resilient and Non-Resilient Adapational Outcomes—

We operationalized symptomatic outcome in a manner specific to each symptom domain, by creating a median split for problematic (symptomatic) functioning on each domain. Thus, for attention problems, we defined the resilient group as those with high adversity yet with attention problems below diagnostic threshold ($T < 65$ on a parent and teacher attention problems rating, and below DSM-IV cutoffs for symptoms of ADHD). For ODD, and CD, resilience involved functioning below DSM-IV cutoff for each disorder based on the DISC-IV interview). As a more general test of these relationships, we also combined diagnoses, which required resilient children to be below cutoff for all three disorders. Thus, the resilient children had “normal” behavioral adjustment in the sense that they did not meet criteria for ADHD, ODD or CD and were below recommended clinical cutoffs for related behavior problems by both parent and teacher report. This resulted in 28 children classified as *resilient*, 69 classified as *vulnerable* (experienced adversity and clinical range behavior problems), 44 classified as *troubled* (low adversity, but still with a diagnosis), and 65 as *unchallenged* (low adversity, no diagnosis).

Operational Definition of Biological Resilience Characteristics

1. Genotype: Overview: Buccal DNA samples were requested and purified using a modified method by Meulenbelt (Meulenbelt et al., 1995). Three polymorphisms were studied, one from each of three candidate genes, by PCR and restriction fragment length polymorphism. The three candidate genes were the dopamine D4 receptor (DRD4), the dopamine transporter (SLC6A3), and the noradrenergic alpha-2 receptor (ADRA2A). For DRD4, the insertion/deletion promoter polymorphism was selected (Kustanovich et al., 2004). For SLC6A3, the intron 9 polymorphism was selected and typed as described previously (Barr et al. 2001). For ADRA2A The DraI polymorphism SNP was chosen (Park et al., 2005). Hardy Weinberg Equilibrium tests were performed using contingency tables. Each of these SNPs was selected for this study because they had an association with ADHD in the literature and also showed a parallel set of relationships in our sample: For DRD4, children homozygous for the insertion in the DRD4 promoter were at increased risk for ADHD ($\chi^2 = 13.51, p=.001$). For SLC6A3, the G allele of the Intron 9 polymorphism was associated with increased risk for ADHD ($\chi^2 = 6.78, p=.034$). The T allele of the DraI polymorphism of ADRA2A also conferred risk for ADHD ($\chi^2 = 7.42, p=.024$). More genotyping details follow.

Noradrenergic Alpha 2A Receptor: The region for the 3'UTR SNP, rs583668 (*DraI* RFLP), was amplified in 20 µl containing 40 ng of genomic DNA, 200 µM dNTPs, 1 µM of each primer, 1.5 mM MgCl₂, 1X PCR buffer, and 0.5 units of Taq DNA polymerase (primer sets: 5'-TACAAGGGCATGGCTCACAA-3' and 5'-CCAAGGCCAGGATTTCAACA-3') using the following cycling parameters: an initial denaturing step at 94 °C for 3 minutes followed by 35 cycles consisting of 30 seconds at 94 °C, 30 seconds at 60 °C, and 45 seconds at 72 °C, and the final extension step for 5 minutes at 72 °C. Digestion of the PCR product was performed with 10 units of *DraI* restriction enzyme at 37 °C for 2 hours. All restriction fragments were detected using 3% agarose gel stained with ethidium bromide (Park et al, 2005).

Dopamine Transporter: The *SLC6A3* intron 9 SNP rs8179029 was detected by PCR amplification using 60 ng of genomic DNA, 200 µM dNTPs, 1 µM of each primer (5'-GTCGTGCCGCCATAGAAG-3' and 5'-CTGCACACAGAGGACAGGGT-3'), 1.5 mM MgCl₂, 1X PCR buffer, and 0.5 units of Taq DNA. The cycling parameters were: initial denaturation for 4 minutes at 94 °C; 35 cycles consisting of 40 seconds at 94 °C, 40 seconds at 57°C, and 30 seconds at 72 °C; and the final extension step of 5 minutes at 72 °C. One ul of buffer 4 (New England BioLabs) was added to the PCR reaction and the amplified DNA was digested by 10 units of *PflFI* restriction enzyme at 37°C overnight. The DNA was detected in a 3% agarose gel stained with ethidium bromide (G allele →191 bp, A allele →173) (Barr et al., 2001).

Dopamine D4 Receptor: The DRD4 120-bp tandem repeat polymorphism was assayed according to the method of McCracken (McCracken et al., 2000) with minor modification to the amplification parameters. A 20 µl reaction mixture containing 20 ng of genomic DNA, 200 µM dNTPs, 1 µM of each primer, 1.5 mM MgCl₂, 1X PCR buffer, and 0.5 units of Taq DNA polymerase with the same primer sets (5'-GTTGTCTGTCTTTTCTCA TTGTTTCCATTG-3' and 5'-GAAGGAGCAGGCACCGTGAGC-3') was amplified by an initial denaturing step at 94 °C for 3 minutes followed by 35 cycles consisting of 30 seconds at 94°C, 30 seconds at 61° C, and 1 minute at 72°C, and the final extension step for 7 minutes at 72°C. After the amplification, the DNA was detected in 1.5 % agarose gel with expected product sizes of 429 bp for the short allele (deletion) and 549 bp for the long allele (insertion).

Creation of a Composite High Risk Genotype Index: Based on the association results for each SNP, genotypes for DRD4, SLC6A3, and ADRA2A were classified as “high risk” or “low risk.” For DRD4, the homozygous insertion genotype was classified as high risk, while the heterozygous insertion/deletion and the homozygous deletion genotypes were labeled low risk. For SLC6A3, the high risk genotypes included those with the ‘G’ allele (A/G or G/G), while the homozygous A/A genotype was classified as low risk. For ADRA2A, those with the ‘T’ allele (C/T or T/T) were classified as having the high risk genotype and those with the C/C genotype were classified as having the low risk genotype. The number of high risk genotypes was computed for each child and served as an index of total genetic risk.

II. Neuropsychological Response Inhibition: Response inhibition, or suppression of a prepotent motor response, is postulated to require activation of a circuit linking basal ganglia and orbitofrontal cortex (Casey et al., 2002) and is often suggested as an ADHD endophenotype (Barkley, 1997; Crosbie & Schachar, 2001). Performance in adults involves the right inferior frontal cortex and basal ganglia (Aron et al., 2003). In our study it was operationalized with the tracking version of the StopTask using the same procedures as Logan et al. (1997) and Nigg (1999). The Stop Task is a computerized choice reaction time task. On a majority of trials, the child chooses whether to press the “X” or the “O” key as rapidly as possible. On 25% of trials, a brief tone indicates that the child should not respond. The timing of these tones is varied, with some tones occurring almost immediately after the onset of the X or O stimulus (making it relatively ‘easy’ to stop) and others occurring later (making it

relatively difficult to stop). In a stochastic tracking procedure, the timing of each tone is earlier or later, depending on whether the child successfully inhibited their response on the last stop trial. In this way, the probability of successful inhibition is maintained at approximately 50%. This enables estimation of the amount of warning time the child needs to stop successfully (termed stop signal reaction time or SSRT). Following two blocks of 32 practice trials, four blocks of 64 trials were administered. In the tracking version of this task, SSRT, the index of inhibitory control, is estimated by subtracting mean stop signal latency from mean go response time (Logan et al., 1997). Simulation data show the estimated stop signal RT to be reliable with 4 blocks of trials and robust to violations of the statistical and theoretical assumptions underlying the task (Band, van der Molen, & Logan, 2003). Cronbach's alpha was $> .88$ for SSRT.

Handling of Missing data: Data were missing to varying degrees due to tester error or changes in study protocol over the years of these projects. Maximum likelihood imputation methods are viewed as superior to older regression methods of estimating missing data (Schafer & Graham, 2002). We imputed missing data using the Estimation Maximization algorithm, which is one form of maximum likelihood imputation ($< 7\%$ imputed data points). The average change in correlations among the variables used in the analysis due to imputation was $r < .01$.

Effect size: For all relevant analyses, we report effect size either in the form of r-squared, or for ANOVA, as partial eta-squared (η^2), interpreted as the percent of variance carried by a given effect.

Results for Study 1

Preliminary Exploration of the Data

Table 1 provides descriptive information for Sample 1 broken down into ADHD and non-ADHD groups. The table indicates that the ADHD and non-ADHD groups differed as expected on the basis of symptom counts, as well as family adversity and genetic and response inhibition measures. Also as expected, more ADHD children came from the high adversity families.

Table 2 provides correlations among the risk and protective factors we measured. As it shows, these measures were generally non-overlapping. There was virtually no association between adversity and either genetic risk or response inhibition, enabling us to meaningfully look at both genetic and neurocognitive characteristics as distinct potential protective characteristics against adversity in relation to behavioral adjustment. To confirm this, we regressed each behavioral outcome on adversity and genotype, and then their interaction. This analysis confirmed that adversity was related to outcome independently of genotype (in all instances, $p < .05$ with genotype in the model). Genotype and adversity did not interact for ADHD ($p = .21$ for hyperactivity, $p = .48$ for inattention symptoms) or for ODD ($p = .10$). It did interact for CD ($p = .001$); adversity predicted presence of CD only in the presence of the high risk genotype. We conducted the same analysis for family adversity and response inhibition: in each instance, adversity predicted outcome with SSRT controlled (all $p < .05$) and did not interact with SSRT (all $p > .55$). The interaction between adversity and SSRT was significant when predicting CD, ($p < .001$), such that effects of adversity were greater when response inhibition was poor.

Higher adversity was related at the zero order level to more child symptoms of inattention ($r = .28, p = .001$), hyperactivity-impulsivity, ($r = .32, p < .001$), oppositional defiant disorder ($r = .33, p < .001$) and conduct disorder ($r = .42, p < .001$). Within the ADHD domain, a regression with both inattention and hyperactivity-impulsivity predicting adversity revealed that only hyperactivity-impulsivity ($\beta = .35, p < .001$) was related to adversity, whereas inattention was not independently related ($\beta = .04, p = .7$). Within the externalizing domain, a regression with both conduct disorder symptoms and ODD symptoms predicting adversity revealed that only

CD symptoms were independently related to adversity ($\beta=.36$, $p<.001$) whereas ODD symptoms were not ($\beta=.12$, $p=.12$). When CD symptoms and total ADHD symptoms were entered into a regression, however, both were independently related to adversity (ADHD, $\beta=.15$, $p=.031$, CD, $\beta=.36$, $p<.001$).

Primary Analyses

These background analyses supported our interest in looking at protective factors against adversity in the realms of genotype and response inhibition. We therefore proceeded to analyze characteristics of resilient children, who were exposed to high adversity yet showed normal levels of behavioral adjustment, taking into account their potential for all three disorders.

Table 3 provides descriptive statistics for the sample re-stratified according to our four outcome groupings created on the basis of adversity and resilience. As the table indicates, the resilient group has normal levels of behavior problems compared to the troubled group, and similar levels to the unchallenged group. Patterns of group differences here were as expected and helped to confirm our definition of the resilient and other groups.

To evaluate whether genotype and response inhibition were protective factors supporting resilience, we were primarily interested in the two-group comparison between resilient and vulnerable children. However, to evaluate whether these same features were resource characteristics (helping a child avoid disorder regardless of adversity), the two-group comparison between unchallenged and troubled children is most relevant. We preceded these planned comparisons with omnibus 4-group ANOVA models to evaluate whether any group differences existed. All models were then rechecked with sex of the child as a second factor, to assess possible interactions between adaptation status and sex of the child (Biederman et al., 2005; Counts et al., 2005). When those interactions were non-significant, we report only the single factor model comparisons (shown in Table 3 by subscripts). When interactions with sex of the child were significant, we report those models in the text in addition.

With regard to these pairwise comparisons, then, the bottom portion of Table 3 provides the results of an omnibus ANOVA comparing the 4 groups on each measure. It shows that the groups differed in symptomatology in the four symptom domains, as well as in risk and protective factors, including genetic risk and response inhibition. Subscripts in the table indicate results of post-hoc pairwise comparisons by Tukey test (to correct for family-wise error), and show that the resilient and vulnerable groups differed on genotype ($\eta^2=.11$, $p=.012$) and SSRT ($\eta^2=.12$, $p=.009$) but did not even approach differences on IQ ($\eta^2=.002$, $p=.970$).

By definition, unchallenged and troubled groups differed on all the symptom measures. However, they did not differ on genotype ($\eta^2=.08$, $p=.081$) or SSRT ($\eta^2=.07$, $p=.076$), indicating that the protective effects are only differentiating under circumstances of high adversity. They also did not differ on IQ ($\eta^2=.05$, $p=.075$), although this effect was qualitatively much larger than the effect between resilient and vulnerable groups. However, when we examined the troubled versus unchallenged group in a model that included a factor for sex of the child, the group x sex interaction was significant [$F(1,85)=6.93$, $p=.01$, $\eta^2=.075$]. For boys, there was no significant difference between the unchallenged and troubled groups in the number of risk genotypes [$F(1,64)=1.79$, $p=.19$, $\eta^2=.027$]. Yet, for girls, this difference was significant [$F(1,21)=18.64$, $p<.001$, $\eta^2=.47$]. Examination of the means revealed that girls in the unchallenged group had significantly fewer high risk genotypes ($M=.60$, $SD=.52$) than girls in the troubled group ($M=1.77$, $SD=.73$). Thus, genotype was a general protective factor in the presence of high adversity, but in the presence of low adversity, the risk genotype was a risk factor only for girls.

Finally, we rechecked these results separately for ADHD, ODD, and CD. To do so, we re-stratified the sample according to whether children exposed to adversity had resilient adaptations to the development of these disorders (i.e., the resilient vs. vulnerable contrast). For ADHD, we divided children into those above and below diagnostic cutoffs on ADHD; resilient, $n = 48$; troubled $n = 48$); for ODD we divided children into those above and below ODD diagnostic cutoffs; resilient, $n = 45$, vulnerable $n = 51$); and for CD, in the same manner (the n 's were: resilient $n = 41$, vulnerable, $n = 55$). Those results (resilient versus vulnerable) showed that genotype was protective against ADHD ($F[1,74]=6.19, \eta^2=.11, p=.004$); ODD ($F[1,74]=9.32, \eta^2=.11, p=.003$); and CD ($F[1,74]=6.67, \eta^2=.08, p=.012$). Response inhibition was protective against ADHD ($F[1,72]=9.52, \eta^2=.12, p=.003$) and CD ($F[1,72]=2.94, \eta^2=.05, p=.045$), but not ODD ($F[1,72]=2.76, \eta^2=.04, p=.10$). Full scale IQ did not differ between resilient and vulnerable groups in any analysis (all $p>.25$).

We checked for interactions among SSRT and genotype; none were found. We also checked whether SSRT and genotype both independently related to outcome; they did, with no evidence that one was mediating the other.

Study 2. Replication of Response Inhibition Protective Effects on Adversity

In Study 2, we had an opportunity to test the replicability of the finding that strong response inhibition was a protective factor against psychosocial adversity in the emergence of symptomatology in a different sample, one with somewhat greater psychosocial adversity. The longitudinal data also available for Sample 2 allowed us to relate early adversity and behavioral problems to later symptomatic outcome rather than simply examining these relationships cross-sectionally. An earlier paper using a subset of this sample examined the relationship of family adversity to behavioral outcome in initially 3–5 year old children but did not examine the role of response inhibition or genotype (Zucker et al., 2003).

METHOD

Participants—Participants were 374 children (254 boys, 120 girls) from 260 families who had completed the MLS Wave 5 outcome assessment (when children were 15–17 years of age) of this ongoing, prospective, multi-wave study. At three year intervals, the study continues to assess a community sample of families with high levels of alcohol and other drug use disorder (AUD/DUD), along with a community contrast sample of families drawn from the same neighborhoods but without the high substance abuse profile (Zucker et al., 2000). Multiple full biological siblings were included per family when present. We limited this analysis to male or female target children (i.e., the main male and female probands entering the study for each family) who had available behavioral outcome data from at least one informant (parent or teacher) at Wave 5, had available family adversity index data at Waves 1, 2, or 3, and had completed the response inhibition measure at least at one wave (Wave 4 (children 12–14) or Wave 5). This provided the sample of 374 children with available complete data from 260 families. These families represented 86% of the 302 families initially recruited for the study when the children were preschoolers; those included did not differ from those excluded with regard to percentage of parents who were alcoholic, socioeconomic status, or level of child total behavior problems on the Teacher Report Form of the Child Behavior Checklist (all $p>.10$). Among the 260 families, 114 families had two children (male and female target child) in the data set; and 146 had one child. This sample produced 180 children of low family adversity, (88 troubled, 92 unchallenged) and 194 of high adversity (75 resilient, 119 vulnerable; see Table 4).

The sample was initially recruited to include a group of children at elevated risk for later alcohol and other drug use disorders (AUD/DUD) due to alcoholism in the father. Men were initially identified through a network covering all courts in a four county wide area. All men with [a]

a drunk driving conviction involving minimum blood alcohol concentrations were potential study candidates. In addition, they were required to [b] make a Feighner et al. (1972) diagnosis for probable or definite alcoholism, [c] have at least one son between three and five years of age, and [d] be living with the child and his biological mother at the time of enrollment. Mother's AUD status was free to vary but presence of child fetal alcohol effects was exclusionary (n=146 court-referred fathers). A contrast group of families who resided in the same neighborhoods as the alcoholic families but with no substance abuse history was also recruited using door-to-door canvassing (n=95). In addition, an intermediate risk group (n=61) was provided by recruiting all families with an alcohol abuse/dependence diagnosis who were found during the community canvass. All parents were re-diagnosed using DSM-IV criteria as described later. For more details of study procedures and recruitment see Zucker et al. (2000). Several years following initial recruitment, all siblings within +/- 8 years of the primary male target child were also recruited and assessed at the appropriate age to correspond to the data collection waves described earlier. Full family assessments involving both parents and participating children then occurred at three-year intervals: age 3–5 (Wave 1), age 6–8 (Wave 2), age 9–11 (Wave 3), age 12–14 (Wave 4), and age 15–17 (Wave 5). Each sibling completed the appropriate wave assessment when they reached the age for that wave, so that siblings might complete the same wave in different years. For more detail on the study, see Zucker et al. (2003) and Nigg et al. (2004).

Operational Definition of Adversity—We defined adversity in an analogous manner to Study 1, but with slightly different specific measures. At Wave 1, Wave 2, and Wave 3, we obtained the following measures of psychosocial adversity.

Socioeconomic Status (SES) was assessed using the Duncan TSEI in a manner identical to that in Study 1. Family SES scores were pooled across waves 1–3 (alpha=.91)

Family conflict: Family conflict was rated by both parents on the Moos Family Environment Scale (FES; Moos, 1974; Moos & Moos, 1976) Conflict subscale. We pooled maternal and paternal reports across waves 1–3 (alpha=.86). The FES is an empirically based taxonomy of family social environments as perceived by the family members themselves. It requires fifth or sixth grade level reading skills. The FES consists of a number of scales that describe dimensions of the family climate with which each individual member must cope. The instrument has been subjected to extensive reliability and validity studies. The Conflict subscale assesses the extent of open aggression, anger, and conflicted interactions among family members (Kuder-Richardson=.75, 8-week test-retest reliability=.85) (see Sanford et al., 1999).

Family stressful events were rated by both parents on the 40 item Oregon Social Learning Center *Family Crisis List* (Patterson, 1982) in the following categories: Work, Home, Financial, School, and Relationship. This list of family troubles was developed by the staff of the Oregon Social Learning Center to record specifically family related stressors, and to document the interaction between stress and patterns of family coerciveness. We pooled all of these individual scale reports across both parents at waves 1–3 (alpha=.85) to obtain a composite family stressor/crisis score.

Parent psychiatric disorder: We assessed Axis I maternal and paternal psychiatric disorders in the past year using the complete DIS-IV at Waves 1–3. Number of psychiatric disorders were totaled at each wave and averaged across waves (alpha=.97 for maternal disorders, .99 for paternal disorders).

Adversity Index: We created an adversity index in a manner similar to Sample 1, as follows. First, we assigned one point for each of the following (a) SES is in bottom quartile, (b) mother

has more than 1 Axis I disorder, (c) father had more than 2 Axis II disorders (median for this sample), (d) family conflict score > 75th percentile for the sample, (e) family crisis score > 75th percentile for the sample. Low adversity families were defined as those ≤ 2 of these risk factors, and high adversity had ≥ 3 of these risk factors present. This was equivalent to a median split on the adversity index in this sample, again maximizing cell size numbers. The higher cut point in this second sample as compared to Sample 1 reflects the fact that this sample has greater risk and greater overall adversity. It also enabled us to evaluate whether the cognitive control results would replicate when a higher level of adversity was required. This resulted in the numbers classified as high and low adversity as noted earlier and detailed in Table 4 We also created a dimensional total-adversity score, which could be correlated with other predictor variables.

Symptomatic Outcomes and Resiliency

Overview: Parents completed the DISC-IV at Wave 5 to assess ADHD, ODD, and CD. Parents and teachers completed the CBCL and TRF respectively; we evaluated the attention problems scale (which includes inattentive, impulsive, and hyperactive symptoms) as a proxy for ADHD-related problems and the aggression and delinquency scales to provide normative data on antisocial behaviors. We defined our outcome groups in the same manner as in study 1 (described below) and used these rating scales to create supplemental composite measures.

Operational Definition of Resiliency: To parallel the definition of resilient that was utilized in study 1, we defined resilient as follows. Resilient children were defined as those who, by Wave 5 (ages 14–17), were (a) below DSM-IV cutoffs for number of ADHD, ODD, and CD symptoms by maternal DISC-IV interview AND (b) were rated at $T < 65$ on teacher TRF attention problems and mother CBCL attention problems. Using these cutoffs we likewise defined our vulnerable (had at least one disorder), troubled, and unchallenged groups.

Protective Factors in Child Neuropsychological Functioning

Response Inhibition: Response Inhibition was assessed exactly as in Study 1, using the same tracking version of the Stop Task. The task was administered at Waves 4 and 5, but because some children only completed it at one wave, we utilized a Stop Signal RT composite across Waves 4 and 5 ($\alpha=.93$) as the index of response inhibition. A higher score indicates a weaker inhibitory ability.

IQ: As an alternative protective factor, IQ was assessed at Wave I with the *Stanford-Binet* form L-M and at Waves 2 and 4 with the *WISC-R* (Wechsler, 1974). A composite IQ score was created by averaging IQ across all available assessments, after standardizing within wave to correct for cohort-wide or instrument-wide variation.

Missing Data, Effect size, and Data Analysis: Missing data and effect sizes were handled identically to Study 1. Again, we analyzed data with ANOVA followed by post-hoc pairwise comparisons. Models were rechecked with sex of the child as a factor and if there as an interaction between sex of the child and adaptation group, those results were reported.

Results of Study 2

Preliminary Exploration of the Data

As in Sample 1, the family adversity index was related to symptoms of ADHD (DISC ADHD symptoms, $r=.18$, $p=.003$, TRF attention problems, $r=.35$, $p<.001$, maternal CBCL attention problems, $r=.60$, $p<.001$), DISC ODD symptoms ($r=.50$, $p<.001$), and DISC CD symptoms ($r=.32$, $p<.001$) (these effects were not merely due to source variance; TRF aggression $r=.46$, $p<.001$; TRF delinquency, $r=.39$, $p<.001$). When DISC CD and ODD symptoms were entered

in a model at the same time to predict the adversity index, CD independently related to adversity ($\beta=.21$, $p=.003$) but ODD fell just shy of association ($\beta=.13$, $p=.056$). When CD and ADHD were entered together, only CD was significant ($p<.01$) and ADHD was not ($p=.10$); however we were concerned that overlapping method variance might have accounted for this (ADHD and CD symptoms, $r=.31$, $p<.001$), so we considered teacher attention problems as well (correlation with parent reported CD symptoms, $r=.08$, $p=.30$). In that model, both CD symptoms ($\beta=.24$, $p<.001$) and TRF attention problems ($\beta=.14$, $p=.041$) were independently related to adversity, partially replicating the effects noted in Study 1. Table 4 shows the means of all of the relevant measures for each adaptation group classification. Note that the resilient group has the best response inhibition of all groups, but not the best IQ. Also of note, SSRT was related to symptoms of inattention (TRF attention problems, $r=.19$, $p<.01$; CBCL attention problems, $r=.13$, $p<.05$) and DSM-IV ADHD symptom total ($r=.12$, $p<.05$) but not to DISC-rated symptoms of ODD ($r=-.03$, $p=ns$) or CD ($r=.06$, $p=ns$).

Primary Analysis

Because we were replicating, we had a strong directional hypothesis for our response inhibition effects in Study 2. We therefore allowed a 1-tailed significance criterion and did not include a correction for familywise error for our two planned orthogonal pairwise comparisons (resilient to vulnerable, and challenged versus troubled; Keppel & Wickens, 2004). The bottom portion of Table 4 shows the means for FSIQ and SSRT; the 4-group test, as shown in the table, was shy of significance for SSRT (1-tailed $p=.054$), but we chose to proceed with our planned comparisons. When we did so, the resilient group had slower SSRT than the vulnerable group ($F[1,192]=3.11$, $\eta^2=.016$, $p=.038$, 1-tailed), though the effect was quite small. The one-tailed test was moot for the troubled versus the challenged group, as inspection of the group means indicates that the troubled group was slightly *faster* (better) than the unchallenged group. IQ was lower in the groups facing higher adversity, and in this sample was lower in the vulnerable than in the resilient group ($\eta^2=.023$, $p=.017$, 1-tailed), but did not differ between the unchallenged and the troubled ($F<1.0$), contrary to sample 1 results. Thus in this sample the resilient group was characterized by superior response inhibition and higher IQ.

Because the sample includes multiple children per family, therefore violating the independence assumption for the general linear model (ANOVA), we rechecked results using a multi-level modeling procedure in which family was the level 1 variable, individual SSRT was the level 2 predictor, and adaptation group was the outcome variable. The pair-wise effect of better response inhibition in the resilient than the vulnerable group was marginally significant at $p=.055$ (1-tailed).

Finally, we checked results separately for attention problems, ODD, and CD as outcomes. Again, we re-stratified the sample according to whether children exposed to adversity were resilient to developing ADHD (dividing children into those above and below diagnostic cutoffs on the DISC-IV, resilient, $n = 85$; vulnerable $n = 109$); ODD (dividing children into those above and below ODD diagnostic cutoffs; resilient, $n = 121$, troubled $n = 73$); and CD (in the same manner, resilient $n = 130$, vulnerable, $n = 64$). Results indicated that response inhibition was protective for ADHD ($\eta^2=.022$, $p=.048$, 1-tailed; in the multilevel model this effect remained significant at $p=.043$). The resilient and vulnerable groups did not significantly differ on SSRT when using ODD and CD symptoms as outcomes ($p=.25$ and $p=.17$ respectively).

DISCUSSION

This study examined potential resiliency factors for child ADHD, ODD, and CD, at two levels of analysis: genotype, and neurocognitive response inhibition. Doing so pursues a recent interest in the field in identifying biological moderators and protective factors in relation to adversity and risk. A main finding was that both genotype and strong response inhibition

abilities provided significant protection against the manifestation of ADHD in the presence of moderate to high adversity in the family. Moreover, the response inhibition effect replicated in two diverse samples, one cross-sectional, the other longitudinal, although the effect in the second sample was small and restricted to ADHD. Results for the externalizing (ODD and CD) disorder analyses were both more complex and less compelling, albeit in the same general direction. The effect of response inhibition was not reliable for oppositional defiant disorder and emerged for conduct disorder only in Study 1. IQ itself was not a replicable protective characteristic in Study 1 but did emerge in the more at-risk second sample.

The two data sets had important differences designed to maximize the reach of our conclusions. The ADHD-sample was younger, had relatively low adversity overall, and was selected based on presence of ADHD and controls. The second sample was a much higher risk sample, with lower SES and considerably more parental psychopathology, which was selected to maximize risk for antisocial and substance abuse outcomes. These sample differences likely account for the differences in results for antisocial related outcomes, which were related to low IQ only in the high risk sample (which had significant rates of conduct problems) and to response inhibition only in the low risk sample (which had lower rates of frank conduct problems) and a greater range of variation in response inhibition as measured by the SSRT.

Yet, it was striking that in both of these data sets, family adversity was associated with increased risk not only for conduct problems and aggression, but also for ADHD and ADHD-related symptoms. This effect was present despite the diversity of the analyses, with one data set being cross sectional, the other longitudinal, one assessing children's outcomes in childhood and the other assessing outcomes in adolescence, and one study with a relatively low risk sample selected for presence of ADHD, and the other with a relatively high risk, low SES sample selected for probability of antisocial and substance use outcomes. Thus, these basic associations between family adversity, child ADHD, and externalizing behavior problems were robust and generalizable. Moreover, the Study 2 analyses, involving a prospective relationship between family adversity and symptomatic outcome imply that the relationship may be causal, involving the emergence of symptomatology with increasing exposure. However, the analyses carried out here do not test this as an epigenetic process, where symptom expression is changed by the exposure. This remains as a next step question to be addressed.

This basic finding is consistent with the existing literature for both groups of behavior problems (see Biederman et al., 2005; Counts et al., 2005). Despite its much-touted high-heritability, ADHD, like CD, is also responsive to environmental adversity. It is important to recognize that some of this adversity could well be related to gene-environment correlations, such that genetically mediated parental dysfunction may contribute to the adverse events as well as the child disorder. Given that we did not have genotyping data available for Sample 2, we were not able to evaluate this hypothesis definitively in a prospective manner.

At the same time, in the face of moderate adversity (defined here as one or more major risk factors in the home in the first sample) or moderate-to-high adversity (two or more risk factors, in the higher-risk second sample), biological characteristics of the child provided broad protection. Those children who escaped all forms of externalizing psychopathology (including ADHD) had protective genotypes or had strong response inhibition or both. Notably, genotype and response inhibition were uncorrelated and did not interact, so these appear to be two distinct neurobiologically based protective mechanisms.

What might these neurobiologically based mechanisms be? Although these comments are necessarily speculative, we can suggest a framework. It may be that the catecholamine genes analyzed here, which are expressed primarily in prefrontal cortex, are involved in executive functions such as working memory, that were not assessed here. In turn, response inhibition,

which may depend on integrity of basal ganglia and striatum, may be influenced by other genes we did not evaluate (e.g., serotonin genes), or by environmental risk factors.

The composite genotype risk index we used was derived from three genes that express in prefrontal cortex (among other areas), including markers on the dopamine D4 receptor gene, the dopamine transporter gene, and the noradrenergic alpha-2 receptor gene. The composite genotype risk score was strongly related to ADHD, not surprisingly, because the genes included in the index have been heavily researched for their potential ADHD risk. However, the composite genotype index operated to provide protection not only against ADHD, but also against CD and ODD in high family adversity environments. This suggests that genetic influence on functioning of prefrontal cortex may be involved in overcoming psychosocial adversity.

Response inhibition is much-examined as a risk factor for externalizing psychopathology in its own right. It involves functioning of a right-lateralized prefrontal-subcortical network that includes the inferior frontal gyrus and probably the caudate. That it functions as a protective factor when its functioning is strong is a novel, albeit not extremely surprising finding in light of its associations with ADHD. This finding adds to our understanding of the nature of this relationship. It illustrates that strong functioning on this ability may be as important to child outcomes as weak functioning, at least in certain contexts. Whereas weak functioning increases risk for psychopathology (and may interact multiplicatively with family risk; Nigg et al., 2005), strong functioning on this parameter appeared across two large samples to protect against effects of adversity, although effect sizes of that protective effect were fairly small and would not have been detected in smaller samples. Nonetheless, these results should stimulate the interest in early intervention programs designed to strengthen response suppression and related control abilities, which may enable children to resist deleterious effects of environmentally adverse events.

These findings are consistent with a multipathway conception of ADHD, in which one route involves moderate to high levels of family adversity, which may disrupt prefrontal cortical functions necessary for adequate coping and regulation. This disruption likely occurs because the consolidation of regulatory abilities, via neural pruning during early childhood, depends heavily on socialization experiences (Cicchetti, 2002). These experiences are likely disrupted in families undergoing greater adversity. It is clear that early stressful experiences can alter neural development in regions such as hippocampus, amygdala, and frontal cortex (Teicher et al., 2003) that are important in inhibitory control. In the case of serious trauma the route for these effects apparently is via neurobiological alterations in the HPA stress-response system. In the case of generalized adversity, we would suspect effects due to socialization breakdown and failure of regulatory systems, instantiated in prefrontal cortex and its associated circuitry, to consolidate. Data to evaluate such neural effects in cases of generalized adversity, and their mediation via socialization breakdown, would be of interest.

Yet these effects emerge only in vulnerable children. Some children are able to avoid this route by virtue of a protective genotype, and/or strong cognitive control abilities. As was clear from the descriptive data in Tables 3 and 4, other routes to ADHD, as well as ODD and to a lesser extent CD, do not require adversity in order to appear.

Limitations of this study should also be noted. We did not examine genes that might be more closely related to conduct problems and aggression (notably, MAOI or 5HTT related genes). We also did not examine a range of other cognitive or emotional measures such as working memory, reinforcement response, or arousal, which might be important protective factors for ADHD, CD, or ODD and might supersede response inhibition. As noted above, we also were not able to evaluate the genetic relationships longitudinally, which has required us to only

speculate about the detailed nature of the prospective effects. Nonetheless, the effects reported here for genotype and response inhibition demonstrate an approach to biological resilience characterization and suggest two such characteristics in relation to ADHD and associated externalizing problems.

In conclusion, when children are faced with moderate to high family adversity, they appear to be protected against developing ADHD and conduct disorder by at least two neurobiological mechanisms involving prefrontal cortex and associated neural connections. One is a safe catecholamine-pathway genotype; the other is effective and efficient response inhibition. It is notable that although these characteristics were not necessarily protective factors in the absence of adversity, they were effective protective factors when adversity was present. Future directions for work should involve a wider examination of genotypes and cognitive operations to identify patterns of cognitive mediation of genetic effects. A more precise specification of the intermediary neurophysiological model for these effects is also needed.

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Table 1
Baseline ADHD and Control Sample Characteristics for Study 1

	Control	ADHD	p-value
N	72	134	
% Boys	59.7	69.4	.170
% White	73.3	71.6	.762
Mean Age (Months)(SD)	115.27 (14.41)	114.08 (15.06)	.590
Mean Inattention Sx	.89 (1.27)	7.84 (1.48)	.000
Mean Hyperactivity Sx	.69 (1.05)	6.04 (2.96)	.000
Mean ODD SX	.58 (1.17)	3.76 (2.69)	.000
Mean CD SX	.26 (.65)	1.25 (1.68)	.000
% ODD	4.3	52.0	.000
% CD	3.2	12.2	.016
FSIQ	111.57 (15.24)	104.93 (14.97)	.003
% DRD4 "high risk genotype"	48.5	72.0	.019
% DAT 1 "high risk genotype"	20.0	35.3	.006
% A2A "high risk genotype"	24.3	43.2	.002
High Risk Genotype Composite	.92 (.68)	1.47 (.85)	.000
SSRT	322.17 (108.14)	418.42 (155.69)	.002
FamilyAdversity	.21 (.20)	.32 (.27)	.006
% High Adversity	38.9	51.5	.04

Note. Behavioral symptoms scores indicate number of DSM-IV symptoms based on parent structured interview (DISC-IV). Total genetic risk is as described in the text.

Table 2

Correlations Among Risk Factors for Study 1

	FyAdversity	DAT1	DRD4	ADRA2A	SSRT	Genotype
FyAdversity	1.00					
DAT1	.023	1.00				
DRD4	.062	.020	1.00			
ADRA2A	.180*	.004	.014	1.00		
SSRT	.133	.048	.040	.002**	1.00	
Genotype	.150	.584**	.601**	.580**	.118	1.00

Note. FyAdversity-Family Adversity; here scored here as a continuous variable. DAT1 = Dopamine transporter gene, DRD4 = Dopamine D4 receptor gene, ADRA2A = Alpha-2A receptor gene, SSRT = stop signal reaction time, genotype = summative high risk genotype composite. N ranges from 161 for SSRT correlations to 206 for all other variables.

* $p < .05$.

** $p < .01$

Table 3

Mean Scores and Group Comparisons for Four Adaptation Groups in Study 1.

	Low Adversity		High Adversity		4-group p-value
	Unchallenged (Low Sx)	Troubled (High Sx)	Resilient (Low Sx)	Vulnerable (High Sx)	
Descriptive Data					
N	44	65	28	69	
% Boys	61.4	61.5	50.0	63.8	.137
% White	73.0	75.5	77.8	64.2	.284
Age (Months)	114.7 (13.9)	113.8 (13.8)	116.4 (15.6)	113.9 (15.8)	.980
Adversity Score	.08 (.10) _a	.09 (.10) _a	.41 (.13) _b	.53 (.19) _b	< .001
Inattention Symptoms	1.09 (1.44) _a	7.65 (1.99) _b	1.04 (1.48) _a	7.83 (1.63) _b	< .001
Hyperactive Symptoms	.53 (.83) _a	5.58 (3.00) _b	.87 (1.21) _a	6.49 (2.83) _b	< .001
ODD Symptoms	.36 (.87) _a	3.43 (2.42) _b	.50 (.88) _a	4.45 (2.65) _b	< .001
CD Symptoms	.14 (.46) _a	.88 (1.27) _a	.33 (.57) _a	1.82 (2.08) _b	< .001
% with ADHD	6.8	95.4	3.6	98.6	< .001
% with ODD	0	53.8	0	53.6	< .001
% with CD	0	7.7	0	20.3	.001
Putative Protective Factors					
FSIQ	114.2 (16.2) _a	107.2 (14.0) _{ab}	103.5 (12.3) _b	101.9 (15.1) _b	< .001
# Risk Genotypes	1.00 (.75) _{ab}	1.44 (.76) _{bc}	.86 (.56) _a	1.48 (1.91) _c	.001
SSRT	330.17 (118.40) _{ab}	404.60 (147.61) _{bc}	308.86 (76.56) _a	426.82 (165.90) _c	.001

Note. Different subscripts indicate $p < .05$ on post-hoc comparison by Tukey test. The primary contrasts of interest are the two groups with high adversity backgrounds, viz, resilient and vulnerable.

Table 4
Mean Scores and Group Comparisons for Adaptation Groups Stratified by Risk and Symptomatic Outcome for Study 2

	Low Adversity		High Adversity		p-value
	Unchallenged (Low Sx)	Troubled (High Sx)	Resilient (Low Sx)	Vulnerable (High Sx)	
Descriptive Data					
N	90	90	64	130	
% Boys	74.4	62.2	78.8	64.8	.059
% White	100	100	100	100	----
Adversity Score	.11 (.10) _a	.10 (.10) _b	.52 (.14) _a	.54 (.17) _b	< .001
TRF Inattention	51.56 (3.07) _a	54.67 (4.73) _b	51.92 (3.46) _a	55.75 (6.25) _b	< .001
CBCL Inattention	51.02 (2.40) _a	53.83 (5.71) _b	51.53 (3.20) _a	54.76 (6.89) _b	< .001
ADHD Symptoms	.49 (1.19) _a	2.68 (4.74) _b	.47 (1.01) _a	4.92 (5.43) _b	< .001
ODD Symptoms	.36 (.84) _a	1.30 (2.20) _b	.62 (1.26) _{ab}	2.37 (2.72) _c	< .001
CD Symptoms	.04 (.21) _a	.43 (1.36) _{ab}	.14 (.39) _a	2.37 (1.78) _b	< .001
Putative Protective Factors					
FSIQ	.31 (1.08)	.40 (1.06)	.001 (.84)	-.29 (1.02)	< .001
SSRT	267.51 (78.40)	259.94 (86.52)	262.01 (77.18)	284.54 (86.67)	.054

Note. ADHD, ODD, and CD symptoms from DISC maternal report. TRF and CBCL-maternal report are T-scores. FSIQ is a z-score because IQ tests were standardized within wave in order to create the IQ composite, as explained in the text. Table does not show post hoc Tukey tests for the protective factors because those were analyzed with planned comparisons as explained in the text.