DISRUPTED EFFECTIVE CONNECTIVITY BETWEEN THE MEDIAL FRONTAL CORTEX AND THE CAUDATE IN ADOLESCENT BOYS WITH EXTERNALIZING BEHAVIOR DISORDERS

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Studies addressing the neural correlates of criminal behavior have focused primarily on the prefrontal cortex and the amygdala. However, few studies have examined dopaminergic inputs to these or other brain regions, despite the fact that central dopamine (DA) dysfunction is associated with both trait impulsivity and novelty seeking. Given long-standing associations between both of these personality traits and externalizing psychopathology, the authors examined effective connectivity between the caudate nucleus and the anterior cingulate cortex, two areas that rely on DA input to facilitate associative learning and goal directed behavior. Dysfunction in top-down and bottom-up processing within this dopaminergically mediated frontostriatal circuit may be an important biological vulnerability that increases one's likelihood of engaging in delinquent and criminal behavior. When compared with controls, reduced effective connectivity between these regions among adolescents with externalizing psychopathology was found, suggesting deficiencies in frontostriatal circuitry.

Keywords: dopaminergic system; caudate nucleus; anterior cingulated cortex; psychopathology; crime

The propensity to engage in criminal behavior presumably results from complex interactions between predisposing biological vulnerabilities and potentiating environmental risk factors. Although the study of biological vulnerabilities has increased only recently, there is a long history in the externalizing behavior literature of examining environmental risk factors for delinquency and criminality. Risk factors that predict escalation of delinquent behavior include associations with deviant peers (Warr, 1998), modeling by parents (Dogan & Conger, 2007), persistent poverty in early childhood (McLeod & Shanahan, 1996), physical maltreatment (Jaffee, Caspi, Moffitt, & Taylor, 2004), and coercive parenting practices (Patterson, 1982; Snyder, 1977), among others.

In contrast, it has been difficult to study central nervous system (CNS) vulnerabilities to antisocial behavior until quite recently. Nevertheless, behavioral genetics studies indicate that about 80% of the variance in externalizing conduct is accounted for by a single heritable trait (Hicks, Krueger, Iacono, McGue, & Patrick, 2004; Krueger et al., 2002). Thus, it is clear that

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externalizing psychopathology—including criminality—has biological bases, although the precise nature of these vulnerabilities has only begun to be described in detail.

The primary exception to this observation lies in studies of autonomic nervous system (ANS) activity and reactivity, which were begun in the early part of the 20th century (Eppinger & Hess, 1914; see Raine, 1996). In general, these studies show that severe externalizing behavioral syndromes, such as antisocial personality disorder (ASPD) and psychopathy, are characterized by abnormally low ANS responding (see Lorber, 2004). Although the study of ANS biomarkers of delinquency and criminality continues to be fruitful (e.g., Beauchaine, Katkin, Strassberg, & Snarr, 2001), the primary task currently facing criminologists and others interested in the biological substrates of externalizing behaviors is to identify their CNS correlates using modern imaging techniques (Davidson, Putnam, & Larson, 2000).

Identifying the neural bases of psychopathology is important for several reasons. For example, predisposing biological vulnerabilities typically precede exposure to environmental risk factors, so their early identification may provide opportunities for targeted prevention programs (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008). Such prevention programs should be designed to reduce exposure to known environmental risk factors, thereby attenuating potentiation of preexisting vulnerabilities to delinquency (Beauchaine & Marsh, 2006). In addition, identifying biological markers of vulnerability in children and adolescents may (a) elucidate underlying etiologies of antisocial and criminal behavior, (b) predict susceptibility to life course persistent delinquency, (c) identify those who may respond differentially to early intervention and treatment, and (d) suggest pharmacological treatments for aggression and related antisocial behaviors (Beauchaine et al., 2008).

THE IMPORTANCE OF PERSONALITY TRAITS IN UNDERSTANDING CRIMINALITY

One means of studying the etiology of criminality is to examine the neural bases of personality traits observed among those who commit crimes. Krueger and colleagues (e.g., Hicks et al., 2004; Krueger et al., 2002) have identified a single latent vulnerability trait, expressed broadly as impulsivity (Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009), that is highly heritable and predisposes to antisocial and criminal behavior (Krueger et al., 2002; Krueger, Hicks, & McGue, 2001). For example, in one study of 626 twin pairs, Krueger et al. (2002) identified a single latent factor that accounted for 81% of the variance in antisocial behavior, conduct disorder (CD), alcohol dependence, drug dependence, and lack of constraint (i.e., attention-deficit/hyperactivity disorder [ADHD]-like behaviors). Furthermore, in a separate twin sample, Young, Stallings, Corley, Krauter, and Hewitt (2000) identified a similar heritable trait, which they labeled "behavioral disinhibition." This trait accounted for nearly all of the shared variance between ADHD, CD, early substance experimentation, and novelty seeking. Together, these findings suggest that a highly heritable "impulsivity trait" confers vulnerability to externalizing psychopathology.

In addition, a biological propensity toward impulsive behavior appears to account for the developmental pathway that begins in preschool with hyperactivity, progresses to CD in adolescence, and ends in substance abuse, ASPD, and criminality (Beauchaine & Neuhaus, 2008;

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Moffitt, 1993). Indeed, impulsivity is the sine qua non of both the hyperactive/impulsive and combined types of ADHD (American Psychiatric Association, 2000). Although many who exhibit impulsivity and/or ADHD early in life do not go on to engage in criminal and delinquent behavior, the vast majority of those with CD or ASPD have a childhood history of ADHD (Klein et al., 1997). Manuzza and Klein (2000) reviewed all prospective long-term follow-up studies of children with ADHD and found that ADHD was overwhelmingly associated with delinquency in young adulthood, including significantly higher rates of CD, ASPD, aggressive offenses, multiple arrests, multiple convictions, and incarcerations. Similarly, CD almost always predates ASPD and is the most reliable predictor of adult antisocial behavior (Robins, 1978; see Moffitt, 1993, for a review). In a recent review of 62 surveys including more than 22,000 prisoners, 46% of all male detainees had a diagnosis of ASPD, with one individual survey reporting a value of 64% (Fazel & Danesh, 2002). Clearly, impulsivity and its developmental sequelae confer risk for lifelong criminality.

BIOLOGICAL BASES OF IMPULSIVITY AND OTHER EXTERNALIZING BEHAVIORS

Historically, lesion studies have provided clues about the neural structures involved in externalizing psychopathology. Perhaps the most well known is the case of Phineas Gage, who experienced a dramatic change in personality after an injury to his frontal lobe, which led to poor judgment and socially inappropriate behavior (Macmillan, 2002). Indeed, deficits in cortical function have been proposed among those who exhibit criminal behavior. Thus, the prefrontal cortex (PFC) has gained much attention in criminality research. In one study, those with ASPD showed an 11% reduction in PFC gray matter compared with controls (Raine, Lencz, Bihrle, LaCasse, & Colletti, 2000). Furthermore, several neuroimaging studies have identified dysfunctional areas of the PFC in aggressive, psychopathic, and antisocial samples (Bufkin & Luttrell, 2005; Kiehl, 2006).

Although lesion studies were invaluable in early research of brain–behavior relationships, several biological theories of personality—including those developed from animal models—have helped elucidate the brain systems and neurotransmitters involved in vulnerability to externalizing behavior disorders. Following from Eysenck (e.g., Eysenck & Eysenck, 1969), Gray (1982, 1987) proposed a phylogenetically based theory of personality (which others extended to psychopathology) that emphasized the role of dopaminergic circuits in approach and active avoidance behaviors. Gray's behavioral approach system (BAS; Gray, 1987), which controls appetitive motivation, reward responding, and active avoidance of punishment, is likely disrupted in those with externalizing disorders (Avila, 2001; Beauchaine, 2001; Fowles, 1980; Quay, 1997). Within the context of high environmental risk, those with excessive approach behavior have minimal "checks" for behavior regulation and increased opportunity to engage in delinquent behavior.

At the neural level, the BAS is subserved primarily by dopaminergic pathways originating in the ventral tegmental area (VTA), projecting forward to the striatum and the frontal cortex (Cloninger, 1987; Stellar & Stellar, 1985). The striatum can be divided into a ventral portion (nucleus accumbens) and a dorsal portion (caudate nucleus and putamen), both of which have been implicated in externalizing disorders. The excessive reward-seeking (approach) behaviors characteristic of externalizing psychopathology appear to result from hypodopaminergic activity in this system (Beauchaine et al., 2001; Sagvolden, Johansen, Aase, & Russell,

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2005; Volkow et al., 1998). Indeed, functional deficiencies in the striatum and frontal cortex have been the primary foci of more than a decade of imaging research on ADHD (Durston, 2003). From this research, well-replicated findings suggest deficits in striatal functioning during reward anticipation among those with ADHD (Scheres, Milham, Knutson, & Castellanos, 2007).

BOTTOM-UP DOPAMINERGIC INPUT TO THE CORTEX

Behavior is ultimately modulated by multiple top-down and bottom-up brain circuits. Animal studies have helped to identify bottom-up dopaminergic pathways, which historically have been divided into three to four separate systems, two of which are relevant to the current study. The mesolimbic pathway, which projects to the ventral striatum, amygdala, septum, and hippocampus, is involved in reinforcement learning, motivation, sustained attention, and behavioral control. The mesocortical pathway projects to the frontal cortex, including areas of the dorsolateral PFC, the medial PFC, the anterior cingulate cortex (ACC), and the temporal cortex, and is involved primarily in executive functioning, attention and planning behavioral responses (Gatzke-Kopp & Beauchaine, 2007). Although separating DA pathways in this way may be useful in understanding the distinct roles and components of dopaminergic reward function, decades of animal studies have elucidated the overlapping and integrative nature of this neural circuitry and suggest that a more accurate perspective is one mesocorticolimbic dopaminergic reward pathway involved in the multiple functions that occur during goal-directed behavior (Björklund & Dunnett, 2007).

Of particular interest in the current study is both top-down and bottom-up processing between the caudate nucleus and the ACC via these two DA systems. The ACC receives afferent connections from the VTA and substantia nigra (Hurd & Hall, 2005). Furthermore, diffusion weighted and tractography studies also suggest structural connections between the ACC and the ventral striatum (Lehericy et al., 2004).

Dopamine is released in the VTA following exposure to novelty and following unexpected delivery of reward. This DA response motivates the organism to increase attention, facilitating learning of stimulus–reward associations (Ljungberg, Apicella, & Schultz, 1992; Schultz, 2002). In contrast, the omission of an expected reward (i.e., extinction) leads to a momentary suppression of DA release (Schultz, Dayan, & Montague, 1997). This "prediction error," which is sent to the ACC, is pivotal in learning new behavioral contingencies and may serve as a training signal for higher-level cognitive control of behavior (Brown & Braver, 2005; Holroyd & Coles, 2002; Schultz, 2002).

IMPLICATIONS OF A BOTTOM-UP DEFICIT

The ACC is also involved in early stages of learning (Brooks, 1986), cost-benefit analysis of choices (Walton, Bannerman, Alterescu, & Rushworth, 2003), incorporating reinforcement information into behavior (Kennerley, Walton, Behrens, Buckley, & Rushmore, 2006), detecting errors in performance (Holroyd & Coles, 2002), and evaluating whether one's overt behavior matches with expected or intended behavior (G. Bush, Luu, & Posner, 2000; Ito, Stuphorn, Brown, & Schall, 2003).

Dysfunction in the ACC may also contribute to trait impulsivity. Deficiencies in the mesocortical DA system and its projections to the ACC may account for maladaptive

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evaluation of the costs and benefits of one's choices or the potential outcome of one's behavior. Indeed, Sagvolden et al. (2005) proposed a theory of ADHD that may extend to other externalizing disorders. They suggested that an underresponsive DA system may result in deficient associative learning and failure to link specific operant behaviors to their probable outcomes. Thus, during extinction, the momentary suppression of DA release is ineffective, resulting in the absence of the training signals that are critical for adapting and monitoring goal-directed behavior and changing environmental contingencies (Sagvolden et al., 2005).

Furthermore, reduced or absent ACC activity is related to apathy in those with antisocial and psychopathic behavior (Kiehl et al., 2001; Viet et al., 2002). Numerous functional neuroimaging studies have also identified the ACC as an area of dysfunction in those with ADHD during tasks that elicit impulsivity, inhibitory responding, and decision making (E. Bush et al., 1999; Durston et al., 2003; Ernst et al., 2003; Rubia et al., 1999; Tamm, Menon, Ringel, & Reiss, 2004). Additionally, chemical suppression of the ACC in monkeys prevents behavioral adaptation to more desirable alternatives after behavioral contingencies change (Shima & Tanji, 1998). Finally, in a previous analysis of the current data set, we found less activation in the ACC during extinction among externalizing adolescents compared with controls (Gatzke-Kopp et al., 2009).

TOP-DOWN MODULATION OF THE STRIATUM

Alexander, DeLong, and Strick (1986) identified five separate but parallel circuits between the basal ganglia (a collection of nuclei which include the striatum) and cerebral cortex, thereby elucidating the neural circuitry of motor control and goal-directed behavior. An "anterior cingulate loop," which begins in the ACC, sends projections to the ventral striatum, thereby modulating activity of midbrain DA cells (Gariano & Groves, 1988). This circuit then projects to the thalamus and back to the ACC (Alexander et al., 1986). Furthermore, primate studies have shown efferent connections of the ACC to the ventral tegmental area and the ventral and dorsal striatum (Kunisho & Haber, 1994). Top-down modulation via frontostriatal circuits is thought to play a major role in facilitating planful behavior and suppressing behavioral impulses that are inconsistent with such goals (Nigg & Casey, 2005). Top-down modulation of lower subcortical structures is assumed to initiate when a prediction error occurs (Nigg & Casey, 2005). For successful modulation to occur, the PFC must store the goal in memory while inhibiting thoughts and behaviors that are inconsistent with the goal.

IMPLICATIONS OF A TOP-DOWN DEFICIT

Deficits in the PFC may lead to deficient modulation of subcortical structures. Prefrontal efferents exert influence on baseline levels of DA in the striatum. If frontostriatal communication is disrupted, influence of the PFC is attenuated, leading to abnormally low baseline DA levels (Grace, 2001; Sagvolden et al., 2005; Solanto, Arnsten, & Castellanos, 2001). This may explain extinction deficits in those with ADHD (Sagvolden et al., 2005). Essentially, if a prediction error is not sent reliably to the PFC as a result of a deficit in bottom-up processing, the PFC is unable to modulate tonic DA levels in the striatum.

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STUDYING CIRCUITS

The preceding discussion illustrates the importance of studying neural circuits in addition to specific brain regions in research on impulsivity and criminology. Accordingly, we investigated effective connectivity between the ACC and the caudate nucleus (dorsal striatum), which has been implicated strongly in deficits in reward functioning. Effective connectivity refers to the degree to which one brain region exerts influence on another brain region and can provide information about neural circuits. Several studies have shown functional connectivity between the ACC and limbic structures and between the ACC and other areas of the frontal cortex (Brázdil, Mikl, Marecek, Krupa, & Rektor, 2007; de Marco, de Bonis, Vrignaud, Henry-Feugeas, & Peretti, 2006; Kondo et al., 2004; Seminowicz et al., 2004). For example, Cohen, Heller, and Ranganath (2005) found significantly greater functional connectivity between the ACC and ventral striatum and between the ACC and areas of the frontal cortex during high-risk decisions versus low-risk decisions. Furthermore, Cohen, Elger, and Weber (2008) examined functional connectivity between the amygdala and other brain regions during feedback-guided decision making and found greater functional connectivity in the ventral striatum, cingulate cortex, and areas of the frontal cortex during wins compared to losses. Fan, Hof, Guise, Fossella, and Posner (2008) tested a model of connectivity within the cingulate and other cortical and subcortical areas. They found connectivity in multiple areas of the ACC and PFC. Furthermore, Büchel, Coull, and Friston (1999) observed a decrease in regional activation during an associative learning task but an increase in effective connectivity. These findings highlight the importance of studying integration among brain regions.

Following from this discussion, we conducted effective connectivity analyses on brain imaging data collected from a sample of externalizing and typically developing adolescent boys. This sample has been well characterized in a previous study (Gatzke-Kopp et al., 2009).

METHOD

PARTICIPANTS

As described by Gatzke-Kopp et al. (2009), 216 parents of potential adolescent male participants first completed a structured interview over the phone, which included portions of the Adolescent Symptom Inventory (ASI; Gadow & Sprafkin, 1997) and the Child Behavior Checklist (Achenbach, 1991). Participants who scored above the 98th percentile on the Aggression scale of the CBCL or met ASI criteria for CD and/or ADHD and did not meet criteria for major depression were invited into the lab for a more extensive interview and diagnostic assessment, including portions of the Diagnostic Interview Schedule for Children (DISC; Shaffer, Fisher, Lucas, Mina, & Schwab-Stone, 2000). Of the 66 participants who were invited to the lab for a diagnostic assessment, 21 were admitted into the externalizing group, and 11 were admitted into the control group. Nineteen participants in the externalizing group met full criteria for ADHD, and 2 met intermediate criteria for ADHD. Of these 2, both met criteria for CD, as did 10 other participants in the externalizing group. Control participants did not meet criteria for any externalizing disorder. See Table 1 for descriptive statistics of the final sample. As expected given our recruitment procedure, large differences in psychopathology scores were observed across groups. Readers are referred to Gatzke-Kopp et al. (2009) for further information about the sample and assessment procedures.

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TABLE 1: Means (and Standard Deviations) of Demographics and Diagnostic Criteria by Group

	N	*Age (years)*	*CBCL Attention Problems* T *score*	*CBCL Aggression* T *Score*	*ASI CD Raw Score*	*ASI ODD Raw Score*	*ASI ADHD Raw Score*
Externalizing	19	13.6 (1.3)	75.4 (8.8)	74.1 (11.5)	8.5 (8.4)	12.1 (6.4)	40.7 (10.7)
Control	11	13.0 (1.0)	51.0 (2.0)	51.1 (2.4)	0.2 (0.4)	2.8 (1.9)	6.2 (5.3)
F-statistic	—	1.7	81.4**	42.2**	10.6**	21.5**	100.3**

SOURCE: Adapted with permission from Gatzke-Kopp et al. (2009).
Note. CBCL = Child Behavior Checklist (Achenbach, 1991); ASI = Adolescent Symptom Inventory (Gadow & Sprafkin, 1997); CD = conduct disorder; ODD = oppositional defiant disorder; ADHD = attention-deficit/hyperactivity disorder. CBCL values represent *T* scores, ASI scores are cumulative symptom counts (scored from 0 to 4 per diagnostic criterion).
*$p < .05$. **$p < .01$.

BEHAVIORAL TASK

During the scan, participants engaged in a reward and nonreward task presented using E-Prime software (Schneider, Eschman, & Zuccolotto, 2002). In each trial, a green square was presented in pseudorandom order to either the right or the left visual field. The square remained on the screen for 1200 ms, during which participants were to press one of two buttons to indicate the side on which the square was presented. For correct responses, a monetary incentive of $0.40 was presented at the point of fixation and was accompanied by a 500-ms tone. The amount of money earned continued to accumulate at the fixation point during blocks of reward, so participants knew how much they had earned. For incorrect responses, or if a response was not emitted within the time that the stimulus was presented, the task advanced to the next stimulus, there was no increase in monetary incentives, and a different tone was presented. The task was conducted in block design with separate blocks of reward and nonreward. During the blocks of nonreward, the monetary value was set to $0.00, and correct responses were not rewarded and were accompanied by a different tone. The task consisted of 10 blocks, which contained 24 trials each, with a 15-s rest period between blocks.

FUNCTIONAL IMAGING

Scan acquisition. Structural and functional magnetic resonance imaging scans were performed on a 1.5 Tesla imaging system (General Electric, Waukesha, WI) with a head volume coil. The functional MRI (fMRI) series was collected using a two-dimensional gradient echoplanar pulse sequence (repetition time [TR]/echo time [TE] 3000/50 ms, axial, 21 slices; 6 mm thick with 1 mm gap; 155 volumes). The matrix size was 64×64 pixels with an in-plane resolution of 3.75×3.75 mm with a 240-mm field of view.

Image processing. Functional data were processed using the latest version of Statistical Parametric Mapping software (SPM8; http://wwww.fil.ion.ucl.ac.uk/spm) in conjunction with ArtRepair software (Mazaika, Whitfield-Gabrieli, & Reiss, 2007). The 155 volumes for each participant were realigned to the first volume of the series and corrected for Rotation × Field effects with an unwarping procedure. Subsequently, data were examined for excessive motion using the ArtRepair software. Individual volumes showing rapid movement (inter-TR movement) of greater than 1 mm were excluded via interpolation of

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the prior and subsequent volumes. Following inspection and removal of artifact volumes, 3 participants (1 control and 2 externalizing) were excluded because of excessive or uncorrectable motion. In the cohort of remaining participants, approximately 4% of volumes were excluded ($M = 5.5$, $SD = 5.0$). Interpolated volumes were then partially deweighted by the inclusion of motion parameters as covariates in the first-level model. Finally, participants' data were normalized to the Montreal Neurological Institute (MNI, Montreal, Canada) echo planar imaging reference brain and smoothed using a Gaussian kernel (8 mm, full width at half maximum).

Prior to calculation of first-level models, data for each participant were high-pass filtered using a cutoff period of 128 s and were corrected for serial correlations by use of a first-order autoregression term. A fixed-effects general linear model (GLM) was then created for each participant and was analyzed voxel-wise to calculate parametric maps of *t*-statistics for conditions of interest. Contrast images for the reward condition minus nonreward (R-NR) were created for each participant and were subsequently entered into a second-level analysis. A random-effects second-level GLM was created for all participants regardless of group membership, and a one-sample *t*-test of the R-NR contrast was created. The resulting parametric *t* map was examined for activation in a priori hypothesized areas of interest, specifically, areas proximate to the head of the caudate nucleus and the ACC. Clusters of activation in these areas were subjected to SPM8's built-in false-discovery rate correction (FDR) and were thresholded at $p < .05$.

DYNAMIC CAUSAL MODELING

To assess connectivity between mesolimbic and mesocortical structures, we used dynamic causal modeling (DCM; Friston, Harrison, & Penny, 2003). DCM is a model-driven approach to determining how one neural system influences another (effective connectivity analysis). In contrast to approaches to measuring neural coupling that rely on the correlation of activity in two or more regions (functional connectivity analysis), DCM relies heavily on a priori specified system models. This allows for assessment of directed influence of one neural system on another. The advantage of the latter approach is that it allows one to infer directionality, which is not possible using functional connectivity analysis.

When using DCM to assess functional MRI data, it is important to remember that this measure of neural activation is arrived at by a series of complex transformation functions, collectively referred to as the hemodynamic response function. DCM accounts for this by assuming that the driving influences to the model (hemodynamic signals) are composed of both local neuronal activity and distributed interactions between neuronal regions and that both are altered by experimental inputs. Using nonlinear differential equations in continuous time, DCM assesses the strength of connections between regions and how they change in response to experimental demands. This explicit generative model of the observed data is unique to DCM and provides a better estimate of both intrinsic connectivity and the modulation of activity in response to task than can be provided using a correlational technique (Friston, 2009).

In applying DCM to functional data to assess neural coupling, one is required to first specify a theoretically based neuronal model. As mentioned earlier, there is substantial

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evidence for interconnections between mesolimbic and mesocortical structures (Björklund & Dunnett, 2007). On the basis of previous work in our lab indicating group differences in activation related to the task in both the caudate and the ACC (Gatzke-Kopp et al., 2009), we created a model with intrinsic reciprocal connections between these regions. Furthermore, because of the role of the ACC in extinction processes (Holroyd & Coles, 2002), we hypothesized that nonreward conditions would modulate the connectivity between these regions. Finally, consistent with previous work demonstrating the role of mesocortical and mesolimbic structures in reward processing (Knutson, Westdorp, Kaiser, & Hommer, 2000), both nonreward and reward task conditions were modeled as having direct effects on activation in the caudate.

DCM models must be specified at the individual participant level. To ensure similarity in regional activation when tested across participants, results from the univariate imaging analyses were used as seed regions for determining functional activation. For each participant, neural responses to reward versus nonreward were assessed using a cluster of activation found in the group analyses as a mask. In contrast, because of the previously mentioned importance of ACC in extinction, voxels found active for nonreward versus reward were identified within a similar mask based on a cluster of activation proximally to the ACC. In both cases, the maximally active voxel for each participant within the respective masks was used as the focus of the participant's activation, and a spherical region of interest (ROI) was constructed around this voxel. A first eigenvariate time series was created using all voxels within each ROI for each participant, and these data were modeled individually using DCM.

After model fitting, individual parameters were estimated for intrinsic connectivity (*A*), task modulation of this connectivity (*B*), and the direct perturbation effects of the task on individual neural regions (*C*). DCM priors and model likelihoods were combined for each participant using an iterative Bayesian statistical approach to produce the maximum posterior solution. This posterior density was then used to estimate the size of each of the connection parameters (Friston et al., 2003).

To assess both within- and between-groups effects, parameter estimates for each participant were entered into post hoc one- and two-sample *t*-tests. A series of one-sample *t*-tests was performed in both the externalizing and control groups to test group parameter estimates against the null hypothesis that they were equal to zero. In addition, independent-sample *t*-tests were used to compare the groups. Because we had strong hypotheses about the direction of effects (externalizing group showing less intrinsic connectivity and less task-related modulation), a one-tailed test was used for this analysis. Post hoc *t*-tests were performed using SPSS software, Version 14.

RESULTS

BEHAVIORAL DATA

As reported in Gatzke-Kopp et al. (2009), there were no main effects of group, or Group × Condition interactions for reaction time, accuracy, or total money earned. However, a main effect of condition indicated a decline in accuracy during conditions of nonreward.

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TABLE 2: Dynamic Causal Modeling Parameter Estimates (Bilinear Time Constants, Hz), Intrinsic (*A*), Modulation (*B*), Perturbation (*C*).

Parameter	*Control*	*Externalizing*	t *Value Group Effects*
A Caudate→ACC-MFG	–0.383**	–0.169*	–2.105*
A ACC-MFG→Caudate	–0.115*	–0.024	–1.957*
B Caudate→ACC-MFG	–0.338**	–0.029	–2.293*
B ACC-MFG→Caudate	–0.065*	0.009	–2.357*
C Reward→Caudate	0.108*	0.198*	–0.998
C Nonreward→Caudate	–0.151**	–0.098*	–1.084

Note. ACC = anterior cingulate cortex; MFG = middle frontal gyrus. Within column, notation indicates significance (two-tailed) of within-group one-sample *t*-test against zero. Column "*t* Value Group Effects" indicates results from between-group independent-samples *t*-test, with significant findings marked (one tailed).
*$p \leq .05$. **$p < .01$.

GROUP FUNCTIONAL DATA

Analyses at the group level revealed two clusters of activation in direct proximity to the caudate and ACC. The caudate cluster was 6,784 mm^3 in size and spanned both left and right caudate (center mass = –2, 17, 1 [x, y, z; MNI], $z = 3.84$, $t = 4.46$, $p < .02$ corrected). As expected, this cluster of activation was limited primarily to the left and right caudate head. However, the area of activation proximate the ACC was slightly more dorsal than expected. This region, 6,656 mm^3 in volume, included voxels in both the ACC and middle frontal gyrus (MFG). The center of the mass was dorsal to the ACC and was located within the MFG (center mass = 3, 50, 25 [x, y, z; MNI], $z = 4.13$, $t = 4.88$, $p < .01$ corrected).

DYNAMIC CAUSAL MODELING

Significant within- and between-groups findings related to neural coupling are represented in Table 2. Consistent with the findings of the within-group analysis of functional activity, both the reward and nonreward conditions directly affected activity within the caudate head for both the control and externalizing groups. Consistent with our hypotheses, reward conditions increased activation within the caudate, whereas nonreward decreased activation within the caudate.

Although the two groups were equivalent in direct, task-related effects on the caudate (*C*), significant differences were found in both intrinsic (*A*) and nonreward modulatory effects on connectivity (*B*). The control group showed significant negative top-down and bottom-up connectivity between the caudate to the ACC-MFG. Negative connectivity values indicate an opposite modulatory effect, such that increases in activity within the caudate resulted in reductions in ACC-MFG activity and vice versa. In contrast to the control group, the externalizing group showed only bottom-up connections from the caudate to the ACC-MFG. No significant intrinsic top-down connections into the caudate from the ACC-MFG were found. Furthermore, consistent with our hypotheses, nonreward significantly modulated the connection between the caudate and ACC-MFG in the control group only (*B*). Strong modulation of the caudate-to-ACC-MFG pathway was found in the controls, whereas a weaker modulation was found for the ACC-MFG back to the caudate. There were no task modulatory effects for the externalizing group.

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DISCUSSION

In this study, we investigated whether disruption in frontostriatal circuitry characterizes adolescents with externalizing disorders relative to age-matched controls. Of note, although we were interested primarily in the intrinsic and modulatory connections between the caudate and ACC, we found a much more diffuse region of connectivity in the frontal cortex, which extended to areas of the MFG. This is consistent with other studies showing less circumscribed patterns of connectivity in child and adolescent samples (Kelly et al., 2009). The MFG is implicated in top-down modulation of midbrain DA neurons (Gariano & Groves, 1988) and reward processing (Knutson et al., 2000). Furthermore, functional deficiencies within the MFG have been observed in those with ADHD during working memory (Schweitzer et al., 2000) and response inhibition and delay tasks (Rubia et al., 1999).

Several findings were consistent with our hypotheses and with literature suggesting deficiencies in frontostriatal functioning during extinction among those with externalizing disorders. We tested the bidirectional intrinsic connectivity of the caudate-ACC-MFG pathway. Both adolescents with externalizing disorders and controls showed significant negative intrinsic connectivity from the caudate to the ACC-MFC. Negative connectivity values indicate an inverse modulatory effect. Thus, increases in activity within the caudate resulted in reduced ACC-MFG activity and vice versa. However, adolescents in the control group showed significantly greater intrinsic connectivity than adolescents in the externalizing group in the bottom-up pathway from the caudate to the ACC-MFG, indicating a deficit in baseline functioning in frontostriatal circuits among adolescents with externalizing psychopathology.

These findings are consistent with several studies indicating decreased fractional anisotropy (FA), an index of white matter integrity, in children with ADHD compared to controls (Ashtari et al., 2005; Hamilton et al., 2008; Pavuluri et al., 2009). For example, Ashtari et al. (2005) reported decreased FA in frontostriatal circuits in children with ADHD. Furthermore, the cingulum bundle, which has fibers that originate in areas of the cingulate gyrus, frontal cortex, and thalamus (Mufson & Pandya, 1984), and is critical in modulating attention and executive functions, was significantly smaller in a group of adults with childhood ADHD compared to controls (Makris et al., 2009).

In addition, we found that the modulatory effect of nonreward on this bottom-up pathway was significantly impaired in our externalizing group. Although the externalizers showed significant intrinsic connectivity in this pathway, they did not show a modulatory effect on the frontostriatal pathway during nonreward. In contrast, control group participants exhibited a strong negative modulatory effect of nonreward (as expected), indicating that a decrease in activity in the caudate leads to an increase in downstream activity in the ACC-MFG during nonreward, consistent with the role of the mesocortical and mesolimbic DA systems in sending a prediction error to the ACC during extinction. Furthermore, a significant difference in the effect of modulation during nonreward between groups supports theories of frontostriatal impairment during extinction among those with externalizing disorders (Sagvolden et al., 2005).

Control participants also showed significant intrinsic connectivity and significant modulation during nonreward in the top-down ACC-MFG pathway; however, those with

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externalizing disorders did not. This indicates an impairment in the top-down modulatory control of the caudate and potentially other areas of the basal ganglia.

Finally, consistent with our previous work (Gatzke-Kopp et al., 2009), we found a significant effect of reward and nonreward on the perturbation of the caudate activation in both groups. However, the difference between groups was not significant. Thus, both reward and nonreward conditions affected caudate activation in both groups. Although this finding is inconsistent with a body of literature implicating deficits in the caudate and other areas of the striatum among those with ADHD and externalizing disorders (Durston, 2003), it does not preclude the possibility of a reward-processing deficit among those with externalizing disorders.

Poor bottom-up baseline connectivity, in conjunction with absent top-down connectivity and modulation suggests that those with externalizing disorders have dysfunctional mesocortical and mesolimbic circuitry, which may underlie several core features of their psychopathology.

In addition, our results demonstrate that individuals with externalizing disorders fail to modulate the mesocortical and mesolimbic DA systems in response to changes in environmental cues. Specifically, although the externalizing group exhibited modulation of caudate activity in response nonreward, they failed to modulate the caudate-to-ACC-MFG pathway. Although healthy controls appeared to increase functional coupling between these regions in response to changes in reward contingencies, the externalizing group exhibited no such change in neural coupling. Failure to increase coupling in response to nonreward may represent dysfunctional signaling within mesocortical and mesolimbic pathways, the result of which may be representative of the failure in extinction processes often seen in individuals with externalizing behavior disorders, which manifests as perseveration and an inability to change behavior according to changing environmental contingencies. Disruption of this pathway may help to explain biological vulnerability to impulsivity, novelty seeking, and delinquent and criminal behavior.

Although we have identified one type of dysfunctional neural circuitry among externalizing youth, criminal behavior is probably associated with several dysfunctional brain regions and circuits (Kiehl, 2006; Raine et al., 1998) and with neurotransmitter systems other than DA (Caspi et al., 2002; Pliszka, Rogeness, Renner, Sherman, & Broussard, 1988). It is important to emphasize that MRI can identify deficits in regional brain activity, but this may not translate directly to specific neurotransmitter deficits. Thus, dysfunction within frontostriatal pathways almost certainly includes disruption in more than just DA functioning.

Additionally, we note again that dysfunction within mesolimbic and mesocortical dopaminergic pathways does not necessarily lead to criminal behavior. Although we and others (Gatzke-Kopp & Beauchaine, 2007; Sagvolden et al., 2005) have hypothesized hypodopaminergic functioning as a potentiator of biological vulnerability toward impulsivity and delinquency, many who manifest impulsivity early in life do not progress to more serious forms of psychopathology (Odgers et al., 2008). Furthermore, structural abnormalities in the caudate nucleus among those with ADHD may normalize in some individuals throughout development (Castellanos et al., 2002). In addition, some of those who are born with a biological vulnerability to criminality and other forms of psychopathology may be protected by living in low-risk environments.

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Some limitations of the present study include a small sample size and the unequal number of participants across groups. In addition, we were unable to examine potential amygdala dysfunction in our externalizing group, which has been well replicated among delinquent, antisocial, and psychopathic samples (Bufkin & Luttrell, 2005; Kiehl, 2006). Finally, given the cross-sectional nature of our study, it is impossible to know whether impaired frontostriatal connectivity serves as a biomarker for externalizing adolescents on a life course persistent path or for externalizing adolescents in general. A longitudinal design would allow increased specificity in the predictive power of dysfunctional frontostriatal connectivity. Furthermore, it is unclear to what extent normative developmental changes in frontal regions contribute to biological vulnerability in the expression of impulsivity and delinquency. However, some have implicated a protective effect of frontal development in attenuating risk for continued difficulties with impulsivity and associated psychopathology (Halperin & Schulz, 2006). Thus, a deeper understanding of neural mechanisms of the expression, remission, and recidivism of delinquency and criminal behavior may influence prevention and treatment efforts. Increased awareness of the neurobiological deficits among those who commit crimes holds promise in contributing to advancing legal systems and the way in which they interact with those individuals (Mobbs, Lau, Jones, & Frith, 2007). Systematic changes in mental health care for antisocial and delinquent individuals will ultimately rely on advances in our understanding of both biological and environmental factors and their interactions that confer risk for criminal behavior.

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