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Brain regions related to impulsivity mediate the effects of early adversity on anti-social behavior

Scott Mackey[1], Bader Chaarani[1], Philip Spechler[1], Catherine Orr[1], Tobias Banaschewski[2], Gareth Barker[3], Arun L.W. Bokde[4], Uli Bromberg[5], Christian Büchel[6], Anna Cattrell[7], Patricia J.Conrod[7,8], Sylvane Desrivières[6], Herta Flor[9], Vincent Frouin[10], Jürgen Gallinat[11], Penny Gowland[12], Andreas Heinz[13], Bernd Ittermann[14], Marie-Laure Paillère Martinot[15], Eric Artiges[16], Frauke Nees[9], Dimitri Papadopoulos-Orfanos[10], Luise Poustka[2,17], Michael N. Smolka[18], Sarah Jurk[18], Henrik Walter[13], Robert Whelan[19], Gunter Schumann[6], Robert R. Althoff[1], Hugh Garavan[1], & The IMAGEN Consortium.

[1]Department of Psychiatry, University of Vermont, 05405 Burlington, Vermont, USA;
[2]Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, 68159 Mannheim, Germany;
[3]Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom;
[4]Discipline of Psychiatry, School of Medicine and Trinity College Institute of Neurosciences, Trinity College Dublin;
[5]University Medical Centre Hamburg-Eppendorf, House W34, 3.OG, Martinistr. 52, 20246, Hamburg, Germany;
[6]Medical Research Council - Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, United Kingdom;
[7]Department of Psychiatry, Universite de Montreal, CHU Ste Justine Hospital, Canada;
[8]Department of Psychological Medicine and Psychiatry, Institute of Psychiatry, Psychology & Neuroscience, King's College London;
[9]Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Square J5, Mannheim, Germany;
[10]Neurospin, Commissariat à l'Energie Atomique, CEA-Saclay Center, Paris, France;
[11]Department of Psychiatry and Psychotherapy, University Medical Centre Hamburg-Eppendorf (UKE), Martinistrasse 52, 20246 Hamburg;
[12]Sir Peter Mansfield Imaging Centre School of Physics and Astronomy, University of Nottingham, University Park, Nottingham, United Kingdom;

[13]Department of Psychiatry and Psychotherapy, Campus Charité Mitte, Charité, Universitätsmedizin Berlin, Charitéplatz 1, Berlin, Germany;
[14]Physikalisch-Technische Bundesanstalt, Abbestr. 2 - 12, Berlin, Germany;
[15]Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 "Neuroimaging & Psychiatry", University Paris Sud, University Paris Descartes - Sorbonne Paris Cité; and AP-HP, Department of Adolescent Psychopathology and Medicine, Maison de Solenn, Cochin Hospital, Paris, France;
[16]Institut National de la Santé et de la Recherche Médicale, INSERM Unit 1000 "Neuroimaging & Psychiatry", University Paris Sud, University Paris Descartes - Sorbonne Paris Cité; and Psychiatry Department 91G16, Orsay Hospital, France;
[17]Department of Child and Adolescent Psychiatry and Psychotherapy, Medical University of Vienna, Austria;
[18]Department of Psychiatry and Neuroimaging Center, Technische Universität Dresden, Dresden, Germany
[19]Department of Psychology, University College Dublin.

Contact Author: Scott Mackey
Nerve Lab, suite 1400 Fletcher Allen Health Care-UHC Campus
1 South Prospect St.
Burlington, VT 05401
msmackey@uvm.edu
1 (802) 656-3774

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Abstract

Background: Individual differences in impulsivity and early adversity are known to be strong predictors of adolescent anti-social behavior. However, the neurobiological bases of impulsivity and their relation to antisocial behavior and adversity are poorly understood.

Methods: Impulsivity was estimated with a temporal discounting task. Voxel-based morphometry was used to determine the brain structural correlates of temporal discounting in a large cohort (N=1830) of 14-15 year old children. Mediation analysis was then used to determine whether the volumes of brain regions associated with temporal discounting mediate the relation between adverse life events (e.g. family conflict, serious accidents) and anti-social behaviors (e.g. precocious sexual activity, bullying, illicit substance use).

Results: Greater temporal discounting (more impulsivity) was associated with i) lower volume in frontomedial cortex and bilateral insula, and ii) greater volume in a subcortical region encompassing the ventral striatum, hypothalamus and anterior thalamus. The volume ratio between these cortical and subcortical regions was found to partially mediate the relation between adverse life events and anti-social behavior.

Conclusions: Temporal discounting is related to regions of the brain involved in reward processing and interoception. The results support a developmental imbalance model of impulsivity and are consistent with the idea that negative environmental factors can alter the developing brain in ways that promote anti-social behavior.

Introduction

Substantial public resources have been allocated to fund education and health initiatives aimed at improving the living conditions of disadvantaged children on the basis of the idea that child development is a sensitive window of opportunity during which the foundations of life-long well-being are established (Center on the Developing Child, 2010). This policy perspective is supported by a wealth of research indicating that adverse events in the formative years of childhood have long-term consequences in terms of physical and mental health (Anda et al., 2006, Norman et al., 2012, Gilbert et al., 2014). However, the biological bases of these effects, particularly those relating to brain development, are as yet incompletely understood.

Among the known consequences of developmental exposure to adversity is a significant increase in the likelihood of engaging in anti-social behavior (ASB) (Farrington, 2005). ASB is defined as risky behavior that does not conform to age-specific standards of conduct. During adolescence, this includes precocious sexual activity, alcohol and drug use, trouble at school and violent aggression. A central feature of ASB is high trait impulsivity, an association that has been observed with a broad range of measures including laboratory tests such as the temporal discounting task (e.g. (Audrain-McGovern et al., 2009)) and independent ratings by teachers and parents (White et al., 1994). Moreover, as impulsivity declines with age from adolescence to early adulthood (Steinberg, 2010, de Water et al., 2014) the prevalence of ASB also decreases (Moffitt, 1993). Here, we asked whether brain regions associated with impulsivity could mediate the relation between early adversity and ASB.

Developmental imbalance models explain the declining rate of impulsivity from adolescence to early adulthood in terms of a temporal gap in the growth trajectories of competing neurobiological systems (e.g. (Jentsch and Taylor, 1999, Bechara, 2005)). In the adult brain, the cortex, in particular the frontal cortex, regulates appetitive approach behaviors mediated by subcortical structures to adaptively align behavior with the long-term goals of the individual. Since the cortex develops more slowly than other brain regions, a process that continues well into the third decade of life (Gogtay et al., 2004, Sowell et al., 2004), the absence of mature cortical regulation during adolescence may result in unconstrained impulsive behavior (Casey et al., 2008, Steinberg, 2010).

Impulsivity is a complex construct that incorporates multiple aspects of decision-making including attention, motor responding and choice (Evenden, 1999). In the present study, impulsivity was assessed by the temporal discounting task which estimates the rate at which the subjective value of an outcome is reduced as the time to delivery is delayed (Ainslie, 1975). Low temporal discounting (i.e. less impulsivity) demonstrates an ability to delay immediate gratification in exchange for larger later

rewards. Temporal discounting has been shown to have trait like stability (Audrain-McGovern et al., 2009) and high discounting rates (i.e. greater impulsivity) have been linked to several problem behaviors, such as substance use and addiction (Mitchell, 1999, Kirby and Petry, 2004, MacKillop et al., 2011), pathological gambling (Alessi and Petry, 2003), poor health and financial decision-making (Bickel et al., 2012), and antisocial personality disorder (Petry, 2002, Bobova et al., 2009). The preference in each of these examples for the immediate reinforcing outcome of the problem behavior despite the potential for larger delayed negative consequences (e.g. to health, professional and social well-being) suggests that temporal discounting may be a trans-disease process (Bickel et al., 2012, Koffarnus et al., 2013). Consequently, clarification of the brain substrates involved in temporal discounting could impact the understanding of several psychiatric disorders characterized by poor impulse-control.

In the present study, the structural correlates of temporal discounting were identified by voxel-based morphometry in a large cohort of European children. **Mediation analysis was then used to determine whether these brain regions mediate the relation between adverse events and ASB. Cortical and subcortical ROIs associated with temporal discounting were tested as mediators separately. To test the developmental imbalance theory of adolescent impulsivity directly, the ratio between the cortical and subcortical ROI volumes was also calculated and used as a mediator in an additional mediation model.**

Methods and Materials

Standard operating procedures. Standard operating procedures for the IMAGEN project are available online at http://www.imagen-europe.com/en/Publications_and_SOP.php. All aspects of the IMAGEN project were performed in compliance with the Declaration of Helsinki.

Participants. A large sample of healthy adolescents was recruited from four European countries (Schumann et al., 2010). A structural MRI brain scan and a temporal discounting score were available in 1830 individuals (51.5% female; 10.3% left-handed; average age 14.55 years). Physical pubertal status was assessed by the Puberty Development Scale (Peterson et al., 1988) and IQ was assessed by the Wechsler Intelligence Scale for Children, 4th edition (WISC-IV)(Wechsler et al., 2004). The Vocabulary and Similarities subscales of the WISC-IV were used to produce a measure of Verbal IQ, while the Block Design, Matrix Reasoning, and Digit Span subscales were used to produce a measure of (non-verbal) Performance IQ. Verbal and Performance IQ scores were adjusted to reflect the age of the participants.

Adverse Life Events and Anti-Social Behavior Scores. Negative life events and anti-social behaviors were surveyed by the Life Events Questionnaire (LEQ) adapted from (Newcomb et al., 1981) and the European School Survey Project on Alcohol and Drugs (ESPAD) (Hibell and Andersson, 1997, Hibell et al., 2004). The ESPAD interview includes items adapted from the Revised Olweus Bully/Victim Questionnaire (Olweus, 1996) and the Youth Risk Behavior Survey (Brener et al., 1995) which assess involvement in bullying as perpetrator and/or victim. Explanatory comments on the relevant subscales within the LEQ and ESPAD and example items are provided in the supplemental online materials. The scales were selected to capture a broad range of negative events and behaviors. In fourteen year olds this includes precocious sexual behavior, use of illicit substances (namely alcohol, cigarettes, and other psychoactive drugs), bullying, and running away from home. The Accident/Illness, Family/Parents and Relocation subscales of the LEQ **as well as the Victim of Bullying subscale of the ESPAD** were individually z-score transformed then summed to produce a composite measure of adverse life events. Similarly, the Deviance, Sexuality, and Distress subscales of the LEQ **as well as the Perpetrator of Bullying** and Lifetime Frequency of Illicit Substance Use subscales of the ESPAD were individually z-score transformed then summed to produce a composite measure of anti-social behavior. **Since adolescents frequently explore the boundaries of the acceptable (i.e. all children misbehave; some do so more than others), the ASB score is a continuous measure of age-specific rule-breaking and does not attempt to set a threshold between normal and abnormal levels of anti-social behavior.**

Estimation of Temporal Discounting. The computer administered version of Kirby's Monetary Choice Questionnaire (MCQ) is an efficient and reliable laboratory measure of temporal discounting (Audrain-McGovern et al., 2009, Kirby, 2009). It contains 27 items probing the subjects' preference for a range of small immediate rewards versus larger delayed rewards. For example, item 5 asks: "Would you prefer €14 today, or €25 in 19 days?" Answers were self-paced and made by clicking on one of two digital response buttons with a computer mouse. The range of delays and euro amounts of the rewards across items of the MCQ were selected to represent nine well-spaced levels of temporal discounting as fitted by a hyperbolic function: $V = A/(1 + kD)$, where V is the current subjective value of the delayed reward, A is the absolute value of the delayed reward, D is the length of delay in days, and k is a constant representing the magnitude of the discounting function (Mazur, 1987). Higher values of k indicate greater preference for small immediate rewards and higher impulsivity. **Although the rewards were hypothetical, previous research indicates that the use of real rewards does not produce a significantly different pattern of results (Madden et al., 2003, Madden et al., 2004).**

The MCQ was scored as described in (Kirby et al., 1999). That is, k is estimated as the geometric mean of the highest value of k for which the subject preferred the small immediate reward and the lowest level of k for which the subject preferred the larger delayed reward. If the subject endorsed a preference for only the immediate or only the delayed rewards, then the subject was rated at the highest or lowest of the nine k-estimate levels on the MCQ, respectively. The relatively few subjects who did not endorse a discrete indifference point were excluded from further analysis (n = 14).

To test reward magnitude effects on temporal discounting, the nine impulsivity levels on the MCQ are reproduced at three different ranges of approximate reward magnitude (i.e. delayed rewards were offered in small €25-35, medium €50-60 and large €75-85 ranges). A k-estimate is produced for each category of reward magnitude. In preparation for regression on brain volume, a single k-estimate per subject was produced by calculating the geometric mean of the three reward categories. The subjects' unique k-estimates were then approximately normalized by logarithmic transformation.

Acquisition of anatomical magnetic resonance images. Details of the MRI acquisition protocols and quality controls have been provided elsewhere (Schumann et al., 2010). Briefly, high-resolution in vivo structural MR-images were acquired, including a three-dimensional T1-weighted scan based on the ADNI protocols (see http://adni.loni.usc.edu/methods/documents/mri-protocols/). To accommodate for effects related to imaging site, location was included as a nuisance covariate in statistical analyses.

Voxel Based Morphometry (VBM). T1-weighted images were processed using the Statistical Parametric Mapping version 8 (SPM8) (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) VBM toolbox (http://dbm.neuro.uni-jena.de/vbm/) with default parameter incorporating the DARTEL toolbox implemented in Matlab 7.0 (MathWorks, Natick MA, USA). The standard 'optimized' method of iterative tissue segmentation and spatial normalization using both linear (12-parameter affine) and non-linear transformations was performed (Ashburner and Friston, 2000, Ashburner, 2007): raw structural images in native space were segmented into grey matter and white matter then spatially normalized to grey and white matter templates, respectively, to determine optimal normalization parameters; these parameters were applied to the raw structural images in native space and tissue segmentation was repeated to produce a grey matter concentration map for each subject. These maps were warped into Montreal Neurological Institute (MNI) space. To preserve information about absolute volume, the grey matter concentration images were modulated by multiplying by the linear and non-linear components of the Jacobian determinants generated during spatial normalization. Thus, the dependent measure in

the subsequent regression analysis was absolute grey matter volume. Voxel resolution after normalization was 1.5x1.5x1.5 mm. To make the residuals in later analyses conform more closely to a Gaussian distribution and to account for individual differences in brain anatomy, the modulated GM images were smoothed with an isotropic Gaussian kernel of 8 mm full-width at half maximum.

Brain Volume Regression for Temporal Discounting. A whole brain voxelwise regression of temporal discounting on regional grey matter volume was performed with the 3dttest++ function from the Analysis of Functional Neuroimages (AFNI) software library (Cox, 1996). Age, sex, handedness, MRI site, puberty status, Verbal IQ, Performance IQ and intracranial volume (ICV) were included as covariates. Regions-of-interest (ROIs) significantly correlated with temporal discounting were identified in the resulting statistical parametric map. To control for multiple comparisons, the AFNI Monte Carlo simulation function, 3dClustSim, was used to determine that a cluster containing more than 688 adjacent voxels (2322 microliters) each significantly correlated with temporal discounting at a voxelwise threshold of $p = 0.01$ ($t = 2.58$) would have an *a posteriori* probability of $p < 0.01$. Average grey matter volume within the four ROIs identified by the regression was extracted from each participant and used in subsequent analyses. Since the volumes of the three cortical ROIs were highly intercorrelated, these were summed to produce a single cortical volume measure per subject. **To assess a developmental imbalance between cortical and subcortical maturation, a ratio of cortical to subcortical volume was calculated by dividing the combined volume of the cortical ROIs by the volume of the subcortical ROI**. Thus, higher ratio values indicate greater cortical volume relative to the subcortical volume.

Magnitude Effect. Previous research has shown consistently that temporal discounting decreases as the magnitude of the delayed reward increases (e.g. delayed rewards in the €75-85 range are discounted less than rewards in the range €25-35 range) (Kirby, 2009, Green et al., 2013). The magnitude effect was tested using a repeated measures ANOVA with the k-estimate as the dependent measure and the three reward categories (small, medium and large) as the within groups factor (SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp). To examine the relation of the magnitude effect to brain volume and ASB, a difference score between the k-estimate for the smallest and largest reward categories was calculated for each individual. Partial correlations between the difference score, the volumes of brain regions identified by the regression analysis and the composite score of anti-social behavior were examined while controlling for age, sex, handedness, MRI site, puberty status, Verbal IQ, and Performance IQ.

Mediation analysis. Mediation analysis was performed on data from 1741 participants **(51.4% female; 89.7% right-handed)** in which all mediation variables were available: the adverse life events and antisocial behavior composite scores and the brain volume ROIs associated with temporal discounting. **The demographic characteristics of these 1741 children were not significantly different than the total group enrolled (Table 1).** The mediation analysis was performed using PROCESS an SPSS macro developed by Andrew Hayes (http://www.processmacro.org/) (Hayes, 2009). PROCESS uses an ordinary least squares path analytic framework to estimate direct and indirect mediation effects. The significance of indirect effects are assessed by bootstrap confidence intervals. Covariates used in the brain volume regression with the exception of ICV were included in the mediation analysis as well. ICV was not included because it was highly collinear with the volumes of the cortical and subcortical ROIs. A separate analysis showed that ICV does not mediate the relationship between adversity and ASB (see Supplemental Results). All paths are reported as unstandardized OLS regression coefficients.

Results

Behavior. Subjects endorsed a wide range of discounting rates on the MCQ. The median k-estimate was 0.013 which corresponds approximately to being indifferent to the choice between 38€ now or 50€ in 24 days. Since k-estimates in the three reward categories of the temporal discounting task were highly correlated (small-large r = 0.80; medium-large r = 0.84; small-medium r = 0.83; $p<0.001$), a single average k-estimate per subject based on the geometric mean was used in the subsequent brain volume regression. All children reported exposure to at least one of the negative life experiences included in the adversity composite score (e.g. parents' divorce, serious accident or illness in the family, severe bullying) **(Supplemental Table 4 & Figure 4).** All children also reported at least some anti-social behavior **(Supplemental Table 5 & Figure 5). Temporal discounting was correlated with ASB (r = 0.144, $p<0.001$) but not adversity (r = 0.024, p = 0.318). Partial correlations between the variables of interest are reported in Table 2. Notably, the adversity score was a significant predictor of ASB (r = 0.357, $p<0.01$).**

Temporal discounting correlates with brain volume. A whole brain voxelwise regression of temporal discounting on regional grey matter volume identified four significant regions (Figure 1) (Table 3). Three cortical ROIs, the frontomedial cortex and the insula bilaterally, exhibited greater volume in individuals with lower impulsivity. A large subcortical cluster that included the ventral striatum, dorsal

hypothalamus and anterior thalamus exhibited the opposite relation, i.e. greater volume in those with greater impulsivity.

Magnitude effect not reflected in brain volume. As expected on the basis of previous research (e.g. Kirby 1999; Petry 2002), discounting rates decreased as the size of the rewards increased ($F(1,1605)=967.6$, $p < 0.001$) (Figure2). The magnitude effect was largest in those who were the least impulsive overall on the MCQ ($r = 0.079$, $p < 0.001$).The magnitude effect score was not significantly correlated to the brain volumes of any of the ROIs, the sum of the cortical ROIs or the ratio of the cortical to subcortical ROIs.

Mediation Analysis. To evaluate the significance of the neuroimaging results within the context of real world events, mediation analysis was used to test the hypothesis that childhood adversity can change brain development in a way that increases ASB (Figure 3). The reported coefficients are unstandardized. After partialing out the effects of the covariates, adverse life events were significantly related to ASB alone (dashed line) and also when the ratio of cortical to subcortical volume was included as a mediator (solid line). The indirect or mediated effect was calculated as the product of the 'a' and 'b' path coefficients. In the PROCESS analysis toolbox, a significant indirect effect is indicated when the bootstrap-confidence interval (CI) does not include zero. There was a significant positive indirect effect of adverse life events on ASB through the ratio of subcortical to cortical volume (indirect effect = 0.0038, SE = 0.0027, 95% CI = 0.0001 to 0.0111). It should be noted that the popular but statistically suboptimal causal steps method developed by Baron and Kenny (1986) was not used in this study. **The indirect effect itself was assessed with bootstrapped CI, not inferred as in the causal steps method on the basis of a set of hypothesis tests. Consequently, the significance of the individual coefficients of the 'a' ($p = 0.086$) and 'b' ($p = 0.001$) pathways in the model are not relevant to the interpretation of the indirect effect (a well developed explanation of this issue is presented in [Hayes, 2009]). Indeed, since hypothesis testing is fallible, every additional significance test (i.e. tests of a' and b' pathways) increases the likelihood that a true effect will be mistakenly overlooked. Simulation research also indicates the bootstrap method is more robust to non-normality and has better Type I error control than the causal steps method and the Sobel test (Hayes, 2009).** Further analyses examining the mediating effects of cortical and subcortical volumes separately indicated that there was a significant indirect effect through cortical volume alone (indirect effect = 0.005, SE = 0.003, CI = 0.001 to 0.013) but not subcortical volume alone (indirect effect = 0.000, SE = 0.001, CI = -0.002 to 0.001) (Fig. 3). **The ROI volumes were not merely a substitute for temporal discounting because temporal discounting did not**

on its own significantly mediate the relationship between adversity and ASB (indirect effect = 0.004, SE = 0.027, CI = -0.003 to 0.013).

Discussion

The present study showed that greater impulsivity on a temporal discounting task is associated with lower grey matter volume in the frontomedial and insular cortex and greater grey matter volume in a subcortical region encompassing the ventral striatum, hypothalamus and anterior thalamus (Table 3; Figure 1). In addition, the relation between adverse life events and ASB was partially mediated by the grey matter volume ratio between the subcortical and cortical regions identified by the task (Figure 3). **A mediation model with cortical volume alone as mediator suggests that the indirect effect may be driven predominantly by individual differences in the cortex.** These results are consistent with developmental imbalance theories of impulsivity and with the idea that negative environmental factors can alter the developing brain in ways that promote problematic behavior.

The association of this specific set of brain regions with temporal discounting draws considerable support from previous research in humans and animals (Cardinal, 2006, Dalley et al., 2008, Christakou et al., 2011, Wesley and Bickel, 2014). The subcortical region identified includes the ventral striatum which receives projections from midbrain dopamine cells signaling the presence or expectation of reward. The frontomedial region identified included portions of the dorsomedial and ventromedial prefrontal cortex. This cortical region encodes the subjective value of future rewards during decision-making (Plassmann et al., 2010). Individuals with lesions in the ventromedial prefrontal cortex make disadvantageous choices on gambling tasks that model real-life decisions and gauge the extent to which the individual can disregard large short term wins and losses in order to make larger longer term gains, an insensitivity for future consequences that has been called ‘myopia for the future’ (Bechara et al., 2000). The insula is located at the center of a network of brain structures involved in the perception and regulation of the internal state of the body (Craig, 2002). It has been proposed that the physiological state of the body plays a central role in emotion and motivation. Damage to the insula has been linked to deficits in decision-making (Naqvi and Bechara, 2009).

A recent functional neuroimaging study reported that the age related decline in temporal discounting from adolescence to early adulthood is associated with changes in the magnitude of neural activity in a set of brain regions closely matching the present findings including the frontomedial cortex, ventral striatum and insula (Christakou et al., 2011). Moreover, more impulsive individuals exhibited

greater activity in the ventral striatum and less activity in the frontomedial cortex, a finding that mirrors the differential volumetric findings in the present study. Only a handful of studies have used structural neuroimaging to search for brain correlates of temporal discounting (Bjork et al., 2009, Schwartz et al., 2010, Cho et al., 2013). These studies found that greater impulsivity was significantly correlated with striatal and frontal cortical grey matter volume in partial agreement with the present findings. White matter differences related to temporal discounting have also been reported in the frontal and temporal lobes (Olson et al., 2009, Yu, 2012).

The current study's results support a developmental imbalance model of impulsivity according to which heightened impulsivity during adolescence is a consequence of the differential growth trajectories of competing brain systems involved in choice behavior (Jentsch and Taylor, 1999, Bechara, 2005, Casey et al., 2008, Steinberg, 2010, Koffarnus et al., 2013). Approach behavior is mediated by the mesolimbic dopamine system, which includes the ventral striatum, and is integrated with the long term goals of the individual by input from the cortex. **The slower development of the cortex (Gogtay et al., 2004, Sowell et al., 2004) produces an imbalance during adolescence favoring immediate gratification at the expense of larger delayed rewards. Consistent with the imbalance model, the current study found that parts of the cortex (i.e. frontomedial cortex and insula) are smaller and a subcortical region encompassing the ventral striatum is larger in adolescents who are more impulsive. Due to the cross-sectional nature of the present study, future longitudinal studies will be required to address whether cortical and subcortical maturation have differently timed periods of greater sensitivity to negative environmental factors and whether the structural differences observed in this study are long-lasting or can be altered by future positive environmental factors.**

Adversity during development produces a wide range of negative physical and psychiatric problems that may manifest only later in life (Anda et al., 2006, Norman et al., 2012, Gilbert et al., 2014). A large number of studies have established that many brain systems in humans and animal models are harmed by early adversity (Lupien et al., 2009, Dannlowski et al., 2012, Van Dam et al., 2014). A few recent neuroimaging studies, like the current one, have begun to search for specific brain mediators of the negative psychiatric effects produced by adversity. For example, Gorka and colleagues report that frontomedial and hippocampal cortical volume mediates the relation between childhood mistreatment and trait anxiety (Gorka et al., 2014) while Rao and colleagues have shown that hippocampal volume mediates the relation between childhood mistreatment and higher risk of depression in adulthood (Rao et al., 2010). An advantages of the current study was that the brain areas examined were identified by

an independent measure of impulsivity rather than by their direct association with adversity. This is also the first study to look for brain mediators of early adversity on ASB.

The interpretation of this study is limited by several factors. ASB is a complex behavior to which many environmental factors likely contribute, including factors not considered here, such as modeling of peer behavior, opportunity, and sensation seeking (Farrington, 2005). **For most of the population, the occurrence of ASB peaks in adolescence when situational ASB is common, even normative, then declines as the individual enters early adulthood (Moffitt, 1993)**. Various explanations of why the incidence of ASB is greater in adolescents than in children who endorse even higher impulsivity compared to adolescents often appeal to these other factors, e.g. sensation seeking (Casey et al., 2008). Like ASB, impulsivity is also a multifactorial construct that likely depends on multiple brain structures (Evenden, 1999, Heinz et al., 2011, Schilling et al., 2013). Separate investigations would be required to examine the potential contribution of these other types of impulsivity to ASB. **Another potential limitation is that the LEQ and ESPAD do not provide information about the extent to which events used to construct the adversity score might have been influenced by each child's behavior (e.g. serious accident or illness in the family, relocation, parental divorce, or victim of bullying all might have been influenced to a greater or lesser degree by the behavior of the individual child). The interpretation of the adversity score as a measure of negative life events experienced by the child should be qualified by the understanding that children interact with their environment and are not merely passive objects in it. In addition, the large size of the sample may have inflated the possibility of detecting small effects and it is possible that individual temporal discounting rates could have been more precisely assessed with other instruments (e.g. (Johnson and Bickel, 2002, Petry, 2002).** Despite these constraints, the results fit well with developmental imbalance theories of adolescent impulsivity and indicate that significant negative life events may alter the developing brain in ways that promote ASB.

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Tables & Figure Legends

Table 1.

	Mean (SE)	Median	Range
Age	14.5 (0.01)	14.5	12.9-16.1
Puberty Status	3.6 (0.02)	4	1-5
Performance IQ	107.6 (0.3)	106	63-149
Verbal IQ	110.8 (0.3)	111	50-152
Adversity Score	0 (0.06)	-0.21	-5.2-11.0
ASB Score	0 (0.07)	-0.38	-6.5-16.1

Table 1. Demographic characteristics of N=1741 participants (51.4% female; 89.7% right-handed) for whom all mediation variables and covariates were available.

Table 2.

	Adversity	ASB	Ratio	Cortical Volume
Adversity				
ASB	.357**			
Cortical/Subcortical Ratio	-.041	-.090**		
Cortical Volume	-.053*	-.089**	.579**	
Subcortical Volume	-.003	.007	-.530**	.373**

Partial correlations controlling for sex, age, handedness, MRI site, Performance IQ, Verbal IQ, and puberty status. Ratio = ratio of the combined volume of cortical ROIs to the volume of the subcortical ROI; * = $p < 0.05$; ** = $p < 0.01$; ASB = Anti-Social Behavior.

Table 3.

	Region	Cluster Size (voxels)	X	Y	Z
1.	Right Insula	3185	48	-8	12
2.	Bilateral Frontomedial cortex	1996	-11	52	12
3.	Left Insula	1529	-48	-14	16
4.	Bilateral Subcortical region	825	3	0	-2

Table 2. Size and stereotactic location of brain regions significantly associated by volume with temporal discounting. Coordinates (x,y,z) are in MNI space.

Figure 1. Top row: Regions associated with temporal discounting by brain volume. Warm and cool colors represent more and less volume, respectively. Bottom row: Scatter plots of brain volume versus temporal discounting score in three regions of interest.

Figure 2. Discounting of future reward decreases as the magnitude of the reward increases. Error bars represent standard error.

Figure 3. Three mediation models of the relationships between adversity, impulsive anti-social behavior and grey matter volume in brain regions associated with temporal discounting. Dotted line denotes the effect of adversity on ASB when the mediating variable is not included. All paths are reported as unstandardized OLS regression coefficients. * $p < 0.05$, ** $p < 0.005$, SE = standard error.

Brain regions related to impulsivity mediate the effects of early adversity on anti-social behavior

Scott Mackey[1], Bader Chaarani[1], Philip Spechler[1], Catherine Orr[1], Tobias Banaschewski[2], Gareth Barker[3], Arun L.W. Bokde[4], Uli Bromberg[5], Christian Büchel[6], Anna Cattrell[7], Patricia J.Conrod[7,8], Sylvane Desrivières[6], Herta Flor[9], Vincent Frouin[10], Jürgen Gallinat[11], Penny Gowland[12], Andreas Heinz[13], Bernd Ittermann[14], Marie-Laure Paillère Martinot[15], Eric Artiges[16], Frauke Nees[9], Dimitri Papadopoulos-Orfanos[10], Luise Poustka[2,17], Michael N. Smolka[18], Sarah Jurk[18], Henrik Walter[13], Robert Whelan[19], Gunter Schumann[6], Robert R. Althoff[1], Hugh Garavan[1], & The IMAGEN Consortium.

Supplemental Methods

Several subscales from the Life Events Questionnaire (LEQ) adapted from the Stressful Life-Event Questionnaire (Newcomb, Huba et al. 1981) and the European School Survey Project on Alcohol and Drugs (ESPAD) (Hibell and Andersson 1997, Hibell, Andersson et al. 2004) were used to produce two composite measures: an adverse life events score and an impulsive anti-social behavior score. A brief explanation and two example items for each of the relevant subscales follows.

Life Events Questionnaire (LEQ)

The LEQ measures the frequency and valence of stressful events i) within the last year and ii) over the lifetime of the child. Only the lifetime frequency of events was considered in the current study. The LEQ samples events from seven domains: Accident/Illness, Autonomy, Family/Parents, Relocation, Deviance, Sexuality, and Distress.

Accident/Illness: The Accident subscale assessed the frequency of negative health events in the life of the child and family, e.g. 'Serious accident or illness', 'Death in family'.

Autonomy: The Autonomy subscale was not included in either composite score because its elements assessed principally pro-social behaviors, e.g. 'Began a time-consuming hobby', 'Joined a club or group'.

Family/Parents: The Family subscale assessed the frequency of negative events in the home environment, e.g. 'Parents divorced', 'Parent abused alcohol'.

Relocation: The Relocation subscale assessed the frequency of disruptive changes in the child's environment, e.g. 'Changed school', 'Family moved'.

Deviance: The Deviance subscale assessed the frequency of illicit activities ("acting out"), e.g. 'Got in trouble with the law', 'Stole something valuable'.

Sexuality: The Sexuality subscale assessed the frequency of early sexual relations, e.g. 'Got or gave sexually transmitted disease', 'Broke up with boy/girl-friend'.

Distress: The Distress subscale assessed the frequency of signs of mental anguish e.g. 'Thought about suicide', 'Ran away from home'.

European School Survey Project on Alcohol and Drugs (ESPAD)

The ESPAD probes the onset and use of alcohol and other drugs i) within the last week, ii) 30 days, iii) year, and iv) over the lifetime of the child. The ESPAD interview also includes items to assess involvement in bullying as perpetrator and/or victim. The bullying questions have been adapted from a questionnaire used in a large international study entitled Health Behavior in School-aged Children (HBSC). These questions were initially utilised in the revised Olweus Bully/Victim Questionnaire (Olweus, 1996), and the Youth Risk Behavior Survey (Brener et al., 1995).

Frequency of Illicit Substance Use: The current study used the combined lifetime frequency of use of alcohol, tobacco, marijuana, and other drugs (including tranquilizers, amphetamines, lsd, glue, mushrooms, cocaine, relevin, heroin, MDMA, ketamine, GHB, and anabolic steroids).

Perpetrator of Bullying: The Perpetrator subscale assessed the frequency of aggressive behavior towards students/peers, teachers and family members, e.g. 'I called another student/ peer mean names, made fun of, or teased him or her in a hurtful way', 'I hit, kicked, pushed, shoved around, or locked a student/ peer indoors'.

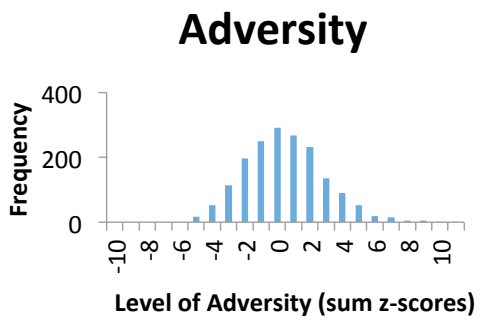
Victim of Bullying: The Victim subscale assessed the frequency of being the target of aggressive behavior from students/peers, teachers and family members, e.g. 'I have bullied a teacher', 'A student/ peer left me out of things on purpose, excluded me from their group of friends or completely ignored me'.

Composite Scores

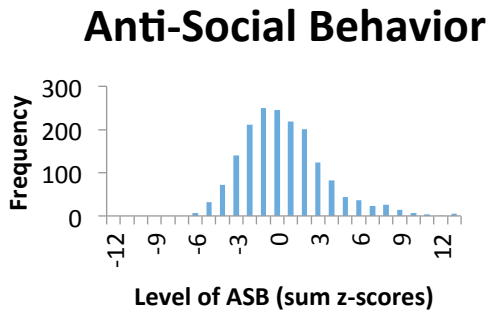
The Accident/Illness, Family/Parents and Relocation subscales of the LEQ as well as the Victim of Bullying subscale of the ESPAD were individually z-score transformed then summed to produce a composite measure of adverse life events. The Deviance, Sexuality, and Distress subscales of the LEQ as well as the Perpetrator of Bullying and Frequency of Illicit Substance Use subscales of the ESPAD were individually z-score transformed then summed to produce a composite measure of impulsive anti-social behavior. All measures were based on the lifetime frequency of events. Since it is normal for adolescents to explore the boundaries of the acceptable (i.e. all children misbehave; some do so more than others), the ASB score is a continuous measure of rule-breaking orthogonal to normative patterns of behavior

Supplemental Results

Additional Characterization of Adversity and Anti-Social Behavior Scores



Supplemental Figure 4. Histogram illustrating the sample distribution of early negative life events as measured by the composite adversity score.



Supplemental Figure 5. Histogram illustrating the sample distribution of anti-social behavior as measured by the composite ASB score.

Supplemental Table 4.

Adversity Score	Sex (% female)	Handedness (% right)	Mean Performance IQ	Mean Verbal IQ	Mean Puberty Status
Lower quartile	47.2	92.6	107.5	108.7	3.53
2nd quartile	50.1	88.5	107.7	110.8	3.63
3rd quartile	52.2	88.5	106.8	110.9	3.63
Upper quartile	56.3	89.5	108.5	112.7	3.76

Demographic information on children grouped by experienced adversity from lower quartile (i.e. least adversity) to upper quartile (i.e. most adversity).

Supplemental Table 5.

ASB Score	Sex (% female)	Handedness (% right)	Mean Performance IQ	Mean Verbal IQ	Mean Puberty Status
Lower quartile	56.6	88.7	108.6	110.5	3.51
2nd quartile	51.2	91.0	109.2	111.9	3.62
3rd quartile	51.0	89.6	107.0	110.3	3.62
Upper quartile	47.2	89.7	105.8	110.5	3.71

Demographic information on children grouped by anti-social behavior from lower quartile (i.e. least ASB) to upper quartile (i.e. most ASB).

Correlation of Temporal Discounting with other Laboratory Measures of Impulsivity. Impulsivity is a complex construct that incorporates multiple aspects of decision-making including attention, motor responding and choice (Evenden, 1999). Temporal discounting is measure 'choice impulsivity'. No other laboratory measure in the IMAGEN datasets appears to assess the same aspect of impulsivity. For example, the Stop Signal Task (SST) assesses motor impulsivity and requires the participant to cancel an already initiated motor response (Fillmore and Rush, 2002, Goudriaan et al., 2006). The time required to stop a response, the stop-signal reaction time (SSRT), is an index of impulse control. SSRT was obtained in large number of the children (N=1033) for whom temporal discounting rates are available. SSRT was uncorrelated with temporal discounting with (r = 0.038) or without controlling for age, sex, site, IQ or puberty.

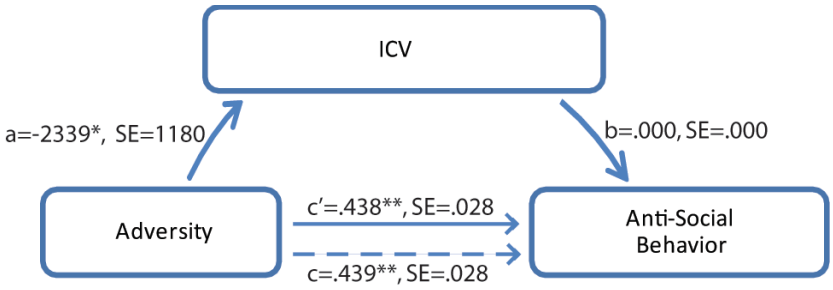
Mediation analysis with ICV

ICV was not included as a covariate in the mediation analysis reported in the main text because it was collinear with the volume of the cortical and subcortical ROIs (see Supplemental Table 3). A mediation analysis was performed to determine whether ICV mediates the relation between adversity and ASB. Age, sex, handedness, MRI site, Performance IQ, Verbal IQ and puberty status were included as nuisance covariates. The significance of the indirect effect was determined by bootstrapped confidence intervals. If the confidence intervals include 0, then the effect is not significant. ICV does not mediate the relation between adversity and ASB (indirect effect = 0.001, SE = 0.002, 95% CI =-0.0005 to 0.0071) (Supplemental Figure 4). In other words, while ICV is significantly lower in individuals who have experienced greater adversity, the results of the mediation model are not consistent with the notion that ICV plays a role in ASB.

Supplemental Table 6.

	Adversity	ASB	Ratio	Cortical Volume	Subcortical Volume
Adversity					
ASB	.357**				
Ratio	-.041	-.090**			
Cortical Volume	-.053*	-.089**	.579**		
Right Insula	*-.042*	*-.076***			
Left Insula	*-.069**	*-.082***			
Frontomedial	*-.041*	*-.084***			
Subcortical Volume	-.003	.007	-.530**	.373**	
ICV	-.048*	-.040	.238**	.787**	.546**

Partial correlations controlling for sex, age, handedness, MRI site, Performance IQ, Verbal IQ, and puberty status. Ratio = ratio of the combined volume of the cortical ROIs to the volume of the subcortical ROI.



Supplemental Figure 6. Mediation model of the relations between ICV, adversity, and impulsive anti-social behavior. Dotted line denotes the effect of adversity on ASB when the mediating variable is not included. All paths are reported as unstandardized OLS regression coefficients. * $p < 0.05$, ** $p < 0.005$, SE = standard error.

Supplemental Discussion

The association of this specific set of brain regions with temporal discounting draws considerable support from previous research in humans and animals (Cardinal, 2006, Dalley et al., 2008, Christakou et al., 2011). The subcortical region identified includes the ventral striatum which receives projections from midbrain dopamine cells signaling the presence or expectation of reward. Hyperactivity of the ventral striatum relative to top-down cortical control mechanisms has been hypothesized to produce impulsive present-oriented choices (Galvan, 2010). Consistent with this perspective, the ventral striatum is more active in response to both positive and negative feedback in individuals with more impulsive temporal discounting (Hariri et al., 2006). The frontomedial region identified included portions of the dorsomedial and ventromedial prefrontal cortex. This cortical region encodes the subjective value of future rewards during decision-making (Plassmann et al., 2010). Individuals with lesions in the ventromedial prefrontal cortex make disadvantageous choices on gambling tasks that model real-life decisions and gauge the extent to which the individual can disregard large short term wins and losses in order to make larger longer term gains, an insensitivity for future consequences that has been called 'myopia for the future' (Bechara et al., 2000). The insula is located at the center of a network of brain structures involved in the perception and regulation of the internal state of the body (Craig, 2002). It has been proposed that the physiological state of the body plays a central role in emotion and motivation. Damage to the insula has been linked to deficits in decision-making (Naqvi and Bechara, 2009). All three brain regions, the ventral striatum, the insula and frontomedial cortex, have consistently been implicated in temporal discounting by functional neuroimaging (Cardinal, 2006).

A recent functional neuroimaging study reported that the age related decline in temporal discounting from adolescence to early adulthood is associated with changes in the magnitude of neural activity in a set of brain regions closely matching the present findings including the frontomedial cortex, ventral striatum and insula (Christakou et al., 2011). Moreover, more impulsive individuals exhibited greater activity in the ventral striatum and less activity in the frontomedial cortex, a finding that mirrors the differential volumetric findings in the present study.

Only a handful of studies have used structural neuroimaging to search for brain correlates of temporal discounting. Cho et al found that the volume of the ventral putamen and the frontomedial cortex was smaller and larger, respectively, in individuals (N=34) with greater impulsivity (Cho et al., 2013), a pattern of results that are the opposite of the present findings. Another study (N=29) found a positive association between preference for delayed rewards and the volume of the lateral frontal cortex (Bjork et al., 2009) while a third larger VBM study (N=105) partially matched the present findings by reporting larger volumes in more impulsive individuals in the anterior part of the putamen extending into the ventral striatum (Schwartz et al., 2010). In contrast to these studies, the present study

examined adolescents rather than adults although differences in results between this and previous VBM studies may more likely be attributable to the much larger sample size of the present study (N=1830). White matter differences related to temporal discounting have also been reported in the frontal and temporal lobes (Olson et al., 2009, Yu, 2012).

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