reward-relevant substrates. Most notably, mesocorticolimbic dopamine circuitry is uniquely sensitive to disruption by drugs in adolescence, resulting in lasting behavioral changes linked to addiction vulnerability [1].

Our recent work in rodents highlights a novel role for guidance cues in (a) the adolescent establishment of mesocorticolimbic dopamine connectivity and cognitive processing and (b) the enduring effects of drugs of abuse on these events. First, we discovered that dopamine axons still grow to the prefrontal cortex (PFC) in adolescence [2]. This is the first concrete demonstration of long-distance axon growth in late postnatal development, which entails targeting decisions by dopamine axons en route to their final postsynaptic partners. Axon targeting relies on the interaction of extracellular guidance cues and their receptors. We find that the guidance cue Netrin-1 and its receptor DCC dictate dopamine axon targeting in adolescence. Specifically, mesolimbic dopamine axons have high levels of DCC and recognize the nucleus accumbens as their final target in adolescence. In contrast, mesocortical dopamine axons have little or no DCC and therefore fail to recognize this region as their final target and grow to the PFC instead. Reduced DCC expression in mesolimbic dopamine axons induces targeting errors in the nucleus accumbens and their ectopic growth to the PFC. By segregating dopamine innervation to cortical or non-cortical regions, DCC receptors organize PFC structure and function, including cognitive behaviors that are altered in addiction [2].

Second, we demonstrated that repeated non-contingent exposure to amphetamine in adolescence, at a dose resembling human recreational use, downregulates DCC expression in dopamine neurons [3]. This perfectly positions DCC signaling to mediate the enduring neuroanatomical and behavioral consequences of adolescent drug use. Indeed, amphetamine in early adolescence leads to an increase in the span of dopamine innervation to the PFC. However, it also leads to disorganized synaptic contacts and reduced dopamine turnover in adulthood [4, 5]. These alterations, in turn, produce deficits in behavioral inhibition and exaggerated salience attribution to drug-paired contexts; two behaviors associated with addiction susceptibility [4, 5].

Our findings indicate that DCC signaling wires the adolescent PFC and contributes to amphetamine-induced susceptibility to addiction. Interestingly, amphetamine downregulates DCC via micro-RNAs, which are important biomarkers and mediators of psychiatric conditions [3]. Furthermore, variations in DCC expression occur in humans and lead to altered mesocorticolimbic connectivity [6]. Our work therefore contributes a novel perspective to the ongoing efforts of developing prevention and treatment strategies for addiction. The DCC pathway represents a promising site for targeted intervention during adolescence both to counteract detrimental effects of early drug use and promote healthy brain development.

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The ventromedial prefrontal cortex: a putative locus for trait inattention

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Efforts to identify structural brain correlates of attention-deficit/hyperactivity disorder (ADHD) have yielded inconsistent results, with no common structural biomarker emerging across studies. Methodological factors may obscure underlying brain–behavior

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relations in the study of ADHD symptomatology, including the use of categorical diagnoses [1], relying on behavioral ratings from a single informant, and small sample sizes. Indeed, empirically based assessment of psychopathology has revealed aspects of dimensionality with regard to many psychiatric conditions, including ADHD [2]. Further, recent reports suggest that information from multiple informants increases the validity of ADHD assessment [3]. Population-based neuroimaging studies provide the opportunity to more rigorously characterize the neurobiological underpinnings of ADHD symptomatology by using dimensional, multi-informant behavioral ratings, and by examining convergence across multiple assessment modalities—including genetic and neurocognitive domains.

Studying a population-based sample of adolescents ($N = 1538$; 785 females) ($M = 14.53$ years old, SD = 0.41), we investigated the relationship between dimensional measures of ADHD symptomatology, brain structure, and reaction time variability (RTV)—an objective index of attentional lapses [4]. Parent ratings of ADHD symptoms, adolescent self-reports of ADHD symptoms, and RTV were each negatively associated with gray matter volume (GMV) in an overlapping region of the ventromedial prefrontal cortex (vmPFC). To our knowledge, this study represents the largest voxel-based morphometry (VBM) study to date on adolescent ADHD symptomatology. Despite modest correlations between multi-informant behavioral ratings ($r = 0.36$–0.66), we observed striking convergence in the vmPFC with regard to the anatomical correlates of each behavioral measure. Similarly, while RTV was weakly correlated with behavioral ratings of ADHD symptomatology ($r = 0.11$–0.14), there was considerable overlap with regard to anatomical correlates. Given convergence across dimensional, multi-informant behavioral ratings, and a measure of neurocognitive functioning that has been previously tied to ADHD, our findings indicate that vmPFC structure is a brain-based marker for inattention in adolescents.

Utilizing gene expression data collected as part of the Allen Human Brain Atlas [5], we found that the statistical map representing the relationship between GMV and ADHD symptomatology was differentially correlated with patterns of *DRD1* and *DRD2* gene expression. Our results appear consistent with models of cognitive dysfunction that postulate relative imbalance between D1 and D2 systems; however, it is important to emphasize that these gene expression analyses were meant to be hypothesis-generating in nature. More comprehensive studies of gene expression represent a plausible direction for future research.

The National Institute of Mental Health has placed growing emphasis on the need to, "identify and validate biomarkers and novel treatment targets relevant to the prevention, treatment, and recovery of psychiatric disorders," as evidenced by the new Computational Psychiatry Program (https://www.nimh.nih.gov/about/organization/dtr/adult-psychopathology-and-psychosocial-interventions-research-branch/computational-psychiatry-program.shtml). An exciting avenue of our research has been to examine the extent to which vmPFC structure during adolescence predicts subsequent symptom trajectories into adulthood. Using data from the 5-year follow-up wave of the IMAGEN study, we found that adolescent vmPFC volume predicts adult ADHD symptomatology while controlling for baseline symptomatology [6]. Intriguingly, these latter results suggest that early structural development of the vmPFC may be consequential for the subsequent expression of hyperactive/inattentive symptoms in adulthood.

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