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Application of Research Domain Criteria to childhood and adolescent impulsive and addictive disorders: Implications for treatment

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Abstract

The Research Domain Criteria (RDoC) initiative provides a large-scale, dimensional framework for the integration of research findings across traditional diagnoses, with the long-term aim of improving existing psychiatric treatments. A neurodevelopmental perspective is essential to this endeavor. However, few papers synthesizing research findings across childhood and adolescent disorders exist. Here, we discuss how the RDoC framework may be applied to the study of childhood and adolescent impulsive and addictive disorders in order to improve neurodevelopmental understanding and to enhance treatment development. Given the large scope of RDoC, we focus on a single construct highly relevant to addictive and impulsive disorders – initial responsiveness to reward attainment. Findings from genetic, molecular, neuroimaging and other translational research methodologies are highlighted.

Keywords

dopamine; development; substance use; impulsivity; fMRI; reward sensitivity

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Introduction

The National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project represents the first large-scale attempt to create a classification system based on measurable and dimensional biobehavioral characteristics for psychiatric research. Based on the essential observation that multiple different systems (e.g., reward responses, inhibitory control) are often implicated in a single disorder - and that a single system is often implicated across different disorders (e.g., substance addiction, attention deficit hyperactivity disorder (ADHD), bipolar disorder) - RDoC provides a systematic, transdiagnostic framework for psychiatry research aimed at integrating research findings across multiple domains (e.g., molecular, genetic, behavioral) and disorders with the long-term aim of improving treatments. While RDoC aims to cut across diagnoses, it also recognizes that existing diagnostic categories may be helpful starting points from which to synthesize current findings (Insel, et al., 2010; Insel, 2014). Here, we provide an overview of the RDoC framework as it relates to childhood and adolescent impulsive and addictive disorders and discuss how different aspects of this framework may be used to improve understanding of the development of these disorders and to improve treatments.

The first guiding principle of the RDoC project is that it is: ‘conceived as a dimensional system ... spanning the range from normal to abnormal’ (NIMH, 2011, p. 2). Although not explicitly stated, this dimensional approach may be considered fundamentally developmental in nature, as it encompasses the full range - or progression - of a given system from normal to abnormal. Thus, the RDoC approach is fully complementary to ongoing research efforts aimed at identifying the etiology of psychiatric disorders within a neurodevelopmental framework - and RDoC itself can be strengthened by the successful integration of neurodevelopmental research to the overall framework (Casey, Oliveri, & Insel, 2014). In addition, application of the RDoC approach to childhood and adolescent research may provide insights that cut across traditional diagnoses, offering novel opportunities for successful therapeutic intervention and ultimately improving existing treatments.

As shown in Figure 1, the RDoC framework is provided by a matrix composed of ‘rows’ that are hierarchically organized into domains, constructs and subconstructs (Insel, et al., 2010). Importantly, in order for a construct to be included in the RDoC matrix it must be empirically linked to ‘a specific biological system, such as a brain circuit’ (Cuthbert & Insel, 2013). Constructs and subconstructs may be studied under the ‘columns’ that are organized into seven units of analysis (genes, molecules, cells, circuits, physiology, behavior, self-reports) and one additional column for paradigms (e.g., monetary incentive delay tasks to assess reward responses). The organization of RDoC therefore provides an incredibly rich framework for the incorporation of research findings across different levels of analysis.

The items included within different elements of the RDoC matrix were generated during workshop proceedings conducted between 2010 and 2012 and should not be considered exhaustive; further details on individual workshop proceedings are found on the NIMH website (NIMHa). The general inclusionary criteria for inclusion in the RDoC matrix given to the workshops were: “(1) evidence for a functional behavioral or psychological construct,

(2) evidence for a neural system or circuit that plays a major role in implementing the function, and (3) a putative relationship to some clinically significant problem or symptom” (NIMHb).

As the current matrix includes five domains, each comprised of a number of constructs and subconstructs and each warranting its own review, we will here focus on data relating to the single construct of ‘initial responsiveness to reward attainment’ (a construct within the domain of Positive Valence Systems, highlighted in Figure 1), as it relates to human studies of childhood and adolescent addictive and/or impulsive disorders. In theory, a similar approach may be applied to other RDoC constructs, and the current focus on ‘initial responsiveness to reward attainment’ was selected because of its importance to adolescent addictive and/or impulsive disorders. However, other constructs both within Positive Valence Systems (e.g., approach motivation, sustained responsiveness to reward attainment, reward learning) as well as within other domains (i.e., Negative Valence Systems, Cognitive Systems, Systems for Social Process, Arousal and Regulatory Systems) are also relevant to the development of adolescent addictive and impulsive disorders. Thus, further literature reviews aimed at ‘filling-in’ other elements of the RDoC matrix in relation to these constructs are also needed.

Initial responsiveness to reward attainment

The NIMH workshop on Positive Valence Systems (June 2011) defined ‘initial responsiveness to reward attainment’ as the ‘mechanisms/processes associated with hedonic responses—as reflected in subjective experiences, behavioral responses, and/or engagement of the neural systems to a positive reinforcer—and culmination of reward seeking’ (NIMH, 2011, p.4). Importantly, this definition emphasizes not only immediate hedonic responses, but also the ‘culmination of reward seeking’. As such, we will here discuss aspects of reward responses related to both *initial responses to reward* as well as those more generally related to *approach behaviors* involved in reward seeking (e.g., incentive salience; development of prefrontal cortical (PFC) inhibitory control mechanisms), although we appreciate that some of these latter constructs may map more directly onto other constructs within the RDoC matrix (e.g., approach motivation, cognitive control). We will also discuss aspects of normative brain development (e.g., maturation of white- and gray-matter structures) as these are essential starting points for understanding RDoC constructs – including initial responsiveness to reward attainment - from a developmental perspective. We have adopted this relatively inclusive approach in order to allow for synthesis of existing data as they relate to the development of circuit-related factors influencing reward responses during childhood and adolescence with the long-term goal of synthesizing findings to improve existing treatments. Finally, given the biological emphasis of the RDoC framework, we will primarily focus on data relating to Genes, Molecules and Circuits.

The complete list of the systems proposed in the RDoC matrix on initial responsiveness to reward attainment is shown in Figure 1. The items included in this matrix were generated by the Reward Seeking and Consummatory Behavior Group, a subgroup of the Positive Valence Systems workshop, which also generated the constructs and associated matrix elements for approach motivation and sustained/longer-term responsiveness to reward attainment (NIMH,

2011). As the proceedings from this group specifically notes that some potential matrix elements may have been omitted due to time constraints (NIMH, 2011), Figure 1 also lists some provisional items (shown in italics) that are not included in the current matrix but which are proposed as relevant to this construct. For further details on workshop proceedings relevant to this and other constructs within Positive Valence Systems, see (NIMH, 2011).

Circuits and Physiology¹

The current RDoC matrix on initial responsiveness to reward lists a number of brain regions under the heading of ‘Circuits’: medial orbitofrontal cortex (mOFC), ventromedial prefrontal cortex (vmPFC), anterior insula, dorsal anterior cingulate, nucleus accumbens (NAcc), ventral tegmental area (VTA), ventral pallidum and lateral hypothalamus. While no specific ‘circuit’ is currently listed, many of the brain regions listed may be rather broadly classified as part of the mesocorticolimbic system. The processes associated with these regions as they relate to childhood and adolescent addictive and impulsive disorders are presented in Table 1 along with selected neurodevelopmental evidence from structural and functional MRI studies.

Collectively, these regions (and the circuits they comprise) are sometimes described as pertaining to ‘top-down’ and ‘bottom-up’ processes. Within this framework, the term ‘bottom-up’ generally refers to the encoding of reward and incentive salience by subcortical limbic and related neurocircuitry (e.g., NAcc, VTA, ventral pallidum) with reciprocal projections to the PFC (D’Ardenne, McClure, Nystrom, & Cohen, 2008; Everitt & Robbins, 2005; Matzeu, Zamora-Martinez, & Martin-Fardon, 2014; Schultz, 1997, 2000). Conversely, the term ‘top-down’ is used to refer to the control of subcortical limbic regions by primarily prefrontal cortical (PFC) brain regions involved in cognitive control and executive functioning processes (Goldstein & Volkow, 2011; Kober, et al., 2010; Taber, 1993; Volkow, et al., 2010). Such inhibitory processes are covered elsewhere in the matrix (e.g., ‘cognitive control’ is a construct within the domain of ‘Cognitive Systems’). However, in addition to inhibitory functions, ‘top-down’ regions such as the mOFC and vmPFC are also themselves implicated in the encoding of reward and salience (Goldstein & Volkow, 2011). These systems interact in a dynamic manner to influence a range of complex cognitive processes relevant to reward seeking and impulse control (e.g., encoding of incentive salience; cognitive control mechanisms) (Koob & Volkow, 2010; Volman, et al., 2013), and develop at different rates during childhood, adolescence and adulthood. Thus, one of the challenges for developmental research under RDoC will be to further quantify interactions between different domains over time.

Neurodevelopmental findings from longitudinal and large-scale cross-sectional imaging-based studies of healthy children and adults provide an essential starting point from which to interpret findings from studies conducted in psychiatric and at-risk populations. In the following sections we will therefore first review what is known about the developmental trajectories of white- and gray-matter structures. We will also discuss findings from

¹Although no systems are currently identified under ‘Physiology’ in the RDoC matrix on initial responsiveness to reward attainment, findings from fMRI studies may also be considered under this unit of analysis as blood-oxygenation-level-dependent (BOLD) signals are listed under ‘Physiology’ in other rows of the matrix (e.g., ‘Attention’).

functional magnetic resonance imaging (fMRI) studies that may be used to draw inferences about the neural functional development of top-down and bottom-up neurocircuitry. Finally, we will highlight recent findings from the field of connectomics and discuss how these factors may be studied within the context of adolescent impulsive and addictive disorders.

White matter

Generally speaking, most major white-matter tracts are characterized by increases in fractional anisotropy (FA) and decreases in mean diffusivity (MD) from childhood into early adulthood. Once thought to be linear, evidence from diffusion-weighted MRI studies suggests relatively nonlinear developmental trajectories for most major white-matter tracts (Lebel & Beaulieu, 2011; Lebel, et al., 2012; Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008), as well as different developmental trajectories across different tracts; e.g. (Barnea-Goraly, et al., 2005; Hasan, et al., 2009; Lebel, et al., 2008). Within a developmental context, increases in axon density, myelination and straightening of fiber tracts likely contribute to increases in FA and decreases in MD during typical development (Paus, T., 2010), although it is important to note that other factors (e.g., increases in intracellular vs. extracellular fluid) may influence these measures. As such, further preclinical studies combining *ex vivo* and *in vivo* methods are essential to better characterize cellular factors influencing diffusion-based measures within a developmental context (Paus, T, 2010; Paus, Keshavan, & Giedd, 2008).

FA values within callosal regions such as the genu and splenium appear to stabilize by early adolescence, whereas FA values continue to increase within fronto-temporal-limbic tracts such as the cingulum, uncinate fasciculus and superior longitudinal fasciculus during late adolescence into early adulthood (Lebel & Beaulieu, 2011; Lebel, et al., 2012; Lebel, et al., 2008; Peters, et al., 2012). Age-related reductions in MD values also occur earlier in callosal versus fronto-temporal-limbic pathways, although generally these values stabilize slightly later than do FA values; e.g., (Lebel, et al., 2012; Lebel, et al., 2008). Together, these data demonstrate that maturation of pathways connecting prefrontal cortical and limbic structures – key pathways for the regulation and control of motivated behaviors - is ongoing throughout adolescence into adulthood.

Significant individual variation in the development of white-matter tracts exists. For example, whereas most individuals continue to exhibit increases in FA within fronto-temporal-limbic tracts during early adulthood, a subset of individuals exhibit decreases during this time (Lebel & Beaulieu, 2011). Given that alterations in FA have been reported among adolescents and young adults with bipolar disorder and ADHD and other individuals at-risk for addictions, e.g., (Adler, et al., 2006; Eloffson, Gongvatana, & Carey, 2013; Hamilton, et al., 2008; Yip, Chandler, Rogers, Mackay, & Goodwin, 2013), it is likely that such individual difference factors relate to the development of impulsive and addictive disorders. Within the context of RDoC, longitudinal studies focused on identifying common and distinct aspects of white matter neurodevelopmental trajectories across disorders are needed.

Gray matter: evidence from structural and functional MRI

Generally speaking, gray-matter cortical and subcortical development is ongoing throughout childhood and adolescence into early adulthood, with tissue volumes increasing before puberty and decreasing after puberty to form an inverted-U-shaped trajectory (Giedd, 1999; Giedd, 2004; Gogtay, et al., 2004; Gogtay & Thompson, 2010; Sowell, et al., 2003; Sowell, Thompson, Tessner, & Toga, 2001). These volumetric reductions are thought to result from dendritic pruning and reorganization of neuronal fibers (as opposed to neuronal loss), possibly related to increases in intra-cortical myelination (Giedd, 2004; Gogtay & Thompson, 2010; Paus, 2005; Sowell, et al., 2001).

Within the cortex, gray-matter maturation occurs hierarchically, with maturation of lower-order sensorimotor regions preceding maturation of higher-order association areas (Giedd, 2004; Gogtay, et al., 2004). Regions of the PFC involved in ‘top-down’ processes (e.g., executive function, response inhibition) develop throughout adolescence and do not fully reach adult levels of maturity until the mid 20s (Galvan, et al., 2006; Giedd, 2004). While most studies tend to focus on cortical rather than subcortical maturational changes, ‘bottom-up’ subcortical structures have typically been thought to reach adult maturational levels earlier (Casey, Jones, & Hare, 2008). However, it is important to note that gray-matter development within regions including the pallidum and striatum continues into adulthood (Giedd, 2004; Langen, et al., 2009; Raznahan, et al., 2014; Sowell, Thompson, Holmes, Jernigan, & Toga, 1999).

Findings of protracted development of subcortical limbic structures arguably challenge developmental models emphasizing an imbalance between the development of cortical and subcortical structures (Dennison, et al., 2013; Raznahan, et al., 2014). Notably, a recent study reporting an imbalance between subcortical and cortical development in adolescence did not find an association between this imbalance and self-reported risk-taking (Mills, Goddings, Clasen, Giedd, & Blakemore, 2014). Thus, an important future research goal of the RDoC initiative should involve determining the functional significance of cortical versus subcortical developmental differences during adolescence.

Findings from fMRI studies can also inform understanding of neurodevelopment, as these data can provide insight into the functional development of neural circuits; for reviews see (Casey, 2014; Galvan, 2010). Cross-sectional studies of reward-responses (e.g., as assessed using monetary incentive delay (MID) tasks) comparing neural responses between adolescents and adults have yielded equivocal findings, with both increased, e.g., (Galvan, et al., 2006; Van Leijenhorst, et al., 2010), and decreased, e.g., (Bjork, Smith, Chen, & Hommer, 2010), striatal responses reported among adolescents; for a review, see (Richards, Plate, & Ernst, 2012). A recent longitudinal fMRI study found relatively increased dorsal striatal activity during reward anticipation during late versus middle adolescence (Lamm, et al., 2014), consistent with the general hypothesis of increases in subcortical reward responses during normative development. However, further task-based functional MRI research incorporating multiple time points and larger sample sizes - as has been done in structural and resting state MRI studies, e.g., (Di Martino, A., et al., 2014; Raznahan, et al., 2014) - is needed to clarify the natural trajectory of reward-system activity across development.

For a number of years, findings from fMRI studies have been interpreted as supporting neurodevelopmental models emphasizing relative maturity of subcortical (e.g., ventral striatal) versus cortical (e.g., orbitofrontal cortex; OFC) regions; e.g., (Bunge & Wright, 2007; Galvan, et al., 2006). This imbalance has been invoked to explain heightened reward-seeking behaviors observed in adolescents (Casey, 2014; Crone & Dahl, 2012; Galvan, 2010). However, it is important to note that conflicting data also exist (Crone & Dahl, 2012; Galvan, 2010). For example, several studies indicate that, despite age-related differences in the type of conditions under which maximal PFC engagement is exhibited, magnitudes of maximal engagement may not differ between adolescents and adults; *reviewed in* (Crone & Dahl, 2012). Findings such as these suggest that maturation of cognitive-control processes during adolescence may involve complex functional reorganization of networks, rather than simple linear maturation, consistent with recent findings from resting-state studies employing graph-theory analytical methods (Crone & Dahl, 2012; Di Martino, A., et al., 2014).

A key area for further research will be to determine when and how different contextual factors (e.g., task-related factors, social and emotional factors) influence engagement of different neural networks across development (Braams, Peters, Peper, Guroglu, & Crone, 2014; Casey, 2014; Crone & Dahl, 2012). A complementary area requiring additional study and well-suited to an RDoC approach is the functional significance of increased reward responses during adolescence (Crone & Dahl, 2012). For example, findings from recent studies suggest that increased reward responsiveness (at least as defined by heightened striatal activity) may be an adaptive feature of adolescent development; e.g., (Barkley-Levenson & Galvan, 2014; Hauser, Iannaccone, Walitza, Brandeis, & Brem, 2015).

Systems-level changes: Insights from connectomics

In recent years, a rapidly growing body of research, generally referred to as connectomics, has focused on understanding the development of the human brain from the perspective of large-scale system dynamics via analysis of resting state fMRI and diffusion-weighted imaging data; e.g., (Behrens & Sporns, 2012; Collin & van den Heuvel, 2013; Dennis, et al., 2013; Di Martino, Adriana, et al., 2014; Dosenbach, et al., 2010; Grayson, et al., 2014; Ingalhalikar, et al., 2014; van den Heuvel & Sporns, 2011; Yang, et al., 2014). This line of inquiry has demonstrated that, while much of the macroscopic organization of the connectome is complete by age two (*reviewed in* (Collin & van den Heuvel, 2013; Di Martino, A., et al., 2014)), childhood and adolescence are characterized by a number of complex systems-level organizational changes (Di Martino, Adriana, et al., 2014). These include a shift from predominantly local connectivity during infancy (characterized by primarily short-range connections) to increasingly distributed connectivity (characterized by long-range connections) during adolescence into adulthood (although the most dramatic changes occur during infancy and very early childhood) (Di Martino, Adriana, et al., 2014; Dosenbach, et al., 2010; Fair, et al., 2009; Satterthwaite, et al., 2013). Other significant neurodevelopmental factors include changes in interhemispheric connectivity (Di Martino, Adriana, et al., 2014; Ingalhalikar, et al., 2014) and in the organization of connections (e.g., the development of ‘rich clubs’ or groups of highly connected nodes that are themselves interconnected) (Bullmore & Sporns, 2012; Di Martino, Adriana, et al., 2014; Grayson, et

al., 2014). The overall picture is one of increasing efficiency of connectivity via a range of complex higher order systems-level refinements (e.g., increases in rich-clubness); for reviews see (Collin & van den Heuvel, 2013; Di Martino, A., et al., 2014).

The topological changes outlined above are thought to underlie the development of increasingly sophisticated cognitive processes (Grayson, et al., 2014). This line of research therefore has the potential to significantly enhance understanding of the pathophysiology of psychiatric disorders via similar assessment of atypical neural development (Bassett & Bullmore, 2009; Collin & van den Heuvel, 2013; Di Martino, A., et al., 2014; Grayson, et al., 2014). While specific topological properties (e.g., rich-clubness) are not explicitly listed in the current matrix, connectome-based approaches are consistent with the dimensional focus of the RDoC framework (Castellanos, Di Martino, Craddock, Mehta, & Milham, 2013). Further work is nonetheless required to understand interactions between specific topological properties and other units of analysis (e.g., genes, behavior). Publicly available large-scale neuroimaging datasets represent a powerful resource for future studies in this area; e.g., the Philadelphia Neurodevelopmental Cohort PDN (Satterthwaite, et al., 2015) and Pediatric Imaging, Neurocognition, and Genetics (PING) (Jernigan, et al., 2015) databases.

Individual variation in circuit development – relationship to reward responses under RDoC

As outlined above, neuroimaging data suggest significant inter-individual variation in the developmental trajectories of gray- and white-matter structures, and this may contribute to individual differences in reward processing and/or to vulnerabilities for addictive and impulsive disorders; e.g., (Dennison, et al., 2013; Rahman, Xu, & Potenza, 2014; Samanez-Larkin, Levens, Perry, Dougherty, & Knutson, 2012; Shaw, et al., 2011; Xu, et al., 2012). However, the precise relationship between individual variation in white-matter changes during typical development and factors such as impulsivity during adolescence remains unclear. For example, increased FA values have been associated with both *decreased* delay-discounting behaviors (Olson, et al., 2009) and *increased* risk-taking behaviors during adolescence (Berns, Moore, & Capra, 2009). These seemingly conflicting findings highlight the need for dimensional research studies assessing the relationship between factors such as FA and different measures related to reward responses. Within the specific framework of initial responsiveness to reward attainment, such research might, for example, assess the relationship between longitudinal changes in FA values within corticolimbic tracts and changes in: (i) taste reactivity (behavioral unit of analysis); (ii) scores on the consummatory subscale of the Temporal Experience of Pleasure Scale (TEPS) (Gard, Gard, Kring, & John, 2006) (self-report unit of analysis); and, (iii) neural responses during reward receipt (circuit-related unit of analysis).

Findings of alterations in white- and gray-matter structures among adolescents and young adults with disorders including ADHD, bipolar disorder and alcohol misuse, e.g., (Adleman, et al., 2012; Adler, et al., 2006; Eloffson, et al., 2013; Hamilton, et al., 2008; Shaw, et al., 2007; Yip, et al., 2013), support the hypothesis of pathophysiological involvement of circuit development in conferring vulnerability to a range of impulsive and addictive disorders. Similarly, data from functional MRI studies have demonstrated blunted reward-related

ventral-striatal responses among adolescents and young adults with substance-use disorders, bipolar disorder and ADHD; e.g., (Nymberg, et al., 2013; Peters, et al., 2011; Yip, Worhunsky, Rogers, & Goodwin, 2015). In contrast, data from two recent prospective studies comparing individuals early-on in substance-use experimentation (i.e., prior to dependence) suggest that increased reward-responses may be predictive of future substance-use problems (Dager, et al., 2014; Heitzeg, et al., 2014); for a review of findings from recent prospective studies, *see* (Heitzeg, Cope, Martz, & Hardee, 2015).

Further research is therefore needed to determine the relationship between neural reward responses across different stages of development and in relation to substance-use initiation and other risk factors. The importance of assessing interactions between different risk factors is illustrated by recent data indicating differential neural substrates of illicit substance-use initiation between adolescents with and without prenatal cocaine exposure (Yip, Lacadie, Sinha, Mayes, & Potenza, 2015). Similarly, given the presence of similar findings across a range of disorders, studies directly comparing neural structure and functional responses *across* different diagnostic categories are needed to examine the disease-specificity of existing data (Insel, 2014). Within a developmental framework, similar research could assess the utility of, for example, blunted reward responses during early childhood in predicting the development of different addictive and impulsive disorders by late adolescence, with the long-term goal of identifying clinically meaningful biomarkers.

Although not extensively reviewed here, it is important to note that current data suggest significant sex differences in the longitudinal development of both white- and gray-matter structures; e.g., (Dennison, et al., 2013; Ingahalikar, et al., 2014; Perrin, et al., 2009; Raznahan, et al., 2014; Satterthwaite, et al., 2014). While further research is needed to understand the biological basis of sex differences in neural tissue development, existing data suggest that aspects of gray- (e.g., cortical thickness, tissue density) and white-matter development (e.g., axon diameter growth, myelination) are influenced by the expression of sex hormones including estrogen and testosterone (Arevalo, Santos-Galindo, Bellini, Azcoitia, & Garcia-Segura, 2010; Bramen, et al., 2011; Brouwer, et al., 2015; Paus, 2013; Pesaresi, et al., 2015). Thus, a further area for research under RDoC will be the interaction between sex-specific neurodevelopmental trajectories and dimensional changes in responsiveness to reward attainment as measured across different units of analysis (including neural functional activity).

Circuits and treatment

Collectively, the above data indicate that similar alterations in neural development may contribute to vulnerability for multiple different but related childhood and adolescent disorders. These data also highlight the complex, dynamic trajectories of human neurodevelopment throughout childhood and adolescence and suggest multiple implications for the treatment and prevention of adolescent impulsive and addictive disorders. For example, given the ongoing development of prefrontal cortical regions involved in ‘top-down’ inhibitory processes during adolescence – in conjunction with evidence from adult studies suggesting involvement of these regions in treatment responses to behavioral therapies; e.g., (Brewer, Worhunsky, Carroll, Rounsaville, & Potenza, 2008; DeVito, et al.,

2012) – future research could explore the efficacy of combining existing treatments with specific interventions aimed at strengthening inhibitory mechanisms or in reducing approach tendencies (e.g., working-memory training, cognitive-bias modification) (Eberl, et al., 2013; Wiers, Eberl, Rinck, Becker, & Lindenmeyer, 2011).

Recent data suggest that cognitive-bias modification may be effective in reducing subcortical neural responses to alcohol-cues associated with craving among abstinent adults (Wiers, et al., 2015). Thus, it is possible that cognitive-bias modification might be effective in reducing ‘bottom-up’ reward responses among adolescents at-risk for disorders such as addictions (Houben, Havermans, Nederkoorn, & Jansen, 2012), particularly when combined with existing treatments (Eberl, et al., 2013). A separate but complimentary line of research involves the indirect targeting of reward-related decision-making (e.g., as assessed using delay-discounting tasks) via cognitive training. For example, working-memory training has been found to reduce delay-discounting rates among adults with stimulant dependence (Bickel, Yi, Landes, Hill, & Baxter, 2011); for reviews, see (McClure & Bickel, 2014; Wesley & Bickel, 2014). Further research is needed to determine whether specific interventions aimed at altering approach tendencies (as in cognitive-bias modification) or at increasing ‘top-down’ executive functioning (as in working-memory training) (Eberl, et al., 2013; McClure & Bickel, 2014; Wesley & Bickel, 2014; Wiers, et al., 2011) might be efficacious in altering aberrant reward responses among adolescents. Within this context, fMRI might aid in the *a priori* identification of individuals with altered subcortical versus prefrontal cortical neurodevelopment who might benefit from different forms of cognitive training across a range of disorders. As discussed above, such research should aim to incorporate multiple measures of circuit-level functioning (e.g., task-based fMRI, resting-state connectivity, structural imaging).

Accumulating evidence from primarily adult studies suggests that individual differences in pretreatment neural structure and function are related to individual differences in treatment responses to behavioral therapies across a range of addictions, e.g., (Brewer, et al., 2008; Feldstein Ewing, Filbey, Sabbineni, Chandler, & Hutchison, 2011; Kober, Devito, Deleone, Carroll, & Potenza, 2014; Yip, et al., 2014); for reviews, see (Feldstein Ewing & Chung, 2013; Yip, Carroll, & Potenza, 2015). Further, findings from adult studies directly comparing pre- versus post-treatment fMRI data suggest that the efficacy of treatments such as cognitive behavioral therapy relate to its neuromodulatory effects on regions involved in cognitive control processes, such as the dorsolateral PFC (DeVito, et al., 2012; Goldapple, 2004).

Several recent studies conducted in adolescent populations suggest somewhat similar relationships between pretreatment cortical neural function and behavioral treatment responses; e.g., (Chung, Paulsen, Geier, Luna, & Clark, 2015; Feldstein Ewing, et al., 2013; Feldstein Ewing, et al., 2012; Krishnan-Sarin, et al., 2013). For example, increased pretreatment activations within regions including the inferior frontal gyrus and ventrolateral PFC are associated with better substance-use outcomes following treatments for cannabis and tobacco use in adolescents (Chung, et al., 2015; Feldstein Ewing, et al., 2013; Krishnan-Sarin, et al., 2013). However, data suggest that similar therapies may engage different brain regions in adults versus adolescents. For example, exposure to change-talk – a key

component of motivational interviewing - is associated with activation of the striatum and PFC among adults (Feldstein Ewing, et al., 2011) and with activation of the inferior frontal gyrus and insula among adolescents (Feldstein Ewing, et al., 2013). Taken together, these data suggest possible mechanistic differences in the efficacy of behavioral therapies between adolescents and adults, highlighting the need for further research focusing on circuit-level factors and treatment responses specifically in adolescent populations.

In adults, associations between treatment outcomes and neural function during reward-task performance within subcortical regions have also been reported; e.g., (Jia, et al., 2011; Yip, et al., 2014). For example, a negative association between pretreatment ventral striatal activity during reward receipt and abstinence during treatment has been reported among adults with cocaine dependence (Jia, et al., 2011), and increased pretreatment caudate activity (during loss processing) has been reported among cannabis-dependent young adults who did not subsequently achieve a period of sustained abstinence during treatment (Yip, et al., 2014). Notably, there has been one report of a negative association between subcortical (amygdala, putamen and NAcc) activation early in treatment and symptom severity following treatment in an adolescent population (Chung, et al., 2015), suggesting that individual differences within subcortical regions may also contribute to variations in treatment responses among adolescents. Given the growing body of evidence indicating that development of subcortical structures continues into adulthood, e.g., (Giedd, 2004; Langen, et al., 2009; Raznahan, et al., 2014; Sowell, et al., 1999), further research assessing age-related differences in subcortical structure and function in relation to treatment responses is needed.

Several lines of evidence suggest that pharmacological treatment interventions may impact on neurodevelopmental processes related to reward processing. Meta-analytic data from studies of ADHD suggest normalizing effects of dopaminergic medications on neural activations and gray-matter structural volumes (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013; Nakao, Radua, Rubia, & Mataix-Cols, 2011). Pre-clinical data and data from human adult studies further suggest normalizing and/or ameliorative effects of mood stabilizers on white-matter structures (Benedetti, et al., 2011; Macritchie, et al., 2010; Makoukji, et al., 2012). These findings, in conjunction with data suggesting associations between treatment outcomes and white-matter microstructural characteristics (Xu, et al., 2010; Zhou, et al., 2011), suggest directions for further research, although the benefits of pharmacological treatment for childhood and adolescent disorders should be weighed against any associated risks.

To our knowledge, no studies have assessed the longitudinal effects of behavioral treatments for substance-use (via comparison of pre- versus post-treatment fMRI data) in an adolescent population. Such research will inform the current understanding of the neurobiological mechanisms underlying effective treatments and aid in further treatment development. Large-scale neuroimaging studies assessing the neural correlates of successful behavioral change following treatments (e.g., abstinence) across different developmental epochs (e.g., pre- versus post-puberty) are warranted. Such data could aid in the identification of critical periods for adolescent interventions wherein treatments might be most likely to exert sustained positive change (Casey, BJ, et al., 2014), as it is likely that the effectiveness of

different treatments may change as a functioning of ongoing neurodevelopmental processes (e.g., dendritic pruning, myelination).

Summary of circuits

Unlike ligand-based molecular imaging modalities (reviewed below, see *Molecules and Cells*), functional, structural and diffusion-weighted MRI do not require the use of radiotracers and therefore provide a powerful, non-invasive means of assessing the developing human brain *in vivo*. In general, existing evidence suggests that the adolescent brain may be characterized by increased functional activation of ‘bottom-up’ limbic reward regions (e.g., ventral striatum) relative to that of ‘top-down’ cortical inhibitory regions (e.g., OFC, dorsolateral PFC). While it has long been acknowledged that cortical development is ongoing into early adulthood, emerging data suggest that development of subcortical regions previously thought to stabilize prior to adulthood is also ongoing during this time. Further, significant individual differences in gray- and white-matter development exist, and these may relate to vulnerabilities for a range of disorders. Thus, further study using imaging-based methodologies is warranted to characterize the full range of ‘typical to atypical’ neurodevelopment (Casey, BJ, et al., 2014). In particular, studies conducted among children, adolescents and young adults either very early on in the disease course (e.g., prior to significant clinical intervention such as long-term pharmacotherapy) or even prior to disease onset (e.g., prodromal studies of individuals at increased risk for disorders) are needed to further identify possible biomarkers in order to aid treatment interventions. Ideally, these studies should incorporate different neuroimaging modalities (i.e., multi-modal imaging) to clarify brain structure-function relationships.

Genes

The current RDoC matrix highlights *DRD2* and *DAT1*² as genes relevant to the construct of initial responsiveness to reward attainment. However, it is important to note that other genes including *DRD4*, *OPRM1* and *COMT* are implicated in this construct; e.g., (Camara, et al., 2010; Dreher, Kohn, Kolachana, Weinberger, & Berman, 2009; Foti & Hajcak, 2012; Hendershot, Claus, & Ramchandani, 2014; Perez-Edgar, et al., 2014; Peters, et al., 2011; Ray & Hutchison, 2007; Ray, et al., 2014; Schacht, et al., 2013; Silveira, et al., 2014; Smith & Boettiger, 2012; Stice, Yokum, Bohon, Marti, & Smolen, 2010). Given the breadth of the existing literature in this area, the following section will focus on the relevance of those genes already listed in the RDoC matrix on initial responsiveness to reward attainment – namely, *DRD2* and *DAT1* – to childhood and adolescent addictive and impulsive disorders.

Initial responsiveness to reward attainment – DRD2 and DAT1

Family, twin and adoption studies have demonstrated significant heritability rates for addictive disorders, with estimates ranging from 48-66% for alcohol dependence and 23-54% for opioid dependence; for a review, see (Agrawal, et al., 2012). In addition, genetic association studies have identified multiple allelic variants putatively associated with addictive and impulsive disorders; e.g., (Demers, Bogdan, & Agrawal, 2014; Sklar, et al.,

² *TREK1* is also included in parentheses in the online matrix; see Figure 1.

2002; Sun, Yuan, Shen, Xiong, & Wu, 2014). However, findings have often been inconsistent. For example, studies focusing on *DRD2* and *DAT1* – genes listed in the current RDoC matrix on initial responsiveness to reward attainment – have yielded equivocal results within the context of specific disorders including substance and behavioral addictions (Blomqvist, Gelernter, & Kranzler, 2000; Comings, Muhleman, Ahn, Gysin, & Flanagan, 1994; Comings, et al., 1996; Lohoff, et al., 2010; Moyer, et al., 2011; Sweitzer, Donny, & Hariri, 2012; Ueno, et al., 1999; van der Zwaluw, et al., 2009), bipolar disorder (Gomez-Casero, Perez de Castro, Saiz-Ruiz, Llinares, & Fernandez-Piqueras, 1996; Greenwood, et al., 2013; Greenwood, Schork, Eskin, & Kelsoe, 2006; Keikhaee, et al., 2005; Manki, et al., 1996; Massat, et al., 2002; Pinsonneault, et al., 2011; Wang, et al., 2014) and ADHD (Barr, et al., 2001; Chen, et al., 2003; Greenwood, et al., 2013; Kustanovich, et al., 2004; Lasky-Su, et al., 2008; Nyman, et al., 2007).

Given the somewhat conflicting findings from disorder-specific studies, an alternative research approach has been to identify genetic variants associated with specific aspects of reward processing – e.g., responses to reward attainment. Such research has demonstrated that, in healthy adults, the *DRD2* and *DAT1* genes may mediate individual neural reward responses. For example, increased ventral striatal activations in response to rewarding stimuli have been reported among adult carriers of allelic variants associated with increased synaptic dopamine (DA); e.g., *DRD2* 141C Del, *DAT1* 9-repeat (Dreher, et al., 2009; Forbes, et al., 2009).

Data also suggest that variation in *DAT1* may contribute to individual differences in neural reward responses among adolescents (Paloyelis, Mehta, Faraone, Asherson, & Kuntsi, 2012). However, replication using larger sample sizes and longitudinal designs is needed, as the relative contribution of genetic factors may not be constant over the course of development. For example, differential contributions of genes including *DAT1* and *DRD2* to alcohol use behaviors have been reported across different stages of development; e.g., (Guo, Wilhelmsen, & Hamilton, 2007; Hopfer, et al., 2005). Thus, an important next step will be to characterize the natural developmental trajectory of reward responses across childhood and adolescence among individuals with and without different genetic variants found to impact reward responses. Such research may allow for the identification of critical periods wherein treatment interventions might be most effective for individuals at increased genetic risk for a range of disorders (Casey, BJ, et al., 2014). Additionally, as *DRD2* has been found to be in linkage disequilibrium with *ANKKI* and certain addictive behaviors may link more closely to *ANKKI* than to *DRD2* (Dick, et al., 2007), additional research should investigate the extent to which *ANKKI* variation may relate to adolescent reward processing and addiction vulnerability.

A complementary line of research involves the study of gene-by-environment interactions (GxE), which may be efficacious in understanding how functional genetic polymorphisms interact with other factors to confer vulnerability for a variety of complex behavioral phenotypes, such as addictive and impulsive disorders. Examples of this line of inquiry include data demonstrating increased ADHD-related symptoms among adolescent boys homozygous for the *DAT1* 10-repeat allele with high levels of psychosocial adversity, but not among those with different genotypes or who have experienced lower levels of adversity

(Laucht, Skowronek, Becker, & et al., 2007). GxE data also suggest interactions between the 10-repeat allele, timing of substance use behaviors during early adolescence, and levels of cigarette and alcohol consumption during late adolescence (Schmid, et al., 2009). In addition, two recent studies suggest significant interaction effects between parenting behaviors and *DRD2* genotype on adolescent drinking behaviors (Pieters, et al., 2012; van der Zwaluw, et al., 2010). Studies using this type of GxE approach may be helpful in identifying critical periods for intervention and in reconciling seemingly conflicting findings of associations between specific gene variants in some but not all studies of a given disorder, as they suggest that genetics alone may be insufficient to explain complex behavioral phenotypes (e.g., substance use), which likely relate to multiple different systems (units of analysis).

Despite the potential of GxE research it should nonetheless be noted that findings from studies of locus-specific GxE (such as those highlighted above) are somewhat controversial, e.g., (Duncan & Keller, 2011; Munafo, Zammit, & Flint, 2014a, 2014b; Rutter, 2014), as findings have proved difficult to replicate and are not always borne out in genome-wide-association studies (GWAS) (Duncan & Keller, 2011; Munafo, Durrant, Lewis, & Flint, 2009; Munafo & Flint, 2009).

Relationship to treatment

A growing body of research has explored the relationship between genetic factors and treatment responses for addictive and impulsive disorders among young adults. Examples of this work include studies on the relationship between responses to behavioral treatments for cannabis and alcohol use and genes encoding for aspects of both serotonergic (5HT2A) and dopaminergic (DRD4) functioning; e.g., (Feldstein Ewing, LaChance, Bryan, & Hutchison, 2009; Feldstein Ewing, et al., 2012). However, relatively few studies have assessed the influence of *DRD2* and *DAT1* genotypes on treatment outcomes for childhood and adolescent addictive and impulsive disorders. One notable exception is the relationship between *DAT1* genotype and responses to methylphenidate among children and adolescents with ADHD. However, findings have not been consistent across studies, with some data suggesting that homozygosity for the *DAT1* 10-repeat allele is associated with a reduced response to methylphenidate treatment, e.g., (Cheon, Ryu, Kim, & Cho, 2005; Roman, 2002; Winsberg & Comings, 1999) and other data suggesting that homozygosity for the 9-repeat allele is associated with a poorer response, e.g. (Jooper, et al., 2007; Stein, 2005). Thus, a recent meta-analysis concluded that *DAT1* genotype alone was insufficient to predict methylphenidate responses (Kambeitz, Romanos, & Ettinger, 2014).

To our knowledge, there are no studies that have examined the relationship between *DRD2* or *DAT1* genotype and treatment responses for addictions in a child or adolescent population. However, recent data suggest an interaction between *DRD2* genotype and participation in an alcohol prevention program on subsequent drinking outcomes in youth: In a study of over 900 adolescents, individuals with a *DRD2* risk variant who were not assigned to a drinking prevention program had increased alcohol-use at 2-year follow-up in comparison to individuals with the same risk variant who received a preventative intervention and in comparison to youth without the risk variant (Brody, Chen, & Beach,

2013). Consistent with this, findings from some adult studies further suggest possible involvement of *DRD2* in treatment outcomes. For example, increased relapse rates following 12-Step treatment for alcohol dependence have been reported among individuals with the *DRD2* Taq1A allele (Dahlgren, et al., 2011) and increased Taq1A allelic frequency has been associated with poorer treatment responses among individuals with opioid dependence (Doehring, et al., 2009; Lawford, et al., 2000), although conflicting reports for the latter finding also exist (Barratt, Coller, & Somogyi, 2006; Crettol, et al., 2008). As in the case of disorder-specific genetic association studies, seemingly contrary research findings may relate to small single gene effects or insufficient characterization of ultimately highly heterogeneous behavioral phenotypes (in this case, phenotypes such as ‘responders’ vs. ‘nonresponders’) (Falcone, et al., 2013; Hutchison, 2010).

Multimodal studies combining genotyping with other translational research methods such as fMRI suggest that *DRD2* and *DAT1* allelic variation may relate to individual differences in treatment responses via neural responses during abstinence and cue-induced craving. For example, using perfusion-based MRI, Wang and colleagues (2008) demonstrated greater abstinence-induced changes in regional cerebral blood flow (rCBF) among adult smokers with *DRD2* 141C Del allele within regions associated with subjective experiences of craving; e.g., ventral striatum, dorsolateral PFC (Wang, et al., 2008). FMRI data further suggest a positive association between the *DAT1* 9-repeat allele and increased ventral striatal and dorsolateral PFC responses to smoking-related cues among adult smokers (Franklin, et al., 2009; Franklin, et al., 2011). In a separate study, Moeller and colleagues reported a significant interaction effect between recency of cocaine use, *DAT1* genotype and neural activations, such that individuals with the 9-repeat allele and recent (< 72 hours) cocaine use had increased responses to drug cues in comparison to individuals with a different genotype or without recent cocaine use (Moeller, et al., 2013). Together, these data suggest that genes encoding for DA-related moieties may influence treatment responses via neural reward responses and demonstrate the importance of assessing the multiple systems in relation to a single construct or disorder.

Molecules and Cells³

Relevance of dopamine and dopamine neurons

Despite the inclusion of genes encoding for DA-related moieties in the current RDoC matrix on initial responsiveness to reward attainment, DA itself is not included under ‘Molecules’. One possible reason for this omission is that research has suggested that the DA system does not contribute importantly to the encoding of hedonic responses to food; e.g., as assessed in preclinical studies using taste reactivity paradigms (see ‘Behavior’ for more on taste reactivity). This and other observations have led to a distinction between the encoding of ‘liking’ versus ‘wanting’, with preclinical research indicating that hedonic food ‘liking’ is primarily encoded by opioids, endocannabinoids, orexins and glutamate; for reviews, see (Berridge, Robinson, & Aldridge, 2009; Pecina, Smith, & Berridge, 2006; Wilmouth & Spear, 2009). Notably, relatively little is known about the postnatal development of these

³No systems are currently identified under ‘Cells’ in the RDoC matrix on initial responsiveness to reward attainment. We propose that dopamine neurons may be a possible candidate cell related to this construct.

systems, including how aspects of these systems may differ during adolescence versus adulthood (Wilmouth & Spear, 2009).

Despite the preclinical distinction described above, data indicate that DA is involved in multiple aspects of reward processing, including performance of tasks currently listed under 'Paradigms' in the initial responsiveness to reward attainment matrix (e.g., monetary incentive delay and gambling tasks), and in hedonic responses to drugs of abuse (e.g., (Berridge, 1998; Koob & Volkow, 2010; Schott, et al., 2008; Schultz, 1992, 1997)), including 'drug-liking' in humans (Volkow, et al., 1999; Volkow, et al., 2002).

The mesocorticolimbic DA system is further involved in processes including the encoding of reward value, incentive salience and motivational drives (Volman, et al., 2013; Wahlstrom, White, & Luciana, 2010b) and has been highlighted in neurodevelopmental models of addictive and impulsive disorders; e.g., (Chambers, Taylor, & Potenza, 2003; Phillips, Ladouceur, & Drevets, 2008; Potenza, 2013; Sonuga-Barke, 2005). In addition, development of the human DA system is ongoing throughout childhood and adolescence, with aspects of this system not reaching mature levels until adulthood; Figure 1; *reviewed in* (Wahlstrom, Collins, White, & Luciana, 2010a). As such, we will here focus on what is known about the development of the DA system in relation to reward responses and childhood and adolescent addictive and impulsive disorders. Although we will focus primarily on findings from human studies, preclinical literature related to environmental influences on DA development will also be briefly discussed. For reviews on other molecules listed in Figure 1, see (Aston-Jones, et al., 2010; Baimel, et al., 2014; Berridge, et al., 2009; Pecina, et al., 2006; Wilmouth & Spear, 2009).

Developmental trajectory of the human DA system

Molecular research methods including ligand-based imaging - positron emission tomography (PET); single-photon emission computed tomography (SPECT) - are able to provide information about the endogenous functioning of neurochemical systems at high spatial resolution and can therefore be used for the *in vivo* quantification of specific neurochemical factors including receptor density and neurotransmitter release. However, given the reliance of these methodologies on radiotracers, very few ligand-based studies of healthy human development exist. Nonetheless, existing PET data (Jucaite, Forssberg, Karlsson, Halldin, & Farde, 2010) – in conjunction with evidence from human post-mortem and preclinical studies - suggest that the development of the DA system is ongoing throughout childhood and adolescence (Figure 2); *for reviews, see* (Wahlstrom, et al., 2010a; Wahlstrom, et al., 2010b).

Tissue concentrations of both cortical and subcortical DA are elevated during adolescence in comparison to childhood and adulthood (Goldman-Rakic & Brown, 1982; Haycock, et al., 2003). By contrast, cortical and subcortical densities of both D1-like and D2-like receptors⁴ peak during childhood; however, they remain elevated during adolescence with respect to adulthood (Lidow, Goldman-Rakic, & Rakic, 1991; Montague, Lawler, Mailman, &

⁴Based on structural and functional similarities across the two different receptor types; D1-like refers to D1 and D5 receptors; D2-like refers to D2, D3 and D4 receptors

Gilmore, 1999; Seeman, et al., 1987; Wahlstrom, et al., 2010b). Dopaminergic innervation to regions of the PFC also increases during adolescence, with peak axonal lengths of DA neurons found during this time (Lambe, Krimer, & Goldman-Rakic, 2000; Wahlstrom, et al., 2010b). Collectively, these data suggest heightened dopaminergic activity during adolescence, which, taken together with ongoing changes in white- and gray-matter tissues (discussed above; see *Circuits and Physiology*), likely contribute to the increased rates of impulsive behaviors observed during adolescence (Chambers, et al., 2003; Potenza, 2013; Wahlstrom, et al., 2010a; Wahlstrom, et al., 2010b). Similarly, it is likely that the alterations in dopaminergic activity associated with many adult psychiatric disorders may first become manifest during – or may be traced back to - this time of dynamic neurochemical development.

Evidence of dopamine involvement in initial responsiveness to reward attainment and in addictive and impulsive disorders

Data from adult ligand-based studies suggests that individual differences in subjective responses to drugs of abuse (e.g. ‘drug liking’) are associated with DA-related factors including the availability of DA D2-like receptors (Volkow, et al., 1999; Volkow, et al., 2002). Together with findings from pharmaceutical challenge studies indicating that individual differences in subjective reward responses relate to differences in addiction vulnerability (Davidson, Finch, & Schenk, 1993; Schuckit, 1994; Schuckit & Smith, 1996; Yip, et al., 2012), these data suggest that alterations in reward responses relating to aspects of DA functioning may confer increased vulnerability for addictive disorders. This interpretation is further supported by PET studies demonstrating reduced availability of DA D2-like receptors and reduced striatal DA release among adults with cocaine and other stimulant abuse or dependence; e.g., (Lee, et al., 2009; Martinez, et al., 2004; Volkow, et al., 2001; Volkow, et al., 1993). However, prospective assessment (prior to initiation of substance-use) would be required to determine whether alterations in aspects of DA functioning are a precursor to, or a consequence of, substance-use.

Reductions in D2-like receptor availability have also been reported among non-substance-addicted adults with high levels of impulsivity, including individuals with ADHD, as well as those with morbid obesity (Volkow, et al., 2009; Volkow, et al., 2007; Volkow, et al., 2008), suggesting that reduced D2-like receptor availability and blunted DA release may be a more general marker of increased impulsivity conferring vulnerability for addictions and other impulse-control-related disorders (Trifilieff & Martinez, 2014). Partially consistent with this hypothesis, Casey and colleagues recently reported blunted striatal DA release to acute amphetamine – but no alterations in receptor availability - among young adults at very high risk for addiction (based on both a positive family-history and current personal use) in comparison to individuals matched for current use without a positive family history and in comparison to drug-naïve controls (Casey, KF, et al., 2014), suggesting that decreased DA release may be a vulnerability factor for – as opposed to a consequence of – addictions.

Treatment implications and future directions

While further research is needed in adolescent populations, findings from adult studies suggest that individual differences in DA functioning may be important mediators of

treatment responses. For example, both decreased DA D2/3 receptor availability and blunted methylphenidate-induced striatal DA release are associated with poorer treatment responses following contingency management (CM) among adults with cocaine dependence (Martinez, et al., 2011). Thus, given the dynamic development of different aspects of the DA system throughout childhood and adolescence, it is likely that individuals at different developmental stages may differ in treatment responses to reward-based (and possibly other) therapies. It will therefore be important for future research to further characterize the human DA system across different ages in relation to different disorders in order to guide effective treatment interventions.

However, as mentioned previously, the widespread assessment of *in vivo* DA (and other neurotransmitter) functioning among children and adolescents is limited by the human subjects concerns surrounding current radio-ligand-dependent methodologies. Thus, a remaining challenge is how best to study and understand typical versus atypical DA development in humans. Pre-clinical research can provide a wealth of complex data; however, given evidence of species-specific trajectories for aspects of DA functioning (Wahlstrom, et al., 2010b), the ability of pre-clinical data to directly inform understanding of the human DA system may be somewhat limited. Thus, further human studies using methods such as pharmaceutical challenge (Wahlstrom, et al., 2010b) and post-mortem tissue analysis (e.g., via the NIH NeuroBioBank; <https://neurobiobank.nih.gov/>) are needed to better characterize DA development.

Early environment and development of the DA system: Insights from preclinical research

Preclinical research indicates effects of the early environment on the development of DA (and other neurotransmitter) systems; *reviewed in* (Strathearn, 2011; Suri, Teixeira, Cagliostro, Mahadevia, & Ansorge, 2015). For example, rats reared in isolation exhibit increased levels of extracellular DA (Hall, et al., 1998; Jones, Hernandez, Kendall, Marsden, & Robbins, 1992) and decreases in DA transporter availability (Meaney, Brake, & Gratton, 2002). Isolation-rearing and maternal separation are further associated with increased stress responses, sensitization to cocaine (Li, Robinson, & Bhatnagar, 2003; Meaney, et al., 2002) and hyperactivity (Einon & Morgan, 1978; Hall, et al., 1998; Meaney, et al., 2002; Wilkinson, et al., 1994). Thus, maternal deprivation has been proposed as one environmental regulator of DA development that may predispose to drug abuse (Meaney, et al., 2002). As reviewed above, collective data suggest species-specific trajectories for aspects of DA functioning, *reviewed in* (Wahlstrom, et al., 2010b); thus a further important direction for future research will be the incorporation of measures of maternal attachment and caregiving within the context of reward system development in humans. Given recent data suggesting methylation-dependent regulation of drug-seeking behaviors related to DA functioning in mice (Wright, et al., 2015), further research into epigenetic effects on DA development as related to substance-use initiation is also needed.

Behavior, Paradigms and Self-Reports

One of the fundamental tenets of RDoC is that it is based on the relationship between biology (e.g., molecules, genes, neural circuits) and behavior (Casey, BJ, et al., 2014). As

shown in Figure 1, taste reactivity is proposed as a behavioral measure relevant to the construct of initial responsiveness to reward attainment. First used to study the reaction of human infants to sweet and bitter tastes, taste-reactivity paradigms have since been widely used in studies of non-human animals (for a review, see (Berridge, 2000)) and generally indicate increased hedonic responses to positive tastes – interpreted as increased reward responsiveness - during adolescence in comparison to adulthood (Wilmouth & Spear, 2009). Although no direct analogue to taste-reactivity tasks exist for the study of humans, possible complementary data may be obtained using cue-reactivity or pharmaceutical challenge-type paradigms (e.g., subjective responses to alcohol or drugs of abuse in adults or to highly palatable foods in adolescents) either alone or in combination with fMRI scanning; e.g., (Brumback, et al., 2015; Filbey, et al., 2008; Gilman, Ramchandani, Couss, & Hommer, 2012; Schuckit, Smith, & Kalmijn, 2014; Small, 2001; Tapert, et al., 2003; Yip, et al., 2012).

Although not currently included in the RDoC matrix (and thus not extensively reviewed here) on initial responsiveness to reward attainment, other behavioral measures of relevance to this construct include performance on gambling and decision-making tasks (such as those listed under ‘Paradigms’ in the current matrix; Figure 1); see (Casey, 2014; Hamilton, et al., 2015; Steinberg, 2008). However, as psychological research suggests differing developmental trajectories for related but distinct constructs such as sensation-seeking and impulsivity (Steinberg, 2008), further research into how development of these constructs may confer vulnerability to the development of addictive and adolescent disorders within the context of RDoC is needed. Such research could, for example, explore the interaction between performance on behavioral measures of reward responsiveness and self-report measures (discussed below) and initiation of illicit substance use during adolescence, in order to identify critical periods for intervention (Casey, BJ, et al., 2014).

Self-report measurements are relatively low-cost and thus may be more widely and frequently administered than molecular, genetic and neuroimaging measures. They therefore represent a powerful tool for large-scale, longitudinal assessments of reward-related constructs. However, to our knowledge no studies have yet utilized either of the self-report measures shown related to initial responsiveness to reward attainment – the consummatory subscale of the Temporal Experience of Pleasure Scale (TEPS) (Gard, et al., 2006) and the state version of the Positive and Negative Affect Scale (PANAS) (Watson, Clark, & Tellegen, 1988) - to study reward responses within a longitudinal developmental framework. Such data would provide an important starting point from which to interpret disorder- or symptom-specific findings.

Summary, future directions and challenges

RDoC provides a unique transdiagnostic framework from which to approach developmental neuropsychiatric research. Recently proposed complementary translational research efforts, such as the Alcohol Addiction RDoC (AARDoC) (Litten, et al., 2015), may also be helpful in integrating developmental findings. Significant challenges nonetheless remain. The first challenge involves the synthesis of existing data in relation to different constructs and units of analysis. Thus, further narrative and systematic review is warranted to ‘fill-in’ other matrix elements.

A second challenge will be the acquisition of multi-system data in an integrative manner. In particular, further work is needed to understand the interactions between – and even within – different systems (Casey, BJ, et al., 2014). To take the example of circuits, neuroimaging studies should aim to collect multiple types of data from each subject so that interactions between functional and structural neural features may be explored. It will also be important to apply advanced neuroimaging analysis methods (e.g., independent component analysis (Calhoun, 2001a, 2001b); intrinsic connectivity distribution (Scheinost, et al., 2012)) to examine interactions between different functional networks in relation to different constructs. Similarly, further genetic research is needed to understand how different genetic polymorphisms interact with environmental factors to influence neural responses. Additionally, genes relating to neurotransmitter systems beyond dopamine should be examined in relationship to reward and development, and additional approaches (e.g., utilizing genetic risk scores generated from large-scale studies involving assessments of multiple allelic variants) (Belsky, et al., 2013; Dudbridge, 2013) should be used to understand developmental aspects of reward as related to addiction and impulse control. Large-scale initiatives utilizing longitudinal designs such as the Adolescent Brain Cognitive Development (ABCD) (<http://addictionresearch.nih.gov/adolescent-brain-cognitive-development-study>) will be essential to this endeavor.

A neurodevelopmental approach will be essential to such future research, as characterization of the specific trajectories of different systems along a developmental continuum is needed to truly elucidate interactions between systems, as well as to identify possible ‘critical periods’ for effective interventions (Casey, BJ, et al., 2014). Correspondingly, application of an RDoC framework to existing neurodevelopmental research efforts will inform the understanding of the shared and unique biological factors underlying traditional psychiatric diagnoses, and this may be used to ultimately improve existing treatments.

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Highlights

- Adolescence represents a neurodevelopmental period of vulnerability for impulse-control and addictive behaviors.
- Reward sensitivity represents an important construct relating to addictive behaviors and impulse control.
- Considering reward sensitivity within a Research-Domain-Criteria framework has important implications for adolescent health.

Domains									
Negative Valence Systems									
Positive Valence Systems		Units of Analysis							
Constructs	Subconstructs	Genes	Molecules	Cells	Circuits	Physiology	Behavior	Self-Report	Paradigms
	Approach Motivation								
	Reward Learning								
	Habit								
	Sustained Responsiveness to Reward Attainment								
	Initial Responsiveness to Reward Attainment	DRD2, DAT, (TREK1), DRD4, OPRM1	<i>Mu and delta opioids, orexin, glutamate, plasticity-related genes (CREB; FosB), endo-cannabinoids, dopamine</i>	<i>Dopamine neurons</i>	NAcc, mOFC vmPFC, dorsal ACC, VTA, ventral pallidum, anterior insula, lateral hypo-thalamus	BOLD	Taste reactivity, behavioral response to reward (e.g., gambling task performance, response to drug challenge)	PANAS (state version), consummatory subscale of TEPS	MID, gambling/ guessing tasks, taste reactivity, drug challenge
Cognitive Systems									
Arousal and Regulatory Systems									
Systems for Social Processes									

Figure 1. Schematic diagram depicting organization of Initial Responsiveness to Reward Attainment within the RDoC matrix

Matrix overview: The RDoC matrix is composed of five domains organized into rows. Each domain (e.g., Positive Valence Systems) is hierarchically organized into constructs and subconstructs (due to space limitations, subconstructs are not shown above) also conceptualized as rows. Constructs and subconstructs may be studied across different units of analysis, conceptualized as columns.

Initial Responsiveness to Reward Attainment: Within the matrix for initial responsiveness to reward attainment (a construct within Positive Valence Systems), items shown in bold font correspond to items currently included in the online RDoC matrix. Items shown in italics correspond to items proposed by the authors which are not currently included under this construct in the online matrix (http://www.nimh.nih.gov/research-priorities/rdoc/rdoc-constructs.shtml#initial_responsiveness; November 2015).

NAcc = nucleus accumbens, mOFC=medial orbitofrontal cortex, vmPFC=ventromedial prefrontal cortex, ACC=anterior cingulate cortex, VTA=ventral tegmental area, BOLD=blood oxygenation level dependent, PANAS=Positive and Negative Affect Scale, TEPS=Temporal Experience of Pleasure Scale, MID=Monetary Incentive Delay task

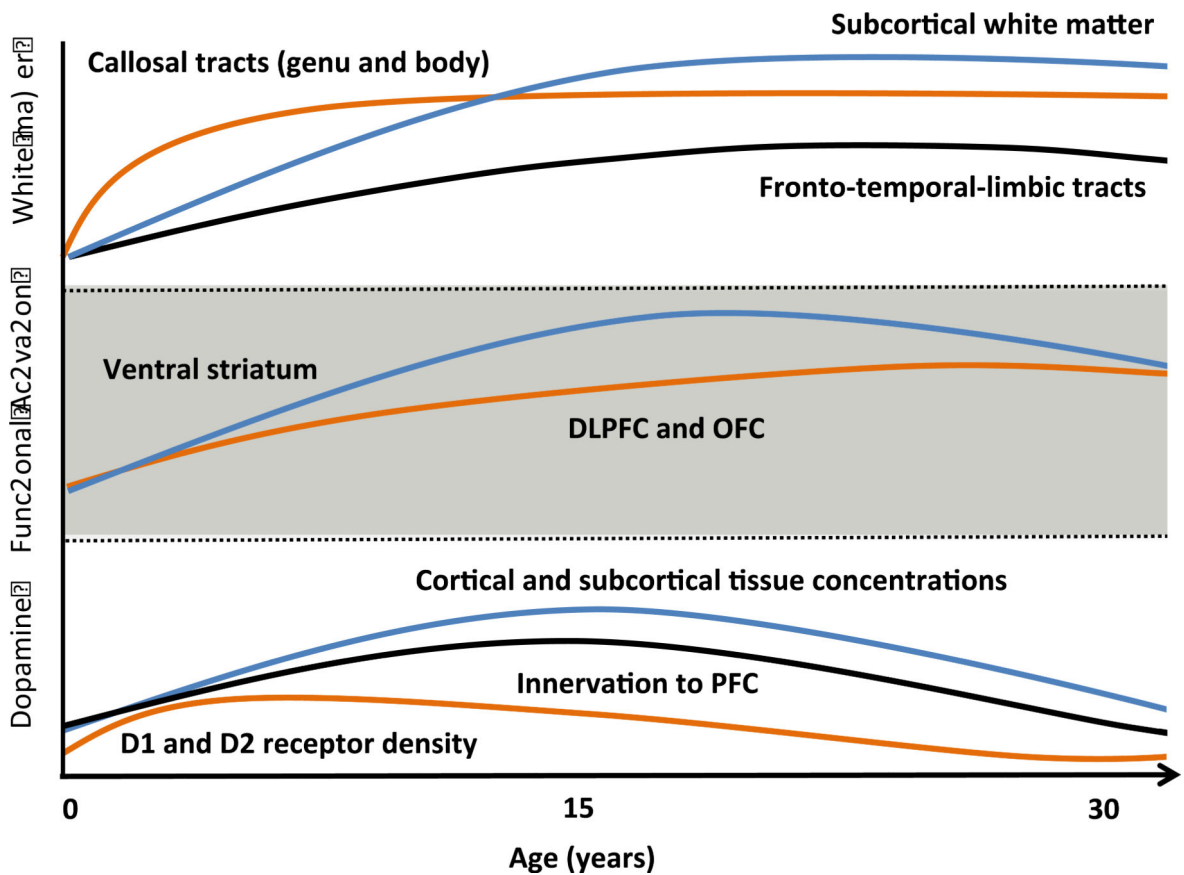


Figure 2. Theorized postnatal development of selected aspects of the human reward system warranting further study

Figure 2 is a schematic diagram depicting the theorized longitudinal developmental trajectories for selected white-matter tissue tracts, functional responses and aspects of dopaminergic development hypothesized to relate to initial responsiveness to reward attainment (RDoC) and to the development of childhood and adolescent addictive and impulsive disorders. Trajectories are based on data reported in (Casey, 2014; Galvan, et al., 2006; Giedd, 2004; Gogtay, et al., 2004; Lebel & Beaulieu, 2011; Lebel, et al., 2008; Raznahan, et al., 2014; Wahlstrom, et al., 2010b).

DLPFC = dorsolateral prefrontal cortex; OFC = orbitofrontal cortex; PFC = prefrontal cortex

Table 1 Selected evidence in support of brain regions proposed in the RDoC matrix on initial responsiveness to reward attainment

	Development	Processes
<i>'Top-down' cortical regions</i>		
Anterior insula	Structural MRI: linear maturation ongoing during adolescence (Shaw, et al., 2008); Functional MRI: Decreased BOLD in children and adolescents in comparison to adults during risky decision-making (Paulsen, Carter, Platt, Huettel, & Brannon, 2011)	Emotion processing, interoceptive awareness (Paulus & Stein, 2006); goal-directed behavior (Naqvi, Gaznick, Tranel, & Bechara, 2014); reward and aversion-based learning (Lasiter, Deems, Oetting, & Garcia, 1985; Lawrence, et al., 2014)
Dorsal anterior cingulate	Structural MRI: inverted 'U-shaped' maturation of anterior cingulate with development ongoing into adulthood (Shaw, et al., 2008); Functional MRI: Decreased BOLD in children and adolescents in comparison to adults during error processing (Velanova, Wheeler, & Luna, 2008)	Inhibitory control, behavioral monitoring (Goldstein & Volkow, 2011)
Medial OFC and vmPFC	Structural MRI: GM development ongoing during adolescence into adulthood (Giedd, 2004; Gogtay, et al., 2004); Functional MRI: OFC development protracted in comparison to subcortical (NAcc) development (Galvan et al., 2006; Casey et al., 2008)	Incentive salience, value encoding, decision-making, emotion regulation (Goldstein & Volkow, 2011)
<i>'Bottom-up' subcortical regions</i>		
Striatum (Nacc and VTA)	Structural MRI: typically thought to stabilize by middle to late adolescence; this view is challenged by recent evidence of protracted development during adolescence (Dennison, et al., 2013; Raznahan, et al., 2014). Functional MRI: Earlier maturation in comparison to OFC (Galvan et al., 2006; Casey et al., 2008)	Reward 'hotspot' (Berridge, et al., 2009); reward learning (Creed, Ntamati, & Tan, 2014); encoding of reward and aversion (Volman, et al., 2013)
Ventral pallidum	Structural MRI: Protracted development during adolescence (Dennison, et al., 2013; Raznahan, et al., 2014).	Encoding of hedonic reward value ('liking') (Berridge, et al., 2009)
Lateral hypothalamus	Structural MRI: Linear decrease in thalamus volume during childhood and adolescence (Sowell, Trauner, Gamst, & Jernigan, 2002)	Reward-seeking (Harris, Wimmer, & Aston-Jones, 2005), motivational encoding and goal-directed behaviors (Boutrel, Cannella, & de Lecea, 2010)

NAcc = nucleus accumbens, mOFC=medial orbitofrontal cortex, vmPFC=ventromedial prefrontal cortex, VTA= ventral tegmental area