



Review article

Transdiagnostic neuroimaging of reward system phenotypes in ADHD and comorbid disorders

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ABSTRACT

ADHD is a disorder characterized by changes in the reward system and which is highly comorbid with other mental disorders, suggesting common neurobiological pathways. Transdiagnostic neuroimaging findings could help to understand whether a dysregulated reward pathway might be the actual link between ADHD and its comorbidities. We here synthesize ADHD neuroimaging findings on the reward system with findings in obesity, depression, and substance use disorder including their comorbid appearance regarding neuroanatomical features (structural MRI) and activation patterns (resting-state and functional MRI). We focus on findings from monetary-incentive-delay (MID) and delay-discounting (DD) tasks and then review data on striatal connectivity and volumetry. Next, for better understanding of comorbidity in adult ADHD, we discuss these neuroimaging features in ADHD, obesity, depression and substance use disorder and ask whether ADHD heterogeneity and comorbidity are reflected by a common dysregulation in the reward system. Finally, we highlight conceptual issues related to heterogeneous paradigms, different phenotyping, longitudinal prediction and highlight some promising future directions for using striatal reward functioning as a clinical biomarker.

1. Introduction

1.1. Clinical aspects of ADHD and comorbid disorders

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder with symptoms of inattentiveness, impulsiveness and hyperactivity, which leads to impairments in everyday life and manifests before the age of 12. The developmental trajectory shows a typical course of clinical symptoms e.g. decrease of hyperactivity, occurrence of comorbid disorders such as addiction and depression, as well as economic costs and social impairments (Franke et al., 2018). Obesity is increased both in children (40 % of children with ADHD, OR = 1.20) as well as in adults (70 % prevalence, OR = 1.55) according to a recent meta-analysis (Cortese et al., 2016). Substance use disorder is heterogeneous and only rarely present in children. In adults with SUD, a meta-analysis reported that 23.1 % of patients with SUD suffer from ADHD (van Emmerik-van Oortmerssen et al., 2012). The developmental trajectory was described in a large sample (n>5000+) in (Charach et al.,

2011). Childhood ADHD leads to an increase in risk for alcohol abuse (OR = 1.35) and especially for nicotine (OR = 2.35). A large (n = 3199) survey in the US found a higher prevalence for depression (OR = 2.75), dysthymia (OR = 7.4) and anxiety disorders in ADHD. In addition, they report a higher rate of alcohol dependence as well as drug dependency. In summary, this gives evidence on an epidemiological level but does not give a mechanistic explanation why this comorbidity occurs. A more complete overview of onset, trajectory and symptoms is given in other reviews in this special issue. There is considerable genetic overlap between childhood and adulthood ADHD samples (Rovira et al., 2020), suggesting that adult ADHD is genetically like childhood ADHD, and that ADHD persistence may have other causes rather than genetic ones. Not only do the symptoms of ADHD lead to an impairment in psychosocial functioning in patients, but the risk of developing psychiatric comorbidities such as affective and anxiety disorders, personality disorders and substance abuse disorders are significantly increased in comparison to the general population (Bernardi et al. 2012). In recent years, an increasing amount of evidence was published that ADHD is

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also associated with a higher burden of somatic disorders like obesity, diabetes mellitus, asthma, migraine and several others (Instanes et al. 2018). A detailed overview of somatic comorbidity is given in this special issue in the review by Brunkhorst-Kanaan et al.

Why is the reward system a promising candidate for ADHD and comorbid disorders? First, the main pharmacological treatment of ADHD, i.e. stimulants, enhances the reward system's main transmitter dopamine (Faraone et al. 2018). Second, disorders comorbid with ADHD (like substance abuse or obesity) have been linked to dopamine neurotransmission. Third, on a psychological level, ADHD can be described with core constructs like motivation or decision-making deficits which are implicitly linked to the functioning of the reward system. In sum, this motivated us to outline and discuss transdiagnostic neuroimaging phenotypes of the reward system in ADHD. The main topic of this review, to systemically look at neuroimaging measures as well as distinct comorbid disorders is graphically depicted in Fig. 1.

Although there are more disorders which have a high comorbidity with ADHD, like Conduct Disorders (CD), autism spectrum disorders (ASD) or Obsessive Compulsive Disorder (OCD), for the purposes of the current review we will focus on those disorders for which there is sufficient literature available to provide a link with the reward system. Other comorbid disorders e.g. CD might show a strong link to disturbed reinforcement learning and the reward system, but we wanted to concentrate on comorbid disorders which have a later onset (in adult) life a might thus reflect the negative ADHD-trajectory. Hence, we will focus solely on the comorbidity between ADHD and Obesity, MDD and SUD.

Before looking at distinct clinical syndromes, we provide a short summary of the reward system which highlights both its unitary structure as well as its different aspects:

1.2. Neuroanatomy and neurophysiology of the reward system

In general, the amount of phasic activity induced in dopaminergic neurons in the midbrain by conditioned stimuli correlates with the amount of reward (reward may e.g. be food or sex) predicted by the stimuli (Tobler et al., 2005): thus, these neurons signal reward, and likewise, firing of these neurons is interpreted as presence of reward.

Such neuronal responses are found similarly in dopaminergic regions of rodents (Simpson et al., 2012) and humans (Burke and Tobler, 2011; Francois et al., 2016; Kahnt & Tobler, 2013). A conditioned stimulus associated with reward (e.g. primary rewards like pizza or secondary rewards e.g. social stimuli like flirty behavior) often triggers a faster reaction than a neutral stimulus. These neural and behavioral responses to the reward-predictive stimulus reflect reward anticipation, i.e. a prediction of the characteristics of the forthcoming reward. One function of reward anticipation is to enable the organism to prepare for obtaining the reward and to approach the source of the reward.

1.3. Neuroimaging of reward in humans

Neuroimaging may aid in establishing a diagnosis and to govern treatment choices. While current neuroimaging technologies are not yet implemented in clinical practice, the possibility of using (f)MRI for diagnosis and prediction is not far away. Due to its specific importance in ADHD and related disorders, we will here concentrate on neuroimaging of the reward circuitry. For psychiatry, the fronto-striatal circuit and its dopaminergic neurotransmission is important because central elements of emotion and motivation are linked to it. On the one hand, the amount of dopamine released in the striatum is used as a proxy for "wanting" the reward (Berridge and Robinson, 1998). On the other hand, the phasic changes in dopaminergic signaling encode errors in reward prediction that occur when the experienced reward deviates from the expected reward (Schultz et al., 1998). Two new studies combine these aspects: Mesolimbic dopamine (DA) release correlates with the value of work during a decision task in rats (Hamid et al., 2016) and this signal is attenuated when no movement is initiated correctly (Syed et al., 2015). These studies show that the changes in DA release are both a motivational and a learning signal. These two aspects of DA should be kept in mind when comparing passive (Pavlovian) conditioning with operant conditioning, as operant conditioning has a stronger motivational component.

In humans, invasive studies on the role of DA are largely absent but have so far supported a role of DA in learning and in predicting error coding (Kishida et al., 2016). In addition, fMRI and raclopride positron emission tomography were performed in parallel during a MID task



Fig. 1. This figure is a graphic illustration of the key topics of the current review with the aim to introduce the different aspects of this review. However, as the (causal) links between the different topics are unclear, the lines in the figure do not imply directions. For example, whether the dysregulations of various aspects of reward in the comorbid disorders of ADHD are independent of ADHD, remain an open question.

Abbreviations: MDD (major depressive disorder). SUD (substance use disorder). DD (delay discounting). MID (monetary incentive delay).

(Schott et al., 2008). The displacement of raclopride by DA is an indirect measurement of physiological DA release. Interestingly, it was found that DA release is related to the striatal fMRI signal during reward anticipation, so that stronger stimulus-induced neural responses (measured with fMRI) in a reward version of the MID task were observed in participants with more striatal DA release (observed with PET). This elegant study provides one of the most compelling evidence that differences in DA release indeed lead to differences in the blood oxygen level-dependent (BOLD) signal. Schlagenhauf et al. (2013) showed an inverse relationship with dopamine in a study with sequential, non-parallel 6-[(18F)]fluoro-L-DOPA measurement using PET and subsequent fMRI measurement during reward anticipation. Other studies used pharmacological fMRI by adding indirect DA agonists and/or DA antagonists and studying their effect on the BOLD signal (e.g., Grimm et al., 2019; Pessiglione et al., 2006) or measuring raclopride PET imaging during reward participation. The relationship between DA and BOLD-fMRI response during reward anticipation with a MID-task was confirmed in an amphetamine-challenge study (Knutson and Gibbs, 2007). Therefore, at least striatal BOLD response measured by fMRI seems to be an adequate surrogate marker for DA-related reward participation. Specific theories suggesting dopaminergic deficits in ADHD allow us to make falsifiable predictions.

1.4. Theories of dopaminergic functioning in ADHD

The **basal ganglia model** (BGM) assumes low tonic DA, particularly in the striatum, in ADHD. This is based on the idea of ADHD as a dopamine deficiency disorder (e.g. Krause et al., 2000; Sagvolden et al., 2005; Solanto, 2002), mainly based on evidence showing that stimulants increase tonic DA (Volkow et al., 2001) as their main mechanism for ADHD treatment.

Phasic DA in the striatum is also thought to be low in ADHD. This assumption is supported by animal work showing stimulants also increase intrasynaptic DA (Ruskin et al., 2001), as well as by the dynamic developmental theory of Sagvolden et al. (2005).

The **dynamic developmental theory** (DDT) (Sagvolden et al., 2005) hypothesizes a reduced tonic DA in ADHD, possibly due to reduced prefrontal glutamatergic drive (Grace, 2001; Solanto et al., 2001b). This reduced tonic DA leads to a reduced positive phasic DA response in ADHD. Support for this hypothesis is derived from an experiment on brain slice preparations from the spontaneous hypertensive rat (SHR) model of ADHD (Russell et al., 1995). Low tonic DA leads to a floor-effect that limits phasic DA reductions in response to worse-than-expected outcomes in ADHD. This hypothesis is deduced from the general association between reward omissions and phasic depressions of DA-neuron firing (Schultz, 2002) and reduced extinction in ADHD (Sagvolden et al., 1998) and in the SHR (Johansen and Sagvolden, 2004).

The **dopamine transfer deficit** (DTD) theory (Tripp and Wickens, 2009, 2008) assumes a deficient transfer of DA response from unconditioned rewards to conditioned stimuli/responses in ADHD. This view is mostly supported indirectly through research showing that such a transfer normally takes place (Schultz, 2002). Adolescents with ADHD also show lower reward-anticipatory neural activity (Scheres et al., 2007) and there is behavioral evidence compatible with alterations of reinforcement sensitivity (Tripp and Alsop, 2001, 1999). The DTD theory assumes that the DA response to immediate rewards is normal in ADHD (which is supported by the clinical presentation of the patients). In support, the authors cite behavioral studies suggesting equal performance in ADHD with continuous reinforcement (Freibergs and Douglas, 1969; Parry and Douglas, 1983).

A much simpler model, an overreaction to salient stimuli versus a blunted response to salient stimuli is very popular in assessing the results of studies in addiction research, the so-called **reward deficit model**. This is explained in more detail in the section about SUD and ADHD.

Maybe the simplest model of striatal, limbic activity is the distinction

between a “cold”, rational, executive functioning “brake” mediated by the prefrontal cortex. This “cold” domain is countered by a “hot” subcortical circuitry related to dopamine in the reward system. This dual-pathway model was proposed by Sonuga-Barke and Castellanos (2005) and easily relates to ADHD symptoms stemming from dysregulation within cortico-striatal circuits, resulting in poor inhibitory control contrasted by accumbens-induced altered reward processing and anticipation.

1.5. fMRI-based measures: monetary incentive delay task

Different fMRI tasks can be used as a proxy measure for dopaminergic signaling in the striatum. So-called reward anticipation can be studied using operant conditioning assessed via the so-called monetary incentive delay task (MID). Here, participants learn to respond to a conditioned stimulus (typically the visual presentation of a symbol on a computer screen), for example, by pushing a button (Knutson et al., 2001; Kirsch et al., 2003; Grimm et al., 2014; Plichta et al., 2012, 2013). The task typically comprises three different phases: (1) anticipation (i.e., delaying the subsequent reward); (2) target (with a necessary reaction e.g., pressing a button); and (3) feedback (reward received yes/no). The anticipation phase begins with the presentation of a symbol indicating the possibility of receiving money, followed by a variable time delay of a few seconds. At the end of this delay the participants see a target stimulus. To win money, the participant must react fast enough by only pressing the button when the target stimulus is presented. The reaction time window is adaptive and has a range of ~160–260 ms. After the participant's response, a feedback on the actual performance is given. The task is designed in such a way that the participants win (or lose) in about 67 % of the attempts by adjusting the length of the reaction time window dynamically: If the respondent was too slow, the RT window is enlarged by a few milliseconds in the following trial. If the subject was fast enough, the RT window is shortened. If they give an appropriate response, they receive a reward: Rodents typically receive a food pellet and humans typically receive a symbol representing some monetary reward. The variation of this reward contingency is a decisive parameter and significantly influences the neuronal response behavior: Fiorillo et al. (2003) showed that sustained dopamine signals between cue and reward are highest when reward results occur under conditions of uncertainty. The conditioned stimulus signaling the incentive and the incentive are separated in time by a short delay termed “monetary incentive delay”. Before learning, the striatum (and dopamine neurons: Schultz et al., 1997) responds to receipt of the reward; after learning, the striatum responds to the conditioned stimulus (Knutson et al., 2001). This task is therefore a typical example of operant conditioning and allows the investigation of two important facets of neural reward processing: (1) reward anticipation, i.e. the anticipation of a potential gain (or avoidance of a potential loss) that occurs between cue and target presentation, and (2) feedback processing during the presentation of performance feedback (including the monetary outcome). A meta-analysis on neural reward anticipation effects in ADHD vs. healthy controls can be found in Plichta and Scheres (2014). Here, an update is pending that (a) also takes into account the different comorbidities and (b) contrasts DD effects with MID effects for the different disorders.

1.6. fMRI-based measures: delay discounting

Delay discounting or intertemporal choice is a behaviorally founded measure of impulsive decision-making which is used in evaluating all kinds of psychiatric disorders related to impulsivity, in particular ADHD. An individual's discounting rate can be calculated after a series of forced decisions between a smaller amount of money available after a smaller delay versus a larger amount of money available after a larger delay is made. This sequence of decisions can be analyzed by calculating a delay discounting parameter based on the fitting of a hyperbolic function. The so-called points of indifference where decisions towards small,

immediate versus large, delayed rewards occur equally are calculated according to $V = 1/(1+kD)$ where V is the proportional present value, D is the delay, and k is the discount rate. The specific discount rate for an individual is graphically equivalent to a steeper drop of the individual value V (D'Esposito et al., 2015).

In neuroimaging, it is of interest to study in event-related fMRI paradigms what happens exactly during decision evaluation depending on the type of decision, e.g. immediate versus delayed rewards. Koffarnus et al. (2017) differentiate between two types of delay-discounting fMRI tasks:

In the *response-focused* type of fMRI-procedure, the task is comparable to behavioral delay discounting paradigms: In these tasks, a series of choices are made between monetary rewards available immediately and a larger amount available after a delayed amount of time (e.g. 5€ now versus €50 in 4 weeks). Afterwards, the analysis looks at the individual's choice., and the analysis focuses on contrasts between choices for the immediate option versus choices of the delayed option or the analysis compares 'hard' choices with 'easy' choices. A 'hard' is almost at the indifference point, therefore the decision is harder to make and takes typically more time.

In another, more *stimulus-focused* type of task, the choice trials consist of two delayed options (e.g. 5€ in 1 week versus €50 in 1 month) and another choice trial type with both a delayed and an *immediate* option. The analysis contrasts immediate trials (about half of them) with non-immediate (delayed trials) independent of the actual choice. Data are typically analyzed as a function of the type of trial that was presented, contrasting whether an immediate option was available

(regardless of participant choice). A common problem (Koffarnus et al. (2017)) however is the non-standardized, sometimes inconsistent reporting, e.g. not all types of contrasts are reported and analyzed.

2. Review Methods: search strategies

The literature search for this review used scientific databases and (meta)search engines (PubMed, ISI web of science and google scholar) and was conducted early 2020 until early July 2020. Search terms included "ADHD", "Attention Deficit Hyperactivity Disorder", or "ADD" or "Attention Deficit Disorder" combined with one of the following terms: "fMRI", "MRI", "neuroimaging", "reward system". Additional references were searched in the resulting publications, including reviews and meta-analyses and by suggestions from mendeley.com and google scholar.

The preferred reporting items for systematic reviews and meta-analysis (PRISMA) diagram in Fig. 2 describes the number of articles identified and their classification. In total, 384 articles were found and after removing duplicates, the titles and abstracts of 373 articles were screened. The following studies were excluded: articles with study populations including other disease groups and patients with genetic syndromes, studies on prenatal alcohol or tobacco exposure or Fetal Alcohol Disorder, review articles, medical hypotheses, non-English articles, and studies on animal models. A compilation of the most relevant studies using a transdiagnostic approach can be found in Table 1.

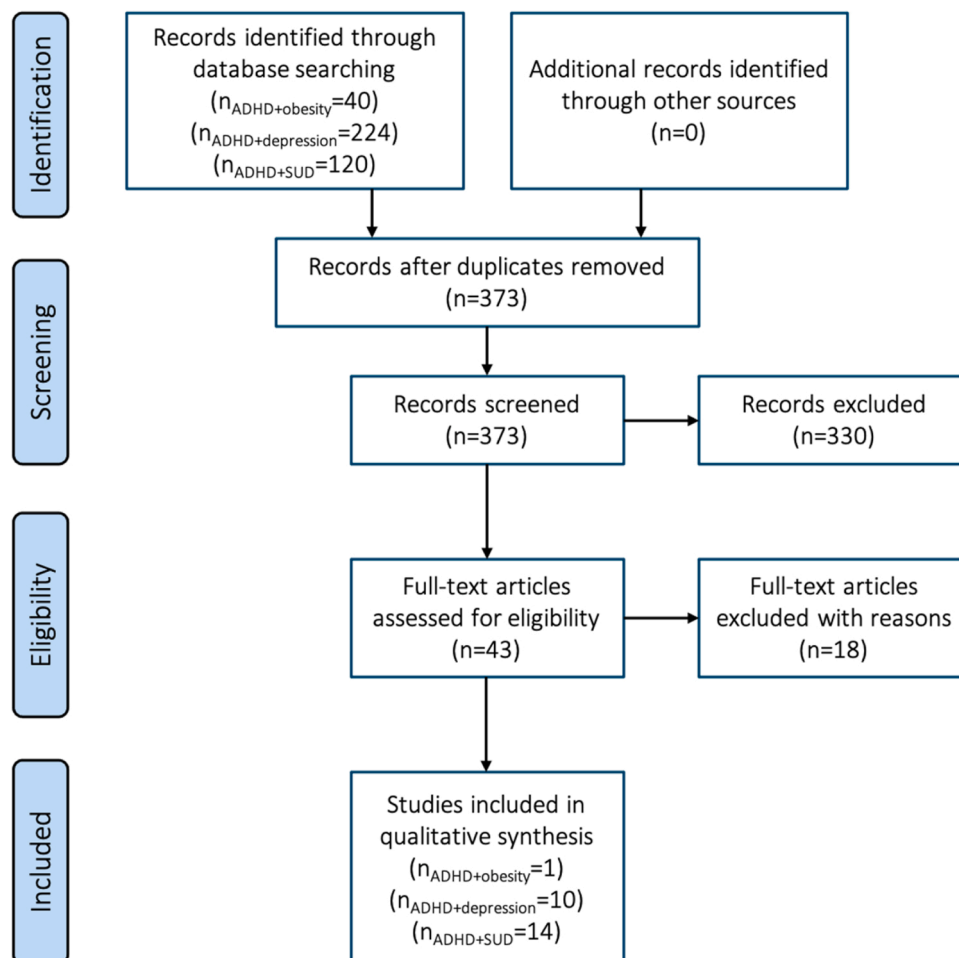


Fig. 2. Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flowchart of the literature search and study selection for qualitative analysis. Note: see <http://www.prismastatement.org> for more information in this reporting system.

Table 1

Overview of relevant articles identified by PubMed search terms for ADHD and comorbid disorders.

ADHD + obesity: 40 studies identified; most relevant studies are listed below				
	Brain imaging modality	Phenotypes studied	Main finding	Reference
ADHD + obesity	fMRI and MID task	Impulsivity symptoms, BMI	Reward-related impulsivity in combination with ADHD PRS showing that shared neural substrate is associated with both ADHD and BMI and PRS scores.	Barker et al., 2019
ADHD + depression: 224 studies identified; most relevant studies are listed below				
	Brain imaging modality	Phenotypes studied	Main finding	Reference
ADHD + depression	sMRI	ADHD diagnosis, current symptoms of depression, current symptoms of anxiety, inattention symptoms, hyperactivity/impulsivity symptoms	Findings revealed smaller total GMV in males with ADHD and a smaller GMV in right medial frontal orbital area extending toward the medial frontal superior, the frontal superior, and the subgenual anterior cingulate cortex (ACC) besides correlations between inattentiveness and ACC (bilaterally) and left cerebellum, hyperactivity/impulsivity and the left frontal inferior orbital, depression and caudate (bilaterally), and the right inferior parietal lobule. Volumes of the left nucleus accumbens and a region overlapping the dorsolateral prefrontal cortex were positively associated with inattention symptoms. Left hippocampal volume was negatively associated with hyperactivity symptoms. The brain volume-inattention/hyperactivity symptom associations were stronger when anxiety/depression symptoms were controlled for.	Klein et al., 2019
		Current inattention symptoms, current hyperactivity symptoms, anxiety symptoms, depression symptoms	Male patients showed reduced right caudate volume compared to male controls, and caudate volume correlated with hyperactive/impulsive symptoms. ADHD patients with previous MDD showed smaller hippocampus volume compared to ADHD patients with no MDD.	Das et al., 2017
		ADHD diagnosis, inattention symptoms, hyperactivity/impulsivity symptoms, one or more depressive episode (remitted)	Amygdala volumes in patients with ADHD were bilaterally smaller than in patients with MDD and healthy controls. In ADHD, more hyperactivity and less inattention were associated with smaller right amygdala volumes, and more symptoms of depression with larger amygdala volumes.	Onnink et al., 2014
	rs-fMRI and sMRI	ADHD diagnosis, inattention symptoms, hyperactivity/impulsivity symptoms, depressive symptoms	Compared with the HC participants, the participants with ADHD had (i) reduced volumes of the left hippocampus and (ii) reduced functional connectivity between the left hippocampus and the left orbitofrontal cortex (OFC); these hippocampal effects were associated with more severe depressive symptoms.	Frodil et al., 2010
		ADHD symptoms, depressive symptoms	ADHD severity was related to age-advanced striatal connectivity across several insula subregions, but to age-delayed connectivity with the nearby inferior frontal gyrus. Aberrant limbic connectivity predicted depression.	Posner et al., 2014
ADHD + depression	rs-fMRI	ADHD diagnosis, anxiety disorder, depressive disorder, substance use (self-report at follow-up)	rs-fMRI study tested intrinsic functional connectivity (IFC) among nodes of putative reward network. Increased left ventral striatum node strength predicted increased risk for future depressive disorder, but not ADHD or substance use.	Barber et al., 2019
		ADHD diagnosis, MDD diagnosis, schizophrenia diagnosis (all separate patient groups)	Only network-based cross-correlation identifies significant functional connectivity changes in all three disorders (ADHD, depression, SCZ) which survive correction. The counterparts of pairs of regions in the opposite hemisphere contribute 60–76% to altered functional connectivity, compared with only 17–21% from the regions themselves.	Pan et al., 2017
	fMRI and emotion processing task	ADHD diagnosis; MDD diagnosis; schizophrenia diagnosis; alcohol dependence (all not comorbid), depressive symptoms	No significant interaction with diagnostic group, nor any correlation with depression scores at the activated clusters or with amygdala connectivity.	Zhang et al., 2015
	fMRI and MID task	ADHD diagnosis; MDD diagnosis; schizophrenia diagnosis; alcohol dependence (all not comorbid), depressive symptoms	During reward anticipation, significant group differences in ventral striatal (VS) activation: patients with SCZ, alcohol dependence, and MDD showed significantly less VS activation compared to healthy controls (not difference for ADHD). Depressive symptoms correlated with dysfunction in reward anticipation regardless of diagnostic entity.	Hägele et al., 2016 Hägele et al., 2015
ADHD + substance use disorder: 120 studies identified; most relevant studies are listed below				
		Phenotypes studied	Main finding	Reference

(continued on next page)

Table 1 (continued)

ADHD + obesity: 40 studies identified; most relevant studies are listed below				
Brain imaging modality				
ADHD + substance use disorder	sMRI	Synthetic cannabinoids users with and without ADHD diagnosis	SC users both with and without ADHD groups have significantly reduced cortical thickness compared to controls in areas of the left caudal middle frontal and left superior frontal. SC users with ADHD showed reduced cortical thickness in the right precentral and postcentral gyri. SC users without ADHD, but not with ADHD, had increased right nucleus accumbens volume, compared to controls.	Çolak et al., 2019
		Smokers and non-smokers with and without ADHD diagnosis	Smokers had a 2.6 % thinner frontal cortex than non-smokers and this difference was not explained by ADHD or other confounding factors. Persistent ADHD was linked with abnormalities in frontoparietal structure. Cannabis users had abnormal frontolimbic brain structure. Adolescent onset cannabis users demonstrated unique structural abnormalities.	Akkermans et al., 2017
		ADHD diagnosis, chronic cannabis use	Poorer Go/No Go performance was associated with thicker cIFG cortex, and this effect was not mediated by ADHD status or history of substance use. However, independent of Go/No Go performance, persistence of ADHD symptoms and more frequent cannabis use were associated with thinner cIFG.	Lisdahl et al., 2016
		ADHD diagnosis, cannabis use, binge alcohol use	ADHD patients with cocaine dependence show more profound gray matter volume reductions in the striatum compared to ADHD patients without cocaine dependence.	Newman et al., 2016
		ADHD diagnosis, with and without comorbid cocaine dependence	Total Corpus Callosum, genu and isthmus areas were significantly smaller in high-risk than low-risk subjects for alcoholism after controlling for age and intracranial area. The total externalizing symptoms score had a significant negative correlation with genu and isthmus areas.	Van Wingen et al., 2013
	rs-fMRI	high-risk than low-risk subjects for alcoholism, ADHD symptoms, conduct and oppositional defiant symptoms	Relative to healthy controls, nicotine dependent individuals had significantly higher ADHD self-report scores and greater dACC-AI coupling. No group differences were noted on inter-salience network coupling. A significant association was found between ADHD self-report scores and dACC-AI coupling both in the entire cohort and specifically when evaluating nicotine dependent individuals alone.	Venkatasubramanian et al., 2007
		Nicotine dependence, ADHD symptoms	rs-fMRI study tested intrinsic functional connectivity (IFC) among nodes of putative reward network. Increased left ventral striatum node strength predicted increased risk for future depressive disorder, but not ADHD or substance use.	Janes et al., 2018
		ADHD diagnosis, anxiety disorder, depressive disorder, substance use (self-report at follow-up)	Brain activation in frontal control and reward-related regions during completion of the combined tasks were related to ADHD and AUD severity (symptom load). During presentation of both alcohol cues and the inhibition task, participants with higher AUD and ADHD symptom load exhibited greater BOLD (blood oxygen level dependent) responses in subcortical reward-related regions.	Pan et al., 2017
		fMRI and interference-inhibition task and alcohol cue-reactivity task	Whole-brain analysis showed significant differences in widely distributed networks related to both reward processing and behavioral control. ROI activations showed that the HR group (high risk, ADHD + familial SUD) had the highest activation in right putamen during both expected rewards and unexpected non-reward outcomes and in the ACC during unexpected non-reward outcomes, while LR (low risk, ADHD only) and HC youth showed similarly low activation during these contrasts. LR and HR groups showed lower activation than HC in the right ACC and the right caudate during flanker contrasts.	Vollstädt-Klein et al., 2020
		fMRI and anticipation-conflict-reward task	Polygenic risk for childhood ADHD was indirectly associated with problematic alcohol use through increased reward-related ventral striatum activity. ADHD participants had less frontoparietal and frontostriatal activity, independent of cannabis use.	Ivanov et al., 2019
fMRI and number-guessing task with monetary reward	Self-reported problematic alcohol use, polygenic risks core for childhood ADHD	No main effects of cannabis use on response inhibition or functional brain activation were observed. An interaction of ADHD diagnosis and cannabis use was found in right hippocampus and cerebellar vermis.	Carey et al., 2017	
fMRI and response inhibition task	ADHD diagnosis with and without cannabis use		Rasmussen et al., 2016	

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Table 1 (continued)

ADHD + obesity: 40 studies identified; most relevant studies are listed below			
fMRI and MID task	ADHD diagnosis; MDD diagnosis; schizophrenia diagnosis; alcohol dependence (all not comorbid), depressive symptoms	ADHD participants had impaired response inhibition combined with less frontoparietal/striatal activity, regardless of cannabis use history. During reward anticipation, significant group differences in ventral striatal (VS) activation: patients with SCZ, alcohol dependence, and MDD showed significantly less VS activation compared to healthy controls (not difference for ADHD). Depressive symptoms correlated with dysfunction in reward anticipation regardless of diagnostic entity.	Hägele et al., 2015
DTI	Synthetic cannabinoid users with and without ADHD	SC users without ADHD had significantly weaker connectivity compared to controls in bilateral hemispheres. SC users with ADHD showed stronger structural connectivity compared to controls. Adolescent SC users with ADHD, but not without ADHD, displayed reduced network organization, indicated by lower clustering coefficient and modularity.	Çelik et al., 2020

Titles and abstracts were evaluated for relevant publications. Articles with study populations including other disease groups and patients with genetic syndromes were not selected. For ADHD + SUD, studies on prenatal alcohol or tobacco exposure or Fetal Alcohol Disorder were excluded. Review articles are not included in this overview. Abbreviations: ACC = anterior cingulate cortex, ADHD = attention-deficit/hyperactivity disorder, AUD = alcohol use disorder, BMI = body mass index, BOLD = blood oxygen level dependent, cIFG = caudal inferior frontal gyrus, dACC-AI = dorsal anterior cingulate cortex - anterior insula coupling, DTI = diffusion tensor imaging, fMRI = functional magnetic resonance imaging, GMV = gray matter volume, HC = healthy control, HR = high risk, iFC = intrinsic functional connectivity, LR = low risk, MDD = major depressive disorder, MID = monetary incentive delay, OFC = orbitofrontal cortex, PRS = polygenic risk score, rs-fMRI = resting-state functional magnetic resonance imaging, SC = synthetic cannabinoid, SCZ = schizophrenia.

3. ADHD-specific neuroimaging section

The following section will give an overview of fMRI-based reward system measures based on MID paradigms, delay discounting or intertemporal choice, resting-state connectivity and structural morphometry.

3.1. fMRI based reward paradigms: monetary incentive delay task

Scheres et al. (2007) investigated the response of neural reward systems in adolescents with ADHD by means of the MID task (Knutson et al., 2000, 2001b) and demonstrated that adolescents with ADHD showed striatal hypoactivation during reward participation as compared to matched controls. In particular, the symptom domain of hyperactivity/impulsiveness was negatively correlated with the VS response. During the feedback phase, no difference in neuronal activation was found. Considering only the existing MID studies, a meta-analysis (Plichta and Scheres, 2014) showed a medium effect size of VS hyperresponsiveness in ADHD vs. healthy controls (Cohen's $d = 0.58$).

Strohle et al. (2008) examined adults with ADHD with the MID task. They replicated striatal hyporesponsiveness in adult patients with ADHD during the reward phase. Plichta et al. (2009) used a reward delay discounting (DD) task according to (McClure et al., 2007), which involves the presentation of monetary rewards that are available to the participant either immediately (i.e. immediately after the fMRI scan) or with a certain time delay (e.g. 2 weeks). Again, striatal hyporesponsiveness was evident in the presentation of monetary reward options. Patients with ADHD showed relative hyperactivation during delayed reward processing in dorsal parts of the striatum and amygdala. Carmona et al., 2012 and Hoogman et al., 2011 replicated the striatal hypoactivation effects in ADHD in larger fMRI studies. Carmona et al. also studied the correlation between striatal reactivity and found activation in the bilateral ventral striatum during reward anticipation to be negatively associated with symptoms of hyperactivity and impulsivity. Hoogman et al., 2011 also looked at the link between striatal reactivity and measures of impulsivity (delay discounting) and found a more complex relationship as there was an interaction with diagnostic status: higher striatal bold response in healthy controls with high impulsivity scores, and low striatal bold response in subjects with ADHD scoring high on impulsivity. Also, genetic factors (in this case the neuronal nitric oxide synthase *NOS1* genotype) modulated striatal bold responses during

reward anticipation. Stoy et al. (2011) reported neural hypo-responsiveness within the putamen when comparing ADHD patients with healthy controls, and finally, Edel et al., 2013 were able to replicate striatal hyporeactivity in patients of the inattentive subtype. In summary, MID anticipation hypoactivity has been replicated as well as linked to clinically meaningful measures such as candidate genes or the trait impulsivity.

So far, only two studies have been published that did *not* replicate striatal hyporesponsiveness in individuals with ADHD during reward expectation. The first study used a modified probability scheme, which may explain the non-replication: Instead of 67 %, money was won in 80 % of trials (Paloyelis et al., 2012). The second study in children by von Rhein et al. (2015) found no group difference during reward anticipation using a modified MID task (win probability was set to 33 %). This might stem from a different MID implementation or alternatively the young age, pointing to potential developmental effects of reward processing (Plichta and Scheres, 2014).

These studies use a categorical ADHD disorder concept. However, there is good reason to believe that the threshold for the clinical diagnosis arbitrarily divides a normal distribution function of symptoms in the general population (Li et al., 2019). The IMAGEN study looked at ADHD symptoms in adolescents and the reward anticipation signal in a large number of healthy volunteers. Blunted reward anticipation in the MID task was significantly associated with a higher number of ADHD-like symptoms.

3.2. fMRI based reward paradigms: delay-discounting paradigm

One of ADHD's core features, impulsivity, can be effectively assessed by using so-called "intertemporal choice" or "delay discounting" tasks. This type of task is thought to capture impulsive behavior as 'impulsive choice': faced with intertemporal choices, patients with ADHD have stronger preferences for smaller but sooner rewards over larger but later rewards. The intertemporal choice paradigm has been employed before to characterize an individual's temporal preference in economic studies (Kahneman and Tversky, 1979) and neuroimaging studies (McClure et al., 2007, Kable & Glimcher, 2007; Plichta et al., 2009)). Application of this paradigm points to alteration in ADHD patients in the form of a steeper course of delay discounting (DD). fMRI studies have identified several abnormalities in this circuitry: Individuals with ADHD exhibit

reduced ventral striatal activity in response to reward. Scheres et al. (2013) suggest that neuronal hyporesponsiveness to expected reward can lead to compensatory increases in reward seeking behavior - this may be related to the delayed decision making in a delay-discounting task. DD tasks regularly show an activation of the ventral striatum, in addition to the posterior cingulate cortex, parts of the prefrontal cortex, the anterior insula and the anterior cingulate cortex. The brain areas found in neuroimaging studies, especially the basal ganglia, correspond in many respects to the results from animal models for DD (Dalley and Robbins, 2017). However, compared to MID-fMRI paradigms, the number of studies on the neural correlates of DD in ADHD is small. In a pediatric sample, boys with ADHD showed lower BOLD activation in the inferior prefrontal cortex, orbitofrontal cortex, and the inferior parietal lobe during reward delay compared to control subjects (Rubia et al., 2009). In another children study, three clinical groups - kids with ADHD, or autism spectrum disorder, or both - were compared with each other and with controls (Chantiluke et al., 2014). Interestingly, the comorbid group showed the most pronounced differences in activation, particularly in areas of the ventromedial prefrontal cortex, anterior cingulate, inferior frontal cortex and ventral striatum, among others. Plichta et al. (2009) found hypoactivation in the striatum during both immediate and delayed reward choices in $n = 14$ adult ADHD patients. In the caudate and the amygdala, BOLD response during delayed rewards was significantly correlated with self-rated ADHD symptoms in the dorsal caudate and amygdala of ADHD participants during delayed reward choice. In another small study by Tanaka et al. (2018), adults with ADHD discounted future losses as much as future gains, although the control participants discounted future losses less than future gains. The control participants had higher activation in the striatum during choices.

Therefore, the results of delay discounting paradigms seem to be comparable to the MID fMRI paradigms: ADHD patients show less activation in the ventral striatum during the decision period, which is a central structure in reward processing, and in other valence-representing brain regions e.g. anterior insula.

3.3. Structural neuroimaging

Structural magnetic resonance imaging (sMRI) enables the measurement of different magnetic properties of brain tissue, such as gray matter, white matter and cerebrospinal fluid. From these measurements, parameters such as volume, cortical thickness, surface area and properties derived from these parameters can be calculated. Previous studies in ADHD have shown that the total brain volume and the total gray matter are up to 2.5–3 % lower compared to controls (Greven et al., 2015). Since hypotheses of brain involvement in ADHD with respect to the reward system mainly refer to regions of the limbic system and functionally connected cortical areas, it is of interest to specifically study areas such as the striatum, insula or even the cingulate gyrus. In a meta-analysis of studies investigating ADHD case-control differences in the brain, significant volume differences were reported in the cerebellar regions, total and right brain volume, right caudal vertebrae and frontal brain areas (Valera et al., 2007). In meta-analyses of studies that applied voxel-based morphometric analysis (VBM) (Frodal and Skokauskas, 2012; Nakao et al., 2011), a reduction of volume in the striatum, insula and prefrontal regions was described (Nakao et al., 2011; Norman et al., 2016). In the largest study on subcortical brain volumes in ADHD, the ENIGMA consortium used a uniform segmentation and quality control strategy for all participating cohorts and performed mega- and meta-analyses to research differences in the brains of those with an ADHD diagnosis versus controls. Interestingly, only in children, but not in adults, differences were found in the volume of the striatum, the amygdala, the hippocampus and in total brain volume (Hoogman et al., 2017). Next, the ENIGMA-ADHD consortium analyses focused on the cortex: smaller surface area of the insula and posterior cingulate cortex were found in children with an ADHD diagnosis, compared with typically developing children (Hoogman et al., 2019). In all, these brain

volumes studies show that regions implicated in the reward system are smaller in size in people with ADHD as compared with controls. It is of course difficult to directly relate these volume differences in the ADHD brain to differences in reward processing, or different activation patterns, respectively.

3.4. Resting-state and functional striatal connectivity fMRI

In contrast to task-based fMRI, resting-state fMRI looks into the functional connectivity of networks rather than in spatial localization. A few studies have investigated how the BOLD response in reward critical brain areas is linked to other brain areas and compared this in ADHD vs. controls. The first studies using this technique concentrated mainly on children, like Posner et al. (2013). This study reported a decreased functional connectivity (FC) of the ventral striatum with the OFC, hippocampus, and anterior PFC in ADHD. On the contrary, an increase in functional connectivity of OFC with NAcc and ACC was found in a large ($n = 247$ ADHD cases) study by Tomasi et al. (2014). Costa Dias et al. (2013) reported in $n = 35$ ADHD cases an increase in FC between NAcc and the anterior prefrontal cortex in ADHD cases. However, in more than 400 participants, Oldehinkel et al. (2016) were not able to find a specific FC alteration in the reward system. Instead, they report a modulation of levels of inattention via FC of the default-mode network.

These studies on fMRI-based reward paradigms, structural imaging of reward related brain regions and resting-state fMRI therefore demonstrate that there is indeed an ADHD-related pattern of blunted fMRI-response to stimuli, less volume in reward-specific brain regions and related connectivity changes. These might relate ADHD to its comorbid conditions, which is reviewed in the following three sections focusing on obesity, depression and substance abuse disorder (SUD).

4. Comorbidity-specific neuroimaging section: ADHD and obesity

Clinically, the link between ADHD and obesity comes somewhat of a surprise as stimulant treatment leads to a suppression of appetite and long-time treatment in children and adolescents is linked to less growth. However, a recent meta-analysis reveals an increase in obesity risk in ADHD of about 70 % in adults and about 40 % in children in comparison to controls (Cortese et al., 2016). On a genetic level, dopaminergic gene sets are significantly associated with obesity as well as ADHD, suggesting shared heritability (Mota et al., 2020). Assuming that there is a specific mechanism (namely, striatal reward processing related to phasic dopamine responses) in ADHD that also mediates weight gain, we might ask whether this mechanism is also implicated in otherwise healthy obese patients and how it is affected by physical fitness.

Importantly, dopaminergic neurotransmission is related to obesity in humans. This has been shown in PET studies investigating the binding of radioligands to the D2 receptor. A reduction in striatal D2 receptors was found in obese participants (Wang and Volkow, 2001). This led to the hypothesis that obesity shares some neurobiological mechanisms with addiction disorders. Second, in MID paradigms – as outlined above, presumably reflecting phasic dopaminergic responses – that used food-cues rather than money (thus, the term food incentive delay would be the more appropriate term), reward anticipation differs in obese or binge-eating patients on the one hand and healthy, non-obese controls on the other (Balodis et al., 2013; Stice et al., 2008; Stoeckel et al. 2008). In overweight adolescents, Stice and colleagues observed overactivation in the striatum as well as in OFC, insula, and opercular regions during anticipation of a food reward (Stice et al., 2008). Decreased activation of the striatum in response to the imagined intake of palatable foods has also been associated with weight gain at a 6-month follow-up (Stice et al., 2010). This is an important finding as it demonstrates that a fMRI-derived neuroimaging biomarker, closely related to striatal reward anticipation, can predict a clinical outcome, in this case, weight gain.

Third, physical activity might impact on brain regions of the limbic

reward system. In a recent study, the effect of training status and acute exercise on report processing was investigated by using a MID paradigm in highly trained and physically inactive men (Bothe et al., 2013). These were randomized into two groups, one running on the treadmill for 30 min, while the subjects in the other group did placebo exercise approximately for one hour. The fMRI measurement took place about 60 min after exercise. The MID task revealed less anticipation in the treadmill group, pointing to a surge in tonic dopamine as consequence of the strong exercise. While the study is preliminary, it clearly shows a direct relation between physical fitness and the limbic reward system.

4.1. fMRI-based reward paradigms: MID in obesity

The number of fMRI studies using a MID paradigm in obesity or similar phenotypes is limited, compared to ADHD and other psychiatric disorders. The reason may be that paradigms using monetary rewards are not as plausible in their application to obesity as paradigms giving high caloric rewards. However, the application of MID paradigms offers the advantage of comparability across diagnostic boundaries and also addresses the question of a general reward deficit. As in the previous section on ADHD, this section will now mainly discuss studies that have used a conventional MID paradigm.

In an exemplary study on changes in the reward system in relation to food or monetary rewards in overweight and obese patients, participants were subjected to both a specific food paradigm and a MID task (Verdejo-Román et al., 2017). In the MID paradigm, the reactivity of the reward system to monetary stimuli seemed to follow an inverted U-curve depending on body weight. The authors interpreted their results as confirmation of the food-reward and incentive sensitization models. The drawback of this study was the completely detached perspective on food and money as a reward.

In contrast, in a previous study, a total of 24 participants underwent functional MRI and performed both a nutritional and a monetary incentive delay task, which allows to measure neuronal activation during the expectation of rewards (Simon et al., 2014). After presenting a clue indicating the amount of food or money to be gained, participants had to react correctly to receive "snack points" or "money coins", which could then be exchanged for real food or money at the end of the experiment. To analyze the specificity of the observed correlations, they performed a correlation between activation in the ventral striatum during the MID task and the BMI. Neither for the current nor for the maximum BMI ever achieved, a significant effect was found.

In a recent study (Barker et al., 2019), researchers investigated whether the phenotypes of impulsiveness and BMI as well as the polygenic risk scores (PRS) of ADHD and BMI have common associations with gray brain matter and the MID task. The ADHD PRS associated with impulsivity symptoms and BMI modulated via activation of the striatum in the MID task. The same applied to the influence of BMI PRS on BMI and impulsiveness by means of activation of the striatum in the MID fMRI task. A common neural substrate – striatal reactivity in the MID – can therefore partially mediate the genetic predisposition for ADHD and BMI, which might relate to the finding that genes encoding for dopaminergic genes are associated with ADHD and BMI (Roth et al., 2020).

4.2. fMRI based delay-discounting paradigm

While most studies looking at delay discounting with or without fMRI only used body weight or body mass index as an independent variable, the conceptualization of obesity is more complex and involves a variety of metabolic parameters. Alternative measures which are comparable, but not identical and provide certain advantages are diabetes status, pre-diabetes, insulin resistance, overweight (BMI > 25), obesity (BMI > 30), body fat or waist-to-hip ratio.

Delay discounting has obviously an appeal to characterize the immediate urge to eat versus self-control in eating. Therefore, several studies look at food or snack related rewards, give liquid sweet drinks or

use monetary rewards in characterizing impulse control in obesity. On the contrary, food-related rewards are rarely used in ADHD research. Therefore, an important question is whether delay discounting in food or monetary reward comes to comparable conclusions. A recent meta-analysis (Amlung et al., 2016) looked at the behavioral level of delay-discounting tasks: While the effect size was larger for food rewards, this meta-analysis nevertheless showed that steeper delay discounting can be found for both food and monetary reward in obesity. However, such a clear effect was not found in another meta-analysis (Tang et al., 2019).

Stoeckel et al. (2013) examined patterns of brain activation during difficult vs. easy trials of a DD task with DD rate (k) in obese women. Easy trials were those where the money amount difference between the immediate and later option was very large (=easy decision for the larger option). In difficult trials the money amount differences were rather small. Steeper delay discounting was correlated with less modulation of activation in putative executive function brain areas, such as the middle and superior frontal gyri and inferior parietal lobule, in response to difficult compared to easy DD trials. These results support the suggestion that increased impulsivity is associated with deficient functioning of executive function areas of the brain. However, the findings in this study do not fall within the core reward network.

Kishinevsky et al. (2012) observed that less activation in executive function areas such as the inferior, middle, and superior frontal gyri during difficult vs. easy DD trials predicted weight gain in a longitudinal follow-up study (after 2–3 years). While this shows the predictive power of the paradigm, it also suggests dysregulated executive function, implicating a suboptimal top-down regulation. However, it did not demonstrate a decisive involvement of reward-related areas.

In example of a sophisticated, but therefore non-standardized paradigm, lean and obese participants (n = 51) were characterized by a DD paradigm which gave monetary rewards and calculated individual indifference points (Morys et al., 2018). Before each decision in the fMRI session, participants were primed by visual and gustatory cues (sweets versus salty tea). This revealed a lower activity in the left dorsolateral prefrontal cortex in obese subjects during priming with negative gustatory cues towards delayed choices as opposed to lean subjects. This points to an important role of environmental cues like visual or gustatory priming stimuli.

Interestingly, these studies did not report significant differences in the nucleus accumbens / the ventral striatum. This region is seen as the core hub of the reward system and is reliably activated in MID tasks as well as in some DD fMRI tasks (Carter et al., 2010). This could depend on the specific contrast used e.g. immediate choice options versus delayed in comparison to hard versus easy trials (Eppinger et al., 2012; McClure et al., 2007). This points to a general problem in standardization of delay discounting trials as discussed in Koffarnus et al. (2017).

4.3. Structural neuroimaging

A recent meta-analysis of 21 studies in more than 5000 participants looked at how voxel-based morphometry was able to capture obesity specific volumetric findings (García-García et al., 2019). The authors report lower gray matter volume in areas including the medial prefrontal cortex, bilateral cerebellum, and left temporal pole for obese patients. Gray matter volume and body mass index were inversely correlated. While these results replicated evidence for a link between obesity and lower gray matter volume in brain areas involved in executive top-down control, the study did not find convincing effects in reward-related subcortical areas like the putamen, caudate or ncl. accumbens.

4.4. Functional (striatal) connectivity

Striatal connectivity is not a well-defined neuroimaging marker, nevertheless some neuroimaging studies in obesity point out its

potential to define decisive pathways in this disorder. Baseline functional connectivity in sleeve gastrectomy patients showed that connectivity of the nucleus accumbens with insula predicted weight loss after one year (12-month post-SG % total weight loss (Cerit et al., 2019). In another small study functional connectivity in a food-related decision-making task was negatively correlated with the dorsal caudate seed and the rostral putamen. This seed connectivity (caudate-putamen rs-FC) negatively predicted BMI change at six-month follow-up (Gao et al., 2018). A further study with a follow-up part found increased functional connectivity between the ventral striatum and the medial PFC and the parietal cortex in obese subjects, while the dorsal striatum connectivity correlated with food craving and predicted BMI after a 3 month follow-up (Contreras-Rodríguez et al., 2017). Finally, in a study with $n = 19$ morbidly obese participants, caudate-amygdala/insula connectivity was higher during a food viewing task (Nummenmaa et al., 2012).

The only study which used a consequent transdiagnostic approach was the PING consortium, which looked at a sample of $n = 926$ participants aged 8–22 and studied striatal seed region-of-interest (Barber et al., 2019). This sample was phenotyped for depression, psychosis, ADHD and general psychopathology. ADHD symptoms were related to age-advanced connectivity across the insula and to age-delayed connectivity to the frontal gyrus. Psychosis was associated with connectivity with the medial prefrontal cortex and superior temporal gyrus. Depression demonstrated dysregulated limbic connectivity. General psychopathology emerged as related to the dorsal posterior insula which has been previously implicated in pain processing.

While these studies used heterogeneous definitions of striatal connectivity, are not replicated and use small sample sizes, they nevertheless highlight the fascinating potential of striatal connectivity as a biomarker for predicting weight over a longitudinal time course. In summary, obesity shows a heterogeneous and not very specific pattern of structural deficits. A question which is not yet completely understood, is whether reward deficits are strictly linked to processing of food-related cues and whether this food-reward-system is independent of other rewards or whether a more generalized reward deficit is found in these patients. A plausible interpretation is that a genetic frame (e.g. ADHD PRS) is associated with impulsive behavior which manifests in a changed reward regulation. And lastly, overeating might induce characteristic changes in the reward system.

5. Comorbidity-specific neuroimaging section: ADHD and depression

As indicated in the introduction, there is a strong link between ADHD and depression. Looking at comorbidity estimates in the population, 13–27 % of patients with ADHD report depressive symptoms over their lifetime, while in clinical samples reports of comorbid depression range from 30 to 50 % (Biederman et al., 1993; Gillberg et al., 2004; Blackman et al., 2005; Kessler et al., 2006; Grunsvold et al., 2008). An ADHD diagnosis in adolescence is a strong predictor for the development of depression in early adulthood (Meinzer et al., 2013). ADHD with comorbid depression has further been linked to both a higher disease burden (Daviss et al., 2009) and less favorable treatment outcome (Fisher et al., 2007; Ohlmeier, 2007) indicating the need for a more integrated understanding of the mechanisms behind high depression comorbidity in ADHD.

The genetic association between ADHD and Major Depressive Disorder is estimated at 0.32 (Lee et al., 2013), and several gene sets have been associated with both disorders (Zhao and Nyholt, 2017), indicating that shared biological mechanisms might be underlying the high rates of comorbidity between these disorders.

However, the role of the reward system as a possible link between ADHD and depression has not yet been thoroughly investigated, despite a large body of research being available on reward sensitivity and the dopamine network in depression. This may be due to the fact that

research on reward sensitivity in depression is focused strongly on the influence of anhedonia upon receipt of a reward, with the consensus stating that anhedonia causes a blunted striatal dopamine response after receipt of a reward (i.e. Admon and Pizzagalli, 2015; Luking et al., 2016a, b; Forbes and Dahl, 2012; Bress et al., 2013; Stringaris et al., 2015). On the other hand, as noted elsewhere in this review, the literature on ADHD is focused mainly on the role of impulsivity on reward anticipation. However, research on the clinical manifestations of ADHD and comorbid depression have indicated both disorders run a largely independent course (i.e. Biederman et al., 1998; Fischer et al., 2007). The question on how these two separable disorders then influence the anticipation and receipt of rewards remains largely unanswered.

5.1. fMRI-based reward paradigms: MID in ADHD and depression

Only a single fMRI study has been performed using the MID paradigm in both subjects with ADHD and depression within the same study (Hägele et al., 2015). This study measured ventral striatal responsiveness in 24 subjects with major depressive disorder, 23 with ADHD as well as similar numbers of subjects with schizophrenia, bipolar disorder and alcohol dependence. They found that depressive symptoms correlate with lower ventral striatal activation during reward anticipation regardless of diagnostic status, and found no main effects of ADHD. This indicates that depressive symptoms may be the driving factor in striatal responsivity across psychiatric disorders, although the limited sample size of this study leaves much room for further investigation.

5.2. fMRI-based reward paradigms: delay discounting in ADHD and depression

Studies of DD in patients with depression have shown mixed results. A 2010 study by (Lempert and Pizzagalli, 2010) showed decreased discounting in anhedonic subjects, which they suggest may be due to reduced responsiveness to immediate rewards in these subjects. However, other studies have found opposite effects, like a 2011 study by (Takahashi et al., 2011), which showed increased discounting, suggesting more impulsive choices in subjects with depression. Similar increased discounting results observed by (Pulcu et al., 2014) were explained by suggesting that depressed patients may hold a bleaker view of the future, which therefore decreased the value of future rewards.

Unfortunately, no studies have been performed using the Delay Discounting paradigm in patients comorbid with ADHD and depression. Although both subjects with ADHD and subjects with depression may show increased discounting of delayed rewards, the proposed underlying mechanisms for both disorders are vastly different. Only studies directly comparing comorbid and non-comorbid subjects of either disorder would be able to answer if the mechanism underlying discounting effects in ADHD and depression are qualitatively different.

An interesting hint might come from a study by (Moody et al., 2016), which investigated subjects with Substance Use Disorder (SUD) and comorbid depression. As discussed in the section about SUD and depression below, SUD is also linked with impulsive decision making and increased discounting of delayed rewards, similar to subjects with ADHD. Subjects with SUD and comorbid depression showed even greater discounting than those subjects with only SUD, suggesting a cumulative effect of both disorders. However, since no MRI measurements were taken, conclusions on overlapping neural mechanisms cannot be made.

5.3. Structural neuroimaging in ADHD and depression

There has been a number of studies comparing structural brain alterations in subjects with ADHD and comorbid depression. A study by Onnink et al. (2014) indicated that subjects with ADHD and previous depression had lower hippocampal volumes as compared to subjects without previous depression. A study in adults with ADHD (Das et al.,

2017) found higher nucleus accumbens with higher inattention scores, but lower hippocampus volumes with higher hyperactivity scores. Both these effects were stronger when correcting for depressive effects, again suggesting differential effects of depression and ADHD on subcortical volumes. Taken together, structural imaging studies do not show a consistent overlap between ADHD and depression, nor a strong focus on the reward network.

5.4. Functional connectivity in ADHD and depression

One recent study linking structural imaging and resting state (Posner et al., 2014) confirmed the finding of smaller hippocampal volumes in children with ADHD, but also showed reduced functional connectivity between hippocampus and the orbitofrontal cortex. Both these effects were associated with the presence of depressive symptoms in these children. A larger scale study by (Zhang et al., 2015) took a whole brain approach, investigating connectivity changes between nodes across the brain in both patients with ADHD and depression. Though they did not find similar regions associated with either disorder, they did observe that similar patterns of connectivity lateralization were shared, suggesting not an overlap in space but in the pattern of connectivity.

Several studies have taken a predictive approach towards resting state imaging and depression in ADHD, looking if depressive symptoms can be predicted at the hand of resting state patterns. Pan et al. (2017) use a community-based sample, showing that altered intrinsic connectivity in the reward network is predictive of future depressive symptoms but not ADHD, suggesting a role for the reward network in predicting disease progression. However, other studies like Whitfield et al. (2019) and Hawkey et al. (2018) all find that connectivity patterns in the frontal executive functioning regions were predictive of both ADHD and depression, while Barber et al. (2019) links frontal connectivity with ADHD symptoms and limbic connectivity with depression.

Taken together these studies on depression and ADHD do not show a strong consensus on whether common or unique neural structural, activation and connectivity profiles are thought to underlie ADHD and depression symptoms in a comorbid population. Although the reward system plays an important role in both disorders, the interplay between disorders is not fully researched or understood.

6. Comorbidity-specific neuroimaging section: ADHD and substance use disorder (SUD)

6.1. Concepts of reward processing in SUD

Reward system functioning as mediated by the mesolimbic dopaminergic reward pathway has been proposed as an important neurobiological risk marker for SUD (McBride and Li, 1998; Piazza et al., 1991; Volkow and Morales, 2015; Volkow et al., 2002) due to its role in processing incentives (Schultz, 1998) and its relevance for the reinforcing properties of drugs of abuse (Robinson and Berridge, 2000). Relevant for the present review we focus on two broader perspectives (Hommer et al., 2011) namely the *reward deficit model* and *reward surfeit model* of SUD. Empirical findings supporting and contradicting the assumptions of these two models will be reviewed and hypotheses for future studies will be developed. Due to the many different aspects in SUD, e.g. type of drugs and their neurochemical actions (Badiani et al., 2011), treatment states of the disorder (addicted vs. detoxified), developmental states (adolescents vs. adults) and interactions of drug intake and neuroadaptations, this section must be selective and will focus on the fMRI reward anticipation literature. As a detailed evaluation of differential effects of drugs of abuse on the reward system (e.g. how strong dopamine is pushed in comparison to natural reinforcers) is outside the scope of our review, we point to previous reviews on this topic (Volkow et al., 2007 and 2015). For simplification, we believe that all relevant drugs of abuse impact via direct (cocaine, amphetamines) or indirect (nicotine, piods etc) ways on the dopaminergic reward system.

The *reward deficit model* (RDM) assumes that subjects with hypoactive, i.e. a less responsive reward circuitry, are more prone to use psychoactive substances in order to compensate for a reward deficit (Blum et al., 2000; Bowirrat, and Oscar-Berman, 2005; Volkow et al., 2003;). The intake of many psychoactive substances will cause DA signaling and activation in the striatum plus other mesolimbic regions (Bowirrat, and Oscar-Berman, 2005; Volkow et al., 2007;). In the framework of RDM drug intake can be understood as a self-medication that compensates for a hyporesponsive state of the reward system.

The *reward surfeit model* (RSM) by contrast assumes that *elevated* reward sensitivity underlies the vulnerability for addictive behaviors (Alloy et al., 2009; Kambouropoulos and Staiger, 2004). It is assumed that elevated reward sensitivity leads to approach behavior towards rewarding stimuli including drugs of abuse and consequently to increased substance use and a higher risk for addiction. Adolescence plays a significant role here, as the reward system seems particularly active during this sensitive phase.

The incentive salience model posits those two independent processes (“liking” versus “wanting”) are independently realized in neural circuitry. Only the carving-related “Wanting” circuitry rests on the dopaminergic system in the midbrain and basal ganglia (Berridge and Robinson, 2016). The “incentive salience” theory states that an extreme amplification of “wanting” without a comparable increase in “liking” is at the core of SUD. SUD leads to changes in the reward system (“neural sensitization”). In the end, most reward responses are blunted, but only drug related-cues are able to produce an adequate signal.

6.2. Monetary incentive delay tasks and other fMRI paradigms in SUD

The empirical evidence stemming from fMRI research, however, is inconsistent. In line with the predictions of RDM, detoxified alcoholics showed less ventral striatal response to anticipated monetary reward (Beck et al., 2009; Wrase et al., 2007) as measured with an MID task. Deficits during reward anticipation, however, have not been replicated in two other studies (Bjork et al., 2008, 2012). In the latter studies alcoholic-dependent patients had a larger positive ventral striatal BOLD response during the feedback phase of the paradigm than controls. In a review paper summarizing the fMRI literature on anticipatory reward processing in SUD (Balodis and Potenza, 2015) the authors conclude that the findings are divergent depending on the different substances of abuse (e.g. cannabis vs. alcohol) and the different (treatment) states of the disorder (addicted vs. detoxified). While the first argument is clearly associated with the neurochemical actions of the specific drugs, the second argument point to the problem of interactions between drug intake and neuroadaptations. For example, chronic nicotine administration may lead to blunted reward signals whereas single nicotine administration in non-smokers lead to higher anticipatory VS activity (Wang et al., 2020). Therefore, developmental and longitudinal studies are needed to characterize (1) VS responsiveness *before* drug-intake starts (favoring RMD or RSM) and (2) short- and long-term changes in VS responsiveness after starting drug-intake and development of SUD. In a promising study by Stice et al. (2013), activity in the reward system was investigated in a group of adolescents (N = 162; mean age = 15.3). In a follow-up one year later, it was determined whether the subjects started using drugs. Reward activity at baseline was found to be a significant predictor of critical substance intake in the future (favoring RSM in adolescents). A second analysis showed that adolescents who reported substance use experience versus abstinence at baseline showed hypoactivation in the ncl. caudate to monetary reward (favoring RDM assumptions).

6.3. Structural morphometry and striatal functional connectivity in substance use disorder

Relatively little is known about structural morphometry and abnormal striatal functional connectivity during reward anticipation as

a risk factor for psychiatric disorders. In a large sample of $N = 1510$ adolescents, Cao et al. (2019) demonstrated widespread cortical and subcortical connectivity during reward processing, including connectivity between reward-related regions with motor areas and the salience network. In a study by Just et al. (2019) the authors investigated subjects at risk for SUD and found abnormal task-related functional connectivity in frontostriatal brain systems that may indicate pre-existing neural vulnerability for SUD. With regards to morphometry, Schneider et al. (2012) showed that greater risk-taking bias was associated with and partially mediated by lower gray matter density in the striatum.

Together, these observations reveal the interconnected nature of the striatum and underscore the importance of examining functional connectivity with the striatum (Wang et al., 2016).

6.4. Functional Connectivity in ADHD and substance use disorder

Only a few studies investigated the relationship between resting-state functional connectivity and ADHD (symptoms) and substance use disorders. Janes and colleagues showed that, relative to healthy controls, nicotine dependent individuals had significantly higher ADHD self-report scores and greater salience network (SN) coupling (Janes et al., 2018). This is of interest as the SN mediates attention to salient internal/external stimuli to guide behavior and is anchored by the dorsal anterior cingulate cortex (dACC) and bilateral anterior insula (AI) (Janes et al., 2018). The intra-SN connectivity was found to be positively associated with ADHD symptoms which may suggest that coupling strength potentially impacts neurocognitive functioning associated with both ADHD symptoms and nicotine dependence (Janes et al., 2018).

As mentioned above in the ADHD and depression section, a large-scale longitudinal study in a childhood community sample showed that increased left ventral striatum node strength predicted increased risk for future depressive disorder, whereas striatal node strength did not predict ADHD or substance use disorder (Pan et al., 2017). However, the participants included in this study were rather young (mean age at MRI scanning 10.6 years) and future studies may want to expand the age span to better capture the co-morbid spectrum of substance use disorders which may still develop during adolescence and early adulthood.

Overall, the extent to which substance use affects ADHD-related alterations in brain functional organization is largely unknown. Therefore, longitudinal studies in larger samples, targeting different classes of substance use, are required to capture the long-term impact of substance use in the context of ADHD on reward-related functional connectivity.

Some promising insights come from the IMAGEN study. While impulsivity and novelty seeking, two traits highly associated with both ADHD and SUD, come with a blunted striatal response in the MID task, this task is not able to longitudinally predict future substance use (Nees et al., 2012). The number of participants with full-blown clinical ADHD is relatively small (<50), nevertheless even when using a dimensional approach this lack of substance use prediction by a well-validated biomarker comes as a surprise. These at-risk individuals might profit from some not yet well-understood protective factors

7. Synthesis and open questions

How do results of studies with morphometry, connectivity, monetary incentive delay tasks and delay discounting tasks converge when it comes to a transdiagnostic overview?

The least promising neuroimaging measure seems to be the volumetry of the reward system. This is not surprising, as the link between structure and function is not 1:1. Studies demonstrating a change in volumetry in patients are rarely specific for e.g. the ncl. accumbens. In the end morphometric strategies based on T1-weighted images might lack sensitivity. This might change with more sophisticated quantitative MRI measures capable of measuring dopaminergic maturation (Larsen et al., 2020), but so far studies in ADHD are lacking.

Regarding the reward-related connectivity patterns in ADHD and

comorbid disorders we identified more studies investigating functional connectivity and the literature on structural connectivity is sparse. While the largest study in ADHD reported no specific functional connectivity alterations in the reward system, smaller studies reported contradictory results. Also, results from studies investigating functional connectivity in relation to BMI and/or obesity were heterogeneous and await replication. A promising perspective was outlined in a study showing that functional connectivity may be predictive of later ADHD and depressive symptom development. This exemplifies the potential and the need for longitudinal studies. Additionally, the coupling strength of the salience network was associated with ADHD symptoms and nicotine dependence.

When looking at the delay discounting task, most studies do indeed find a steeper decline in delay discounting, but this is not reflected in a uniform dysregulation pattern in specific parts of the reward system. The brain regions implicated in changed delay discounting are much more diverse than in the MID task e.g. different parts of the prefrontal cortex and other cortical regions. The ventral striatum as a core subcortical reward region is only rarely found. It is not clear whether this questions the reward system as a bottleneck for all disorders discussed in the review. It might be that the DD tasks are not standardized enough e.g. food-related rewards in obesity versus monetary rewards in other disorders.

Taken together, most of the studies using MID tasks point to dysfunctional reward processing in ADHD and comorbid disorders. There are inconsistencies that clearly call for the need of prospective longitudinal studies to shed on light the two major question (1) whether there is pre-morbid VS hypo- or hyper-responsiveness and (2) how VS responsiveness changes due to medication, (legal and illegal) substance and non-substance consumption. Future studies should address these two questions to complete our picture of the role of the reward system in ADHD and comorbid disorders.

7.1. Why do we need more transdiagnostic studies?

Table 1 demonstrates that there is only little research regarding dysfunction of the reward system in ADHD in relation to its comorbidities, as well as transdiagnostic neuroimaging studies. As outlined in the introduction, the reward system is likely a crucial neuronal module which acts as an effective bottleneck for both ADHD and other mental disorders, which as a consequence are comorbid with ADHD. Also, Table 1 demonstrates that such studies often lack common read-outs and methodology.

7.2. Is there a homogenous ADHD core pathophysiology?

Most recent empirical fMRI studies that aimed to identify causal mechanisms in ADHD centered around a single core dysfunction. Often, this core dysfunction is then localized in a single brain region e.g. the nucleus accumbens. Furthermore, these studies are mainly based on simple case-control comparisons. Only rarely, studies compare across age, dimensional symptomatology or diagnostic boundaries. An implicit assumption of this approach is that ADHD represents a homogeneous patient group. It would however be surprising if this would actually be reflected in neuroimaging studies, as there is considerable clinical evidence for multiple developmental and pathophysiological pathways which converge to ADHD symptomatology (Fair et al., 2013; Nigg et al., 2005). When combining different subgroups in unitary samples, this may relate in only modest effect sizes as opposing effects within these groups cancels out and regress to the mean.

This is a general problem in research of mental disorders and might need more transdiagnostic research, which is rather informed by underlying neurobiological mechanisms. This led to the Research Domain Criteria (RDoC) approach, focusing on basic pathophysiological core modules which can be tested via objective measurements (Insel et al., 2010). The neuroimaging features discussed in our review are

sub-modules of this RDoC system.

Therefore, in addition to case-control studies, emphasis should be put on studies using dimensional approaches, e.g. investigating neuroimaging phenotypes which are not bound to diagnoses and link them to clinical scores. In a second step, this can be extended to include more and more complex disorder clusters. Most small studies exclude patients suffering from comorbid disorders to compensate for small numbers by studying a “pure” phenotype. However, this is a highly artificial situation as in clinical reality, comorbidity is the norm rule rather than the exception (even more so in ADHD). Excluding patients suffering from depression or substance abuse in ADHD research thus might lead to opaque results which are hard to interpret. By using a transdiagnostic, dimensional approach, we might be able to identify neural circuits related to the etiology of relatively homogeneous neural core components (or modules) related to RDoCs. As outlined in the above sections, only rarely there are distinct findings in reward circuitry for specific disorders.

7.3. Is reward dysregulation an epiphenomenon in comorbid disorders?

When turning to the question whether ADHD-related reward dysregulation is an integral part of the comorbid disorders we must consider alternative explanations. It might be that the reward dysregulation is actually part of the pathology of MDD/obesity/SUD or, alternatively, just an epiphenomenon. First, while a “epiphenomenal” dysregulation of reward regulation might lead to a similar pathology in adults e.g. concentration deficits in depression or during substance withdrawal, it is explicitly stated in the diagnostic criteria that the ADHD-related pathology is not explained by other factors. *Second, it is an interesting question how a dysregulated reward system links to so-called “late-onset” ADHD in adults. While it is an ongoing debate (see other articles in that issue) whether this entity actually exists, the question remains whether adults with a history of childhood ADHD show different neural activation patterns than adults with atypical late-onset ADHD-symptoms. If a hypoactive reward anticipation response predisposes to subsequent comorbid disorder, why does this manifest in comorbid disorders like e.g. SUD and not e.g. obsessive-compulsive disorder? A speculative interpretation is that a blunted reward system is prone to SUD or obesity (to lift the reward system in a homeostatic way) and if this does not happen, MDD develops. However, this trajectory is speculative and needs further empirical validation.* Third, when framing the question in a neuroimaging context, we believe that ADHD is early related to a developmentally shaped reward regulation deficit. This gives rise to a negative developmentally trajectory manifesting later in SUD, depression or obesity. Therefore, longitudinal studies of reward-related biomarkers are the best solution to answer this question. An outstanding example is the Adolescent Brain Cognitive Development (ABCD)-study which will look at the longitudinal effect of reward-related data e.g. MID-task and other multimodal neuroimaging modalities in more than 5000 children over the course of several years (e.g. Owens et al., 2021).

7.4. Do we need standardization of neuroimaging assessment?

However, these overlapping and heterogeneous findings might not only come from the neurobiology of reward pathways but from overlapping but not identical methods. This calls for the use of very specific reward test paradigms, yet there will be a trade-off between highly specialized paradigms (such as described in the section about obesity) and less-sensitive measures, e.g. structural morphometry. As the section about morphometry in the striatum / reward system demonstrates, morphometric changes are broad, general, often subtle and lack functional specificity. On the contrary, delay discounting tasks tend to lack simple, standardized designs (cf. Koffarnus et al., 2017). Therefore, a compromise is the use of reward anticipation in the MID task. This has already shown good transdiagnostic potential (cf. Hägele et al., 2016). One route to study large sample sizes is to use simple and robust,

ecologically valid and simple measures based on resting-state connectivity, e.g. striatal connectivity. While there has been some promise in using this a proxy for therapeutic prediction and its link to impulsivity has been studied (Grimm et al., 2019), the exact definition of striatal connectivity is not that straightforward. In principle, resting-state fMRI variance should explain and predict most of the variance of task-based measures. Therefore, it would be highly promising to use existing datasets (as obtained in the ENIGMA consortium or human connectome project) and to look at transdiagnostic features in ADHD and comorbid disorders.

7.5. How are developmental and maturation aspects of ADHD mirrored in neuroimaging?

Especially in SUD, the prediction of therapeutic success is of interest. Obviously, addiction has a characteristic time dynamic with a first trigger by the drug (“chasing the first high”) and consecutive maladaptation of the reward system. A practical application in ADHD would not only be to predict abstinence, as done in the aforementioned study by Stice et al., 2013, but to characterize the SUD risk for a specific patient.

If this can be done for adult patients, why not step earlier in time: In the case of comorbid depression, developmental aspects also play an important role. In most cases, ADHD symptoms arise early in childhood, but the presence and persistence of these symptoms are important predictors for the emergence of subsequent affective symptoms and major depressive episodes in early adulthood. Like with SUD, more insight into the developmental trajectory of comorbid ADHD and depression is necessary to predict disease progression and treatment response in individual cases.

Most studies ignore neurodevelopmental aspects by excluding children, treating adults equally irrespective of age or by using an only linear age-adjustment. The importance of development is exemplary demonstrated by the PING consortium (Barber et al., 2019) which did not use a longitudinal design but a cross-sectional study with a huge age range (8–22). They used a growth-chart-approach and were able to demonstrate ADHD- and other psychopathology found only when looking at the normative growth trajectory patterns of striatal connectivity. Future studies should try to build on these results by using longitudinal designs. As these are difficult to achieve, cross-sectional studies should make use of growth-chart-analysis for transdiagnostic characterizations beyond striatal connectivity. In summary, this might help in developing clinical biomarkers. Growth charts have been established in clinical medicine for a long time.

A drawback in studies looking at the general population is the reduced range of psychopathological symptoms which renders effect size smaller in comparison to same-size clinical populations. On the other hand, medication effects which are generally hard to interpret are absent in general population samples. Developmental trends of reward-related fMRI-processing, morphometric measures and striatal connectivity should not be ignored as they might reveals distinct neurodevelopmental pathways different psychopathological subtypes. Identification of such neuroimaging markers will indicate early clinical risk and yield hints for selection of preventive measures.

7.6. Is neuroimaging useful for diagnosis and therapy prediction?

With the rise of neuroimaging techniques in the late 1990s, Kosslyn asked “If neuroimaging is the answer, what is the question?” (Kosslyn, 1999). More than 20 years later, a possible answer is both rooted in clinical psychiatry as well as the application of machine learning to clinical populations. If machine learning algorithms capture specific dimensions of psychopathology related to ADHD in neuroimaging datasets, then it would be possible to characterize the degree of a brain’s “ADHD’ness” in a dimensional way. This would lead away from categorical diagnosis and underscore a dimensional, symptom-oriented

approach. Such an approach will stand and fall with its success in real-life prediction of therapy response.

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