Cross-disorder genetic analyses implicate dopaminergic signaling as a biological link between Attention-Deficit/Hyperactivity Disorder and obesity measures

Nina Roth Mota, Ph.D.[1,2#], Geert Poelmans, M.D., Ph.D.[1], Marieke Klein, Ph.D.[1,3], Bàrbara Torrico, Ph.D.[4,5,6,7], Noèlia Fernàndez-Castillo, Ph.D.[4,5,6,7], Bru Cormand, Ph.D.[4,5,6,7], Andreas Reif, M.D., Ph.D.[8], Barbara Franke, Ph.D.[1,2]*, and Alejandro Arias Vásquez, Ph.D.[1,2]*#

[1]Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Department of Human Genetics, Nijmegen, The Netherlands

[2] Radboud university medical center, Donders Institute for Brain, Cognition and Behaviour, Department of Psychiatry, Nijmegen, The Netherlands

[3] Department of Psychiatry, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands

[4] Departament de Genètica, Microbiologia i Estadística. Facultat de Biologia, Universitat de Barcelona, Barcelona, Catalonia, Spain

[5] Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Spain

[6] Institut de Biomedicina de la Universitat de Barcelona (IBUB), Barcelona, Catalonia, Spain

[7] Institut de Recerca Sant Joan de Déu (IR-SJD), Esplugues de Llobregat, Catalonia, Spain

[8] Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt am Main, Germany

Corresponding authors

* shared final responsibility

Corresponding authors:

Nina Roth Mota, PhD

Department of Human Genetics (route 855)

Radboud university medical center

Postbus 9101, 6500 HB Nijmegen, The Netherlands

Telephone: +31243614286

Email: Nina.RothMota@radboudumc.nl

Alejandro Arias Vasquez, PhD

Department of Human Genetics (route 855)

Radboud university medical center

Postbus 9101, 6500 HB Nijmegen, The Netherlands

Telephone: +31243616722

Email: Alejandro.AriasVasquez@radboudumc.nl

Running title: Dopamine genetics linking ADHD and obesity measures

Keywords: ADHD, obesity, BMI, dopamine, genetics, comorbidity, DARPP-32

ABSTRACT

Attention-Deficit/Hyperactivity Disorder (ADHD) is frequently comorbid with other psychiatric disorders and also with somatic conditions, such as obesity. In addition to the clinical overlap, significant genetic correlations have been found between ADHD and obesity as well as body mass index (BMI). The biological mechanisms driving this association are largely unknown, but some candidate systems, like dopaminergic neurotransmission and circadian rhythm, have been suggested. Our aim was to identify the biological mechanisms underpinning the link between ADHD and obesity measures. Using the largest GWAS summary statistics currently available for ADHD (N=53,293), BMI (N=681,275), and obesity (N=98,697), we first tested the association of dopaminergic and circadian rhythm gene sets with each phenotype. This hypothesis-driven approach showed that the dopaminergic gene set was associated with both ADHD ($P=5.81x10^{-3}$) and BMI ($P=1.63x10^{-5}$), while the circadian rhythm gene set was associated with BMI only ($P=1.28x10^{-3}$). We then took a data-driven approach by conducting genome-wide ADHD-BMI and ADHD-obesity gene-based meta-analyses, followed by pathway enrichment analyses. This approach further supported the implication of dopaminergic signaling in the link between ADHD and obesity measures, as the *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway was significantly enriched in both the ADHD-BMI and ADHD-obesity gene-based meta-analysis results. Our findings suggest that dopaminergic neurotransmission, partially through DARPP-32-dependent signaling, is a key player underlying the genetic overlap between ADHD and obesity measures. Uncovering the shared etiological factors underlying the frequently observed ADHD-obesity comorbidity may have important implications in terms of preventive interventions and/or efficient treatment of these conditions.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric disorder characterized by developmentally inappropriate and impairing levels of inattention and/or hyperactivity and impulsivity symptoms. The prevalence of ADHD is estimated as 5.3% during childhood/adolescence [1] and around 2.8% during adulthood [2]. ADHD is among the most heritable psychiatric disorders, with heritability estimates around 74% [3]. It follows a multifactorial pattern of inheritance, where multiple genetic and environmental factors, each of small effect, as well as their interplay, can contribute to its pathophysiology. A recent genome-wide association study (GWAS) meta-analysis identified the first genome-significant associations for ADHD [4].

High comorbidity rates are a hallmark of ADHD, further increasing disease burden. These comorbidities include both psychiatric [5, 6] and non-psychiatric (somatic) diseases and traits. One of the most frequently and consistently reported comorbid somatic conditions in ADHD is obesity [7]. Obesity is nowadays one of the major health problems worldwide, resulting in a large economic burden and significant decrease in life expectancy [8], and its prevalence keeps rising substantially [9, 10]. Obesity is usually classified according to body mass index (BMI), which is calculated as weight in kilograms divided by the height in meters squared (kg/m^2). A BMI higher than 25 kg/m^2 signals overweight and a BMI above 30 kg/m^2 is regarded as obesity, which can be further subdivided into classes defined based on increasing BMI [11]. The genetic contribution to obesity and related phenotypes has been extensively studied, and heritability estimates range from 50% up to 90% [12]. Several GWASs have been conducted on obesity and BMI. For BMI, the most recent GWAS meta-analysis was performed in a sample of nearly 700,000 individuals and identified 536 associated genomic loci [13]. A previous GWAS on 158,864 participants with BMI information compared normal weight individuals to those with obesity classes I, II, and III [14]. The authors of this study concluded that associations found with the categorical phenotypes are highly overlapping with the ones obtained by using BMI as a quantitative trait [14].

The prevalence of ADHD among adults seeking weight loss treatment for obesity has been reported to be around 27%, reaching up to 43% when considering only those with extreme obesity (i.e. class III) [15, 16]. This

rate is more than ten times higher than the prevalence of ADHD in adults in the general population [2]. Likewise, two recent meta-analyses show a higher than expected prevalence of overweight and/or obesity in individuals with ADHD, both during childhood/adolescence and adulthood, with odds ratios up to 1.55 and the strongest effects being observed in adults [17, 18]. Importantly, the association between ADHD and obesity was no longer significant when the analysis was limited to participants receiving pharmacological treatment for ADHD [17].

The specific factors underlying the comorbidity between ADHD and obesity remain largely unknown. Recently, significant genetic correlations between ADHD and BMI (rg=0.21–0.26, [4, 19], as well as between ADHD and obesity (ranging from rg=0.285 to rg=0.338, according to the different obesity classes) and other obesity-related phenotypes, have been reported [4]. These findings highlight the involvement of genetic factors in the observed epidemiological overlap between ADHD and obesity measures and provide an entry point for the investigation of the specific biological mechanisms and processes involved. Some candidate biological processes have been suggested, including dopaminergic neurotransmission and circadian rhythm signaling. These two candidate mechanisms have been selected as the main focus of a large European Union consortium aimed at studying comorbid conditions of ADHD (CoCA; https://coca-project.eu/), of which this study is part.

Altered reward processing and impaired inhibitory control, key features of ADHD, are thought to be the outcome of dysregulated dopaminergic neurotransmission [20]. Studies in humans and animal models have also linked disturbances in dopaminergic neurotransmission and downstream processes to obesity [21, 22]. It has been suggested that overeating may represent an attempt of obese people to compensate for their reduced sensitivity to rewards [21].

Circadian rhythm-related traits (e.g. eveningness) and disturbances (e.g. sleep problems) have been repeatedly associated with ADHD and/or ADHD symptoms [23]. These problems have also been linked to BMI variation and obesity [24]. Disrupted circadian rhythm signaling may lead to obesity through temporal alterations in eating behavior and changes in metabolic hormones [25]. Two manifestations of circadian

rhythm disruption in particular, sleeping problems (i.e. altered sleep duration) and an unstable eating pattern (e.g. skipping breakfast and binge eating later in the day), may mediate the observed association between ADHD symptoms and BMI [26].

In this paper, we aimed to identify the shared etiological factors underlying the observed associations between ADHD and obesity measures. Specifically, we conducted (i) candidate gene-set association analyses and (ii) genome-wide gene-based cross-disorder(/trait) meta-analyses, followed by pathway enrichment analyses. Across our hypothesis-driven and data-driven analyses, we found altered dopaminergic signaling pathways to be implicated in ADHD and BMI/obesity.

MATERIALS AND METHODS

Participant samples

This study used summary statistics of ADHD, BMI, and obesity GWAS meta-analyses that have been made publicly available. These studies had been approved by local ethics committees and had obtained the required informed consents (as described in earlier publications [4, 13, 14]).

The ADHD data was derived from 19,099 cases and 34,194 controls, composed by samples from the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH) population-based cohort and the Psychiatric Genomics Consortium (PGC) samples of European ancestry [4]. The iPSYCH-PGC ADHD summary statistics were downloaded from the PGC website (https://www.med.unc.edu/pgc/results-and-downloads) and filtered to include only SNPs with minor allele frequency (MAF) >0.01 and an imputation quality (INFO) >0.8, totalizing 8,094,094 variants.

For BMI, we used summary statistics from the most recent BMI GWAS meta-analysis that combined the earlier BMI summary statistics of the Genetic Investigation of ANthropometric Traits (GIANT) consortium [27] with new GWAS results from participants in the UK Biobank [13]. In total, this GIANT-UK Biobank BMI GWAS meta-analysis reached a mean sample size of N=681,275 participants of European ancestry [13]. After downloading the summary statistics from https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files, we filtered the data in order to include only SNPs with MAF >0.01 in our analyses, which yielded a total of 2,336,056 SNPs (see Yengo *et al.* [13] for further information on GWAS summary statistics quality control).

For obesity, summary statistics from a GWAS meta-analysis from European ancestry cohorts within the GIANT consortium on obesity class I were used [14]. Subjects in that study were considered as cases for obesity class I if they had BMI ≥30 kg/m^2; controls had a BMI <25 kg/m^2. In total, summary stats were based on 32,858 cases and 65,839 controls, and were downloaded from https://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files. Data was

filtered to SNPs with MAF >0.01, resulting in 2,353,324 SNPs (see Berndt *et al.* [14] for further information GWAS summary statistics quality control).

ADHD – BMI genetic correlation analysis

Given the large sample increase of the most recent BMI GWAS, we conducted LD score regression analysis [28] to (re-)estimate the genetic correlation between ADHD and BMI using summary statistics of the largest GWAS currently available for each phenotype (samples described above). For this analysis, we used pre-computed LD scores based on European samples from the 1000 Genomes Project as indicated in https://github.com/bulik/ldsc/wiki/Heritability-and-Genetic-Correlation.

Hypothesis-driven, candidate gene-set approach

Gene-set association analyses

In order to assess the links between the dopaminergic neurotransmission and circadian rhythm pathways and ADHD, BMI, and obesity, we assembled gene sets and tested their associations to the individual phenotypes of interest using the GWAS summary statistics described above. Dopaminergic neurotransmission and circadian rhythm gene sets were assembled based on the *Kyoto Encyclopedia of Genes and Genomes (KEGG)* and the *Gene Ontology (GO)* databases. The final dopaminergic (DOPA) and circadian rhythm (CIRCA) gene sets comprised 264 and 284 unique autosomal genes, respectively. Details on the selection of the gene sets are provided in the **Supplementary Material**.

Gene-set association analyses were performed using MAGMA software (version 1.05b [29]). The first step was to carry out single gene-based analysis to assess the degree of association of each gene (i.e. gene-based P-values) with each phenotype. The second step was to test the association of each gene set, through competitive analyses, by aggregating the gene-based P-values according to their presence (or not) in the gene sets (see **Supplementary Material** for a more detailed description). We used a conservative Bonferroni correction to account for multiple testing by dividing the significance P-value threshold of 0.05

by the six gene-set tests that were performed (i.e. (DOPA, CIRCA) x ADHD, BMI, obesity) and hence, the gene-set significance P-value threshold was set to 8.33×10^{-3}.

Data-driven, genome-wide approach

Gene-based cross-disorder/trait meta-analyses

In addition to the hypothesis-driven approach described above, we performed genome-wide gene-based cross-disorder(/trait) meta-analyses by using gene-based P-values for ADHD, BMI, and obesity (obtained as described above) and the gene meta-analysis option in MAGMA software (version 1.05b [29]). The weighted Stouffer's Z method was used to combine the Z-scores for each gene across cohorts, with weights set to the square root of the sample size each Z-score is based on (i.e. therefore accounting for the fact that sample sizes vary per SNP – and thus per gene – within and between GWAS summary statistics). Since we were interested in the combined effect of each gene on both phenotypes in each pair-wise meta-analysis (i.e. the ADHD-BMI or the ADHD-obesity meta-analyses), only genes present in both gene-based GWAS results were included. The gene-based P-value threshold for genome-wide significance was set to 0.05 divided by the number of genes in each gene-based meta-analysis.

Canonical pathway enrichment analyses

From each pair-wise gene-based cross-disorder(/trait) meta-analysis, we selected the genome-wide significant genes that increased significance by at least one order of magnitude compared to each of the original gene-based results (i.e. $P_{meta\text{-}analysis} < P_{ADHD}/10$ and $P_{meta\text{-}analysis} < P_{(obesity\ or\ BMI)}/10$). The set of genes meeting this criterion was then tested for enrichment of canonical pathways using Ingenuity Pathway Analysis (http://www.ingenuity.com; QIAGEN Bioinformatics, Redwood City, California, USA) set at its default parameters and using Benjamini-Hochberg correction for multiple testing (see **Supplementary Material** for details).

RESULTS

ADHD–BMI genetic correlation

The ADHD-BMI genetic correlation was estimated as r_g=0.3157 (SE=0.0246; P=8x10^{-38}). This is similar to estimates based on smaller BMI datasets as well as to estimates for the obesity classes previously reported [4, 19] and mentioned in the introduction.

DOPA and CIRCA gene-set associations with ADHD, BMI, and obesity

We tested the association of two gene sets – DOPA (264 genes) and CIRCA (284 genes) – with ADHD, BMI, and obesity. Results of these gene-set analyses are shown in **Table 1.** The DOPA gene set was significantly associated with both ADHD (P=5.81x10^{-3}) and BMI (P=1.63x10^{-5}); the CIRCA gene set was only associated with BMI (P=1.28x10^{-3}). These results do not seem to be driven solely by one or very few individual genes that were highly associated with either ADHD or BMI (**Supplementary Table S1**).

ADHD-BMI and ADHD-obesity gene-based meta-analyses

The gene-based cross-disorder(/trait) meta-analysis between ADHD and BMI resulted in 1684 genome-wide significant genes, while the one for ADHD and obesity resulted in 22 significant genes. Of those, 211 genes for the ADHD-BMI meta-analysis and 9 genes for the ADHD-obesity meta-analysis, showed an increase in their association significance (i.e. decrease in P-value) of at least one order of magnitude compared to both individual GWASs. These genes, which were all at least nominally significant in the original GWASs being meta-analyzed, are listed in **Supplementary Tables S2** and **S3**.

Canonical pathway enrichment analyses

Based on the 211 genes from our ADHD-BMI gene-based meta-analysis, the enrichment analysis identified four significant canonical pathways, as shown in **Table 2**. These were *CREB Signaling in Neurons, Synaptic Long Term Depression, Synaptic Long Term Potentiation,* and *Dopamine-DARPP32 Feedback in cAMP Signaling*. The enrichment analysis for the 9 ADHD-obesity genes also rendered four significant canonical

pathways: *GABA Receptor Signaling, Corticotropin Releasing Hormone Signaling, Dopamine-DARPP32 Feedback in cAMP Signaling*, and *Huntington's Disease Signaling* (**Table 3**).

One pathway, the *Dopamine-DARPP32 Feedback in cAMP Signaling*, was found enriched in the two analyses. In total, proteins encoded by eight unique genes derived from our meta-analyses operate in this canonical pathway (**Tables 2** and **3**). Combining the enrichment analysis with a literature search, we constructed a schematic representation of the *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway, which is shown in **Figure 1** and described in detail in the **Supplementary Material**.

In addition, a secondary ADHD-BMI gene-based cross-disorder(/trait) meta-analysis was carried out in order to address a small sample overlap between the datasets: Welcome Trust participants had been included both in the iPSYCH-PGC and the GIANT GWASs (for further information, see **Supplementary Material**). This resulted in 202 genes of interest, highly overlapping with the 211 genes from the main ADHD-BMI meta-analysis results (182 overlapping genes), where the *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway remained significantly associated with the phenotype through the canonical pathway enrichment analysis.

DISCUSSION

In this paper, we aimed to uncover the biological mechanisms underlying the observed genetic associations between ADHD and obesity measures. Based on known and self-derived genetic correlation estimates for ADHD and BMI/obesity obtained from the world-wide largest datasets for each phenotype, we first applied a hypothesis-driven testing approach of two selected gene sets (DOPA and CIRCA), which showed that the dopaminergic neurotransmission system partially explains the genetic overlap between ADHD and BMI. Our data-driven, genome-wide approach subsequently showed that dopaminergic signaling, specifically *Dopamine-DARPP32 Feedback in cAMP Signaling*, was significantly enriched in both the ADHD-BMI and the ADHD-obesity gene-based meta-analysis results.

Both ADHD and obesity measures have been linked to disturbances in dopaminergic signaling. Alterations of the brain's executive and reward circuits – modulated by mesocortical and mesolimbic dopamine, respectively – have been postulated as the basis of the deficient inhibitory control and impaired reward processing characteristics of ADHD [20]. The ability to resist the impulse to eat desirable foods, and an appropriate reward-response to those, also require proper functioning of these dopamine-regulated processes [21, 22]. For example, impulsive eating, as a result of a high arousal response to a potential reward and impaired inhibitory control, can lead to weight gain and obesity [30]. In addition, eating behavior is also dependent on the hypothalamic homeostatic system, which is comprised by hormonal regulators of energy balance – such as insulin, leptin, and gut hormones – and controls hunger, satiety, and adiposity levels [21]. Increasing evidence suggests that such metabolic hormones can also affect food-related sensitivity of the dopaminergic reward system [31], pointing to an overlap between the homeostatic and reward/reinforcement systems related to obesity [21].

Also confirming our hypothesis, the CIRCA gene set was associated with BMI, but the absence of a significant association with ADHD was unexpected. ADHD has previously been associated with altered circadian rhythmicity at molecular, endocrine, and behavior levels [32]. Furthermore, mutations of a key gene in circadian rhythm regulation, *per1b*, in zebrafish have been shown to induce hyperactive, impulsivity-like,

and attention deficit-like behaviors [33]. The lack of a significant association between ADHD and the CIRCA gene set in our study may be due to a true lack of effect of the circadian rhythm pathway on ADHD. However, it is also possible that there is a true (unobserved) effect but that the gene set we assembled was not appropriate/informative enough to detect such association.

Going beyond candidate gene-set analyses, we conducted data-driven, genome-wide gene-based cross-disorder(/trait) meta-analyses to identify biological pathways underlying the shared heritability. Several pathways showed significant enrichment in the ADHD-BMI and in the ADHD-obesity results. Dopamine signaling was, again, at the heart of the pathway that was significantly enriched in both analyses, i.e. the *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway. This postsynaptic pathway centers around the Dopamine- and cAMP-regulated neuronal phosphoprotein (DARPP-32; also known as Protein phosphatase 1 regulatory subunit 1B (PPP1R1B)), the phosphorylation state of which modulates dopaminergic neurotransmission (see **Figure 1** and description in the **Supplementary Material** for details).

DARPP-32 is highly expressed in postsynaptic dopaminergic neurons in the dorsal striatum (i.e. caudate and putamen), which is involved in certain executive functions, such as inhibitory control, and in the ventral striatum (i.e. nucleus accumbens), which is the main brain region responsible for reward processing (https://gtexportal.org/home/gene/PPP1R1B). As described above, poor inhibitory control and altered reward processing, in the form of steeper delay discounting, are key neurobiological circuitries implicated in both ADHD and obesity [20, 21]. Further evidence linking dopamine-DARPP-32 signaling, reward processing and the brain comes from findings in animal models. Upon investigation of the consequences of frustrated expected reward of palatable food on gene expression in the mouse brain, *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway was found to be enriched among differentially expressed genes, both the ventral striatum and in frontal cortex [34].

DARPP-32 modulates the effects of dopamine on cAMP/PKA-dependent gene transcription through transcription factors of the cyclic AMP-responsive element-binding (CREB) complex (**Figure 1**), and CREB dysregulation has been linked to both ADHD [35] and obesity [36]. Of note, the *CREB Signaling in Neurons*

pathway was also significantly enriched in our ADHD-BMI gene-based meta-analysis, along with two other partially overlapping pathways involved in synaptic plasticity processes (namely, the *Synaptic Long Term Depression* and the *Synaptic Long Term Potentiation* pathways; **Table 2**), which are also closely related to dopamine DARPP-32 signaling.

Additional evidence for an involvement of DARPP-32 signaling to the ADHD-BMI/obesity overlap comes from the study of rare variants. The most common form of monogenic obesity is caused by mutations in the melanocortin 4 receptor (*MC4R*) gene [37] and MRC4 signaling is known to activate DARPP-32 [38]. In addition to early-onset obesity, a higher prevalence of ADHD has been reported in *MC4R* mutation-carriers [39]. It has been hypothesized that such co-occurrence may be, in part, underpinned by reward processing deficits [40], and animal studies provide further support regarding the involvement of MC4R signaling and dopaminergic-dependent reward processing [38, 41].

Our study has strengths and limitations. A clear strength is that we make use of the largest GWAS meta-analysis results available for each of the phenotypes being investigated. The sample sizes used to generate the (European ancestry) summary statistics used here were, in total, more than 53,000 for the iPSYCH-PGC ADHD GWAS, up to 700,000 for the GIANT-UK Biobank BMI GWAS, and almost 99,000 for the GIANT obesity GWAS. Another strength is that we did not restrict our gene set assembly to single GO-terms or KEGG pathways, but applied a more inclusive approach regarding the processes involved. For dopaminergic neurotransmission, we thus assembled a gene set (DOPA) that was subsequently found to be significantly associated with ADHD and BMI. This contrasts with the approach adopted in the iPSYCH-PGC ADHD GWAS paper, which tested dopaminergic candidate genes and GO-term pathways only individually, failing to detect significant associations with ADHD [4]. The large difference in sample sizes between the phenotypes imposed some difficulties when analyzing them together. We minimized such limitations by carrying out gene-based cross-disorder(/trait) meta-analyses in MAGMA, which allows sample sizes to vary between and within samples and accounts for such variation by weighting the effects accordingly. We also opted for performing gene-based – rather than SNP-based – cross-disorder(/trait) meta-analyses. Apart from

assuming that the (combined effect of SNPs within) genes represent entities closer to the biological mechanisms, this approach has a reduced statistical burden compared to SNP-based analyses and seems most suitable for these data given the difference in SNP density between the ADHD and the BMI and obesity GWASs (the later ones being restricted to about 2.4 million SNPs present in HapMap 2). Another limitation we addressed was the presence of overlapping samples, since Welcome Trust participants had been included both in the iPSYCH-PGC ADHD GWAS and the GIANT BMI and obesity GWASs. The reduction in sample size reduced power of our analysis, but findings from the canonical pathway enrichment analysis remained stable.

Overall, the findings of the present study identify dopaminergic neurotransmission as a key player underlying the shared heritability of ADHD and BMI/obesity, implicating mechanisms involving DARPP-32 signaling in particular. This is especially interesting since DARPP-32 has been directly implicated in the mechanism of action of ADHD medication [42, 43], which has been suggested to attenuate the increased risk for obesity in people with ADHD [17]. Uncovering critical aspects of the shared etiology underlying the prevalent ADHD-obesity comorbidity may have important implications for clinical outcome, preventive interventions, and/or efficient treatment of these conditions.

Acknowledgements

This work was supported by the European Community's Horizon 2020 Programme (H2020/2014 – 2020) under grant agreements n° 667302 (CoCA), n° 728018 (Eat2beNICE), and n° 643051 (MiND). The work was also supported by the ECNP Network 'ADHD across the Lifespan'. Barbara Franke was supported by a personal grant from the Netherlands Organization for Scientific Research (NWO) Innovation Program (Vici grant 016-130-669). Bru Cormand received funding from the Spanish 'Ministerio de Economía y Competitividad' (SAF2015-68341-R) and AGAUR, 'Generalitat de Catalunya' (2017-SGR-738) and Noelia Fernández-Castillo was funded by 'Centro de Investigación Biomédica en Red de Enfermedades Raras' (CIBERER, Spain). Andreas Reif received support from the DFG (SFB CRC 1193 Z03) and the BMBF (BipoLife). Statistical analyses were carried out on the Genetic Cluster Computer (http://www.geneticcluster.org) hosted by *SURF*sara and financially supported by the Netherlands Scientific Organization (NWO 480-05-003 PI: Posthuma) along with a supplement from the Dutch Brain Foundation and the VU University Amsterdam.

Disclosures

Barbara Franke discloses having received educational speaking fees from Shire and Medice. Andreas Reif is part of advisory boards and has received speaker fees from Shire, Medice, Janssen, Servier and Neuraxpharm, as well as research grants from Medice. All other authors report no biomedical financial interests or potential conflicts of interest. This publication reflects only the author's view and the European Commission is not responsible for any use that may be made of the information it contains.

REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 2007; **164**(6)**:** 942-948.

2. Fayyad J, Sampson NA, Hwang I, Adamowski T, Aguilar-Gaxiola S, Al-Hamzawi A *et al.* The descriptive epidemiology of DSM-IV Adult ADHD in the World Health Organization World Mental Health Surveys. *Atten Defic Hyperact Disord* 2017; **9**(1)**:** 47-65.

3. Faraone SV, Larsson H. Genetics of attention deficit hyperactivity disorder. *Mol Psychiatry* 2018.

4. Demontis D, Walters RK, Martin J, Mattheisen M, Als TD, Agerbo E *et al.* Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet* 2018.

5. Katzman MA, Bilkey TS, Chokka PR, Fallu A, Klassen LJ. Adult ADHD and comorbid disorders: clinical implications of a dimensional approach. *BMC Psychiatry* 2017; **17**(1)**:** 302.

6. Franke B, Michelini G, Asherson P, Banaschewski T, Bilbow A, Buitelaar JK *et al.* Live fast, die young? A review on the developmental trajectories of ADHD across the lifespan. *Eur Neuropsychopharmacol* 2018; **28**(10)**:** 1059-1088.

7. Instanes JT, Klungsoyr K, Halmoy A, Fasmer OB, Haavik J. Adult ADHD and Comorbid Somatic Disease: A Systematic Literature Review. *J Atten Disord* 2018; **22**(3)**:** 203-228.

8. Engin A. The Definition and Prevalence of Obesity and Metabolic Syndrome. *Adv Exp Med Biol* 2017; **960:** 1-17.

9. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; **384**(9945)**:** 766-781.

10. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A *et al.* Health Effects of Overweight and Obesity in 195 Countries over 25 Years. *N Engl J Med* 2017; **377**(1)**:** 13-27.

11. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser* 2000; **894:** i-xii, 1-253.

12. Elks CE, den Hoed M, Zhao JH, Sharp SJ, Wareham NJ, Loos RJ *et al.* Variability in the heritability of body mass index: a systematic review and meta-regression. *Front Endocrinol (Lausanne)* 2012; **3:** 29.

13. Yengo L, Sidorenko J, Kemper KE, Zheng Z, Wood AR, Weedon MN *et al.* Meta-analysis of genome-wide association studies for height and body mass index in approximately 700000 individuals of European ancestry. *Hum Mol Genet* 2018; **27**(20)**:** 3641-3649.

14. Berndt SI, Gustafsson S, Magi R, Ganna A, Wheeler E, Feitosa MF *et al.* Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nat Genet* 2013; **45**(5)**:** 501-512.

15. Altfas JR. Prevalence of attention deficit/hyperactivity disorder among adults in obesity treatment. *BMC Psychiatry* 2002; **2:** 9.

16. Fleming JP, Levy LD, Levitan RD. Symptoms of attention deficit hyperactivity disorder in severely obese women. *Eat Weight Disord* 2005; **10**(1)**:** e10-13.

17. Cortese S, Moreira-Maia CR, St Fleur D, Morcillo-Penalver C, Rohde LA, Faraone SV. Association Between ADHD and Obesity: A Systematic Review and Meta-Analysis. *Am J Psychiatry* 2016; **173**(1)**:** 34-43.

18. Nigg JT, Johnstone JM, Musser ED, Long HG, Willoughby MT, Shannon J. Attention-deficit/hyperactivity disorder (ADHD) and being overweight/obesity: New data and meta-analysis. *Clin Psychol Rev* 2016; **43:** 67-79.

19. Anttila V, Bulik-Sullivan B, Finucane HK, Walters RK, Bras J, Duncan L *et al.* Analysis of shared heritability in common disorders of the brain. *Science (80-)* 2018; **360**(6395).

20. Sonuga-Barke EJ. Causal models of attention-deficit/hyperactivity disorder: from common simple deficits to multiple developmental pathways. *Biol Psychiatry* 2005; **57**(11)**:** 1231-1238.

21. Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn Sci* 2011; **15**(1)**:** 37-46.

22. Kenny PJ. Reward mechanisms in obesity: new insights and future directions. *Neuron* 2011; **69**(4)**:** 664-679.

23. Coogan AN, McGowan NM. A systematic review of circadian function, chronotype and chronotherapy in attention deficit hyperactivity disorder. *Atten Defic Hyperact Disord* 2017; **9**(3)**:** 129-147.

24. Um YH, Hong SC, Jeong JH. Sleep Problems as Predictors in Attention-Deficit Hyperactivity Disorder: Causal Mechanisms, Consequences and Treatment. *Clinical psychopharmacology and neuroscience : the official scientific journal of the Korean College of Neuropsychopharmacology* 2017; **15**(1)**:** 9-18.

25. Engin A. Circadian Rhythms in Diet-Induced Obesity. *Adv Exp Med Biol* 2017; **960:** 19-52.

26. Vogel SW, Bijlenga D, Tanke M, Bron TI, van der Heijden KB, Swaab H *et al.* Circadian rhythm disruption as a link between Attention-Deficit/Hyperactivity Disorder and obesity? *J Psychosom Res* 2015; **79**(5)**:** 443-450.

27. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nat New Biol* 2015; **518**(7538)**:** 197-206.

28. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Patterson N *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 2015; **47**(3)**:** 291-295.

29. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput Biol* 2015; **11**(4)**:** e1004219.

30. Michaud A, Vainik U, Garcia-Garcia I, Dagher A. Overlapping Neural Endophenotypes in Addiction and Obesity. *Front Endocrinol (Lausanne)* 2017; **8:** 127.

31. Cassidy RM, Tong Q. Hunger and Satiety Gauge Reward Sensitivity. *Front Endocrinol (Lausanne)* 2017; **8:** 104.

32. Baird AL, Coogan AN, Siddiqui A, Donev RM, Thome J. Adult attention-deficit hyperactivity disorder is associated with alterations in circadian rhythms at the behavioural, endocrine and molecular levels. *Mol Psychiatry* 2012; **17**(10)**:** 988-995.

33. Huang J, Zhong Z, Wang M, Chen X, Tan Y, Zhang S *et al.* Circadian modulation of dopamine levels and dopaminergic neuron development contributes to attention deficiency and hyperactive behavior. *J Neurosci* 2015; **35**(6)**:** 2572-2587.

34. Martin-Garcia E, Fernandez-Castillo N, Burokas A, Gutierrez-Cuesta J, Sanchez-Mora C, Casas M *et al.* Frustrated expected reward induces differential transcriptional changes in the mouse brain. *Addict Biol* 2015; **20**(1)**:** 22-37.

35. D'Andrea I, Fardella V, Fardella S, Pallante F, Ghigo A, Iacobucci R *et al.* Lack of kinase-independent activity of PI3Kgamma in locus coeruleus induces ADHD symptoms through increased CREB signaling. *EMBO Mol Med* 2015; **7**(7)**:** 904-917.

36. Chiappini F, Cunha LL, Harris JC, Hollenberg AN. Lack of cAMP-response element-binding protein 1 in the hypothalamus causes obesity. *J Biol Chem* 2011; **286**(10)**:** 8094-8105.

37. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N Engl J Med* 2003; **348**(12)**:** 1085-1095.

38. Cui H, Mason BL, Lee C, Nishi A, Elmquist JK, Lutter M. Melanocortin 4 receptor signaling in dopamine 1 receptor neurons is required for procedural memory learning. *Physiol Behav* 2012; **106**(2)**:** 201-210.

39. Agranat-Meged A, Ghanadri Y, Eisenberg I, Ben Neriah Z, Kieselstein-Gross E, Mitrani-Rosenbaum S. Attention deficit hyperactivity disorder in obese melanocortin-4-receptor (MC4R) deficient subjects: a newly described expression of MC4R deficiency. *Am J Med Genet B Neuropsychiatr Genet* 2008; **147b**(8)**:** 1547-1553.

40. Porfirio MC, Giovinazzo S, Cortese S, Giana G, Lo-Castro A, Mouren MC *et al.* Role of ADHD symptoms as a contributing factor to obesity in patients with MC4R mutations. *Med Hypotheses* 2015; **84**(1)**:** 4-7.

41. Klawonn AM, Fritz M, Nilsson A, Bonaventura J, Shionoya K, Mirrasekhian E *et al.* Motivational valence is determined by striatal melanocortin 4 receptors. *J Clin Invest* 2018; **128**(7)**:** 3160-3170.

42. Napolitano F, Bonito-Oliva A, Federici M, Carta M, Errico F, Magara S *et al.* Role of aberrant striatal dopamine D1 receptor/cAMP/protein kinase A/DARPP32 signaling in the paradoxical calming effect of amphetamine. *J Neurosci* 2010; **30**(33)**:** 11043-11056.

43. Heyser CJ, McNaughton CH, Vishnevetsky D, Fienberg AA. Methylphenidate restores novel object recognition in DARPP-32 knockout mice. *Behav Brain Res* 2013; **253:** 266-273.

Table/Figure Legends

Table 1. Gene-set association results of dopaminergic (DOPA) and circadian rhythm (CIRCA) systems with ADHD, BMI, and obesity.

Table 2. Canonical pathways with significant enrichment in the ADHD-BMI gene-based meta-analysis.

Table 3. Canonical pathways with significant enrichment in the ADHD-obesity gene-based meta-analysis.

Figure 1. Schematic representation of the *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway. The proteins encoded by the eight genome-wide significant genes derived from the ADHD-BMI gene-based meta-analysis results (**Table 2**) are contextualized and highlighted in red in the pathway. A detailed description of the pathway in provided in the **Supplementary Material**. For clarity and simplicity, additional proteins in the pathway are omitted. Protein groups or complexes are shown with double margins.

Table 1. Gene-set association results of dopaminergic (DOPA) and circadian rhythm (CIRCA) systems with ADHD, BMI, and obesity.

	DOPA[a]	**CIRCA**[b]
ADHD[c]	**P=5.81x10^{-3}**	P=0.521
BMI[d]	**P=1.63x10^{-5}**	**P=1.28x10^{-3}**
Obesity[e]	P=0.050	P=0.205

Significant associations are highlighted in bold.

[a.] DOPA gene-set analyses are based on 261, 245, and 248 genes from the ADHD, BMI, and obesity GWAS summary statistics, respectively.

[b.] CIRCA gene-set analyses are based on 281, 272, and 273 genes from the ADHD, BMI, and obesity GWAS summary statistics, respectively.

[c.] European ancestry iPSYCH-PGC ADHD GWAS [4].

[d.] GIANT-UK Biobank BMI GWAS [13] .

[e.] GIANT obesity (class I) GWAS [14].

Table 2. Canonical pathways with significant enrichment in the ADHD-BMI gene-based meta-analysis

	CREB Signaling in Neurons	**Synaptic Long Term Depression**	**Synaptic Long Term Potentiation**	**Dopamine-DARPP32 Feedback in cAMP Signaling**
P-value	4.11×10^{-5}	5.68×10^{-5}	2.17×10^{-4}	2.19×10^{-4}
P-value - B-H corrected	7.95×10^{-3}	7.95×10^{-3}	1.53×10^{-2}	1.53×10^{-2}
Canonical Pathway size (number of molecules)	226	189	134	178
ADHD-BMI genes[a] in the pathway	10	9	7	8
	CACNA1D [b,c] *CREB3L3* [b] *GNAT1* *GRIA1* [b,c] *GRID2* *GRIK5* *GRM4* *ITPR3* [b,c] *PLCL1* *PRKAG1* [c]	*CACNA1D* [b,c] *GNAT1* *GRIA1* [b,c] *GRID2* *GRM4* *IGF1R* *ITPR3* [b,c] *PLCL1* *PPP2R3A*	*CREB3L3* [b] *GRIA1* [b,c] *GRM4* *ITPR3* [b,c] *PLCL1* *PPP1R3A* *PRKAG1* [c]	*CACNA1D* [b,c] *CREB3L3* [b] *CSNK1G2* *ITPR3* [b,c] *PLCL1* *PPP1R3A* *PPP2R3A* [b] *PRKAG1* [c]

[a.] Genes from the ADHD-BMI gene-based meta-analysis results, only considering genome-wide significant (at $P_{threshold}=2.99 \times 10^{-6}$) genes with association P-values lower by at least one order of magnitude in the meta-analysis compared to the gene-based results of both ADHD and BMI individually.
[b.] Also part of DOPA in the gene-set analysis
[c.] Also part of CIRCA in the gene-set analysis

Table 3. Canonical pathways with significant enrichment in the ADHD-obesity gene-based meta-analysis

	GABA Receptor Signaling	**Corticotropin Releasing Hormone Signaling**	**Dopamine-DARPP32 Feedback in cAMP Signaling**	**Huntington's Disease Signaling**
P-value	6.69×10^{-4}	1.45×10^{-3}	2.05×10^{-3}	4.19×10^{-3}
P-value - B-H corrected	2.81×10^{-2}	2.87×10^{-2}	2.87×10^{-2}	4.40×10^{-2}
Canonical Pathway size (Number of molecules)	101	149	178	256
ADHD-obesity genes[a] in the pathway	2 *CACNA1D* [b,c] *DNM1*	2 *BDNF* *CACNA1D* [b,c]	2 *CACNA1D* [b,c] *CSNK1G2*	2 *BDNF* *DNM1*

[a.] Genes from the ADHD-obesity gene-based meta-analysis results, only considering genome-wide significant genes (at $P_{threshold}=2.97 \times 10^{-6}$) with association P-values lower by at least one order of magnitude in the meta-analysis compared to the gene-based results of both ADHD and obesity individually.
[b.] Also part of DOPA in the gene-set analysis.
[c.] Also part of CIRCA in the gene-set analysis.

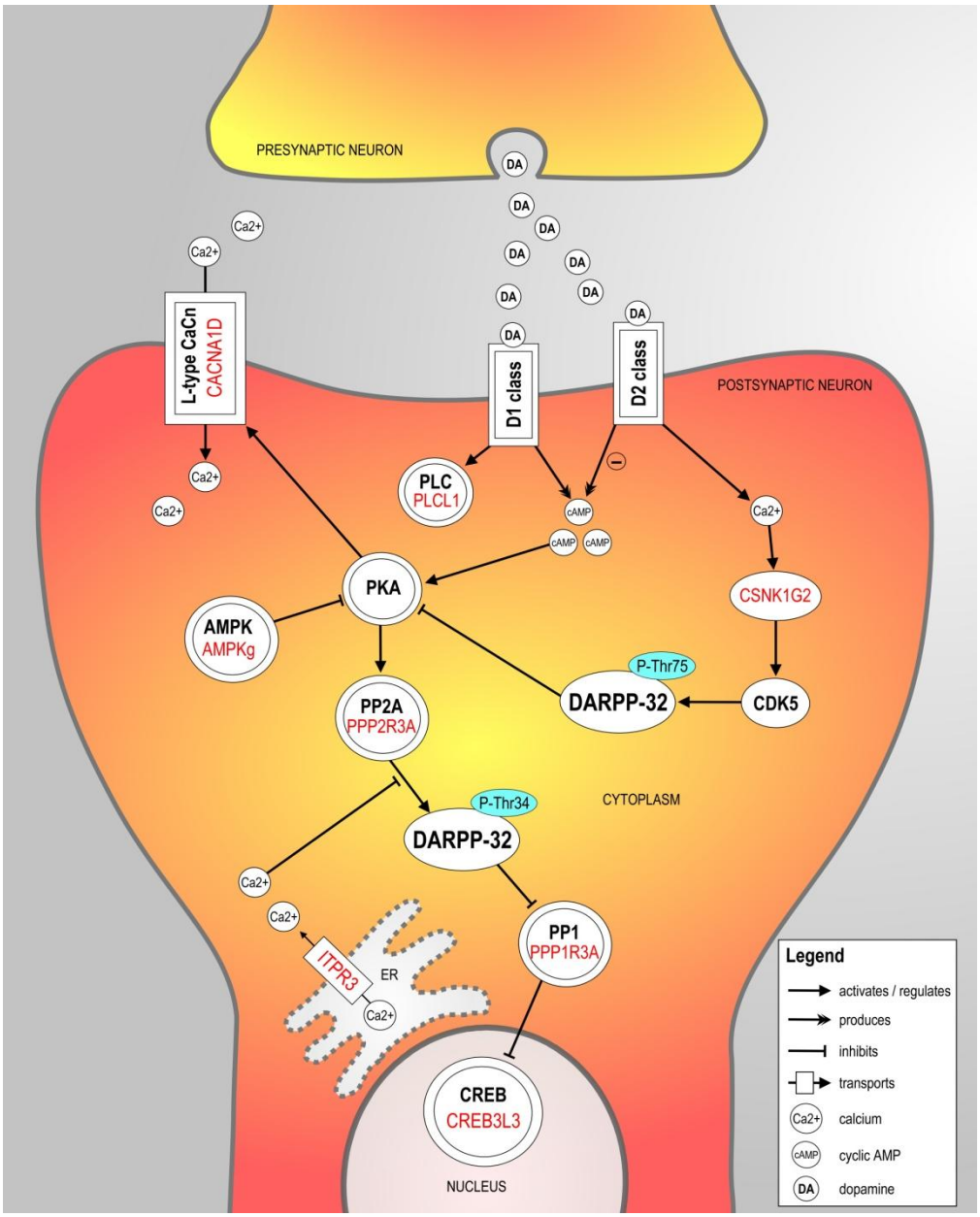

Figure 1. Schematic representation of the *Dopamine-DARPP32 Feedback in cAMP Signaling* pathway. The proteins encoded by the eight genome-wide significant genes derived from the ADHD-BMI gene-based meta-analysis results (**Table 2**) are contextualized and highlighted in red in the pathway. A detailed description of the pathway in provided in the **Supplementary Material**. For clarity and simplicity, additional proteins in the pathway are omitted. Protein groups or complexes are shown with double margins.