increased food anticipatory activity (F (4, 88)=12,12, p<0,0001), a readout of their motivation to engage in intense physical activity. Corticosterone plasma levels were enhanced at P42 (+551±196 ng/mL vs Controls, F (1, 19)=11,38, p=0,0032) while reduced at P49 (-510±65 ng/mL, F (1,20)=5,697, p=0,0270) in ABA rats. At P42, ABA showed reduced levels of glucocorticoid receptor (-26±7% vs Controls, F (1, 20)=5,544, p=0.0289), caldesmon (-26±3%, F (1, 19)=29,12, p<0,0001) and neuroligin-1 (-17±7%, F (1, 20)=8,713, p=0,0079), molecular markers of cytoskeletal stability and glutamatergic homeostasis. Accordingly, reduced dendritic spine density (-3,15±0,36 spine/10mm vs Controls, F (1, 28)=4,706, p=0,0387) and number of mushroom-shaped spines (-11,8±4,36%, df=14, p=0,0345), together with an increased number of thin-shaped spines (+13,05±3,26%, df=14, p=0,0054) were found. These events were paralleled by impairment in spatial memory measured in the SOOR test (DI= -0,435±0,06 vs Controls, F (1, 34)=5,864, p=0,0209). These effects persisted even after bodyweight recovery.

Conclusions: Our findings indicate that ABA induction orchestrates hippocampal maladaptive structural and functional plasticity contributing to cognitive deficits, providing a putative mechanism that could be targeted in AN patients.

References

[1] A. E. van Eeden, D. van Hoeken, e H. W. Hoek, «Incidence, prevalence and mortality of anorexia nervosa and bulimia nervosa», Curr. Opin. Psychiatry, vol. 34, fasc. 6, pp. 515–524, nov. 2021, doi: 10.1097/YCO.0000000000000739. [2] «DSM-V. Diagnostic and Statistical Manual of Mental Disorders: DSM-V. Washington DC: American Psychiatric Association. 5th ed.; 2013. [3] R. Bou Khalil, L. Souaiby, e N. Farès, «The importance of the hypothalamo-pituitary-adrenal axis as a therapeutic target in anorexia nervosa», Physiol. Behav., vol. 171, pp. 13–20, mar. 2017, doi: 10.1016/j.physbeh.2016.12.035. [4] E. Collantoni et al., «Hippocampal volumes in anorexia nervosa at different stages of the disorder», Eur. Eat. Disord. Rev. J. Eat. Disord. Assoc., vol. 29, fasc. 1, pp. 112–122, gen. 2021, doi: 10.1002/erv.2806. [5] B. S. McEwen, C. Nasca, e J. D. Gray, «Stress Effects on Neuronal Structure: Hippocampus, Amygdala, and Prefrontal Cortex», Neuropsychopharmacology, vol. 41, fasc. 1, pp. 3–23, gen. 2016, doi: 10.1038/npp.2015.171.

Conflict of interest

The authors declare no conflicts of interest. This research was supported by grants from MIUR PRIN (grant number: P2022E4MLS), Cariplo Foundation (grant number: 2017-0865), Nutricia Research Foundation (grant number: a2020-E3), Young IBRO Maternity/Parenthood Grant 2021, Nando and Elsa Peretti Foundation (grant number: 370) and Banca d'Italia, MIUR Progetto Eccellenza 2023-2027, and from Finanziamenti PNRR (DM351).

https://doi.org/10.1016/j.nsa.2024.104522

P2047

NEUROSCIENCE APPLIED 3 (2024) 104521

IMPAIRMENT OF PHYSICAL ACTIVITY NYCTHEMERAL PATTERN IN GHSR DEFICIENT MICE IN RESPONSE TO UNDERNUTRITION AND PATIENTS WITH ANOREXIA NERVOSA

J. Mattioni [1], S. Aidat [2], N. Lebrun [1], N. Ramoz [1], P. Gorwood [1], P. Duriez [1], O. Viltart [2], V. Tolle [1]. [1] *Université Paris Cité, Institut de Psychiatrie et Neuroscience de Paris IPNP- INSERM- U1266- Vulnerability of psychiatric and addictive disorders, Paris, France;* [2] *University of Lille, SCALab UMR CNRS 9193, Villeneuve d'Ascq, France*

Introduction. Anorexia Nervosa (AN) is a psychiatric disorder characterized by voluntary restriction of food intake, resulting in weight loss and severe undernutrition. Observational studies have associated AN with circadian rhythms alterations, including hormonal secretion, sleep-wake cycle, and rest-activity. Yet, mechanisms that link circadian rhythm shifts to abnormal eating in AN are poorly understood. We previously demonstrated that plasma ghrelin concentrations, an orexigenic hormone secreted by the stomach and acting through the GHSR (Growth Hormone Secretagogue Receptor), was elevated in AN despite restraint eating.

Aim of the study. We aimed to test the hypothesis that impaired ghrelin signaling may contribute to altered nycthemeral rhythm observed in patients with AN. We investigated how GHSR deficiency affects the nycthemeral pattern of activity in female mice submitted to chronic food restriction, a condition associated with elevated ghrelin, and compared the chronotype of AN patients and healthy controls.

Methods. Wild-type (Ghsr+/+) and KO (Ghsr-/-) mice were singly housed in cages equipped with running wheels placed in circadian cabinets with controlled 12h light/dark light cycles (lights-off at 6 pm), and their physical activity was monitored throughout the experimental protocol. Habituation to running wheels was performed over a 7-day period and baseline 24h food intake was monitored to determine 100% ad libitum food consumption (ALW conditions). In the subsequent 16-day, mice were provided with 70% of their baseline food intake in order to reach 80% of their initial body weight while maintaining unrestricted access to the running wheel (FRW, Food restriction + Wheel). Food pellets were provided daily at 05:00 pm. The number of wheel revolutions was recorded and the following time periods were analyzed: 24 hours, 12h light phase and 12h dark phase for each experimental day. For chronotypes analyses, Morningness-Eveningness Questionnaire (MEQ) was used to differentiate between morning, neutral or evening chronotype.

Results. In ALW conditions, the nycthemeral pattern of activity and the total number of wheel counts were similar in (Ghsr+/+) and KO (Ghsr-/-) mice. In FRW conditions, the total number of wheel counts over 24h was identical between genotypes but the nycthemeral pattern was different: daytime activity was lower (p<0.01) while night-time activity was higher (p=0.07) in Ghsr-/- compared to Ghsr+/+ mice. Daytime activity progressively increased over the course of food restriction in both genotypes but this increase was of lower amplitude in Ghsr-/- compared to Ghsr+/+ mice. From Day10 to Day16, daytime activity was greater than night-time activity in Ghsr+/+ mice (Delta Day-Night activity, p<0.01). When analyzing hourly activity, Ghsr-/- mice displayed higher activity than Ghsr+/+ mice from 6 to 11 pm and lower activity from 6 am to 6 pm. AN patients displayed a morning chronotype while healthy controls displayed a neutral chronotype (Chi-square test, p=0.053).

Conclusion. These data suggest a reciprocal interaction between altered nycthemeral pattern and AN and indicate that GHSR signaling may play a role in adapting the nycthemeral pattern of activity to the undernutrition state in this disorder.

References

Conflict of interest

Acnowledgements: This work was supported by Agence Nationale de la Recherche and Fondation de France. J.M. is a recipient of a Fullbright fellowship.

https://doi.org/10.1016/j.nsa.2024.104521

P2048

NEUROSCIENCE APPLIED 3 (2024) 104522

META-ANALYSIS OF DURATION OF UNTREATED ILLNESS IN OBSESSIVE-COMPULSIVE DISORDER: THE NEED FOR EARLY INTERVENTIONS

L. Pellegrini [1], S. Burato [1], S. Giobelli [1], G. Maina [2], N. Fineberg [3], U. Albert [1]. [1] *University of Trieste, Department of Medicine- Surgery and Health Sciences- UCO Clinica Psichiatrica- University of Trieste- Italy, Trieste, Italy;* [2] *University of Turin, Rita Levi Montalcini Department of Neuroscience, Turin, Italy;* [3] *University of Hertfordshire, School of Life and Medical Sciences, Hatfield, United Kingdom*

Introduction: Obsessive compulsive disorder (OCD) is a chronic neuropsychiatric disorder and often begins early in childhood. Patients with OCD are known to seek help late after disorder onset[1,2]. This delay could account for a large part of the duration-of-untreated-illness (DUI), which is found to correlate with negative clinical outcomes[1]. No meta-analysis has previously investigated this issue, therefore we conducted a systematic review and meta-analysis to estimate the pooled-mean-interval between age at disorder onset and help-seeking behaviors and the pooled-mean-DUI in OCD. Secondarily, we aimed to investigate specific factors that could potentially associate with DUI.

Methods: Our protocol was pre-registered with PROSPERO-(CRD42020165226). We followed PRISMA-guidelines. We searched for relevant articles in PubMed/Medline, PsycINFO, Web-of-Science and CINAHL databases from the date of the first available article to Dec 14th, 2023. Meta-analyses of means based on random-effects (Der-Simonian-and-Laird-method) was used to derive the pooled estimates. Subgroup-analyses and meta-regressions were conducted to explore possible factors affecting DUI. JASP Statistical Software (JASP (Version 0.18. 3)[Computer software]) was used for the analyses.

Results: We found 13 studies reporting a value for the DUI and 18 studies providing data for age at disorder onset and age at first help-seeking behavior. The pooled mean DUI was 88.9 months (CI 81.830-95.975, p < .001), while the pooled mean interval between age at disorder onset and age at help-seeking behavior was 71.9 months (CI 64.23-82.34, p < .001). Mean score on the compulsions subscale of the Yale-Brown Obsessive-Compulsive Scale, depressive symptoms rated through the Beck Depression Inventory and the presence of somatic obsessions were found to be associated with a longer DUI, while the

presence of either checking compulsions or aggressive obsessions were linked to a lower DUI.

Conclusions: Patients with OCD on average report a long delay in seeking help that substantially contributes to the long DUI associated with a negative prognosis. The severity of compulsions was related to a longer DUI and this could be explained by the fact that the longer the duration of untreated illness, the more the compulsions could become habitual in nature and intensify in severity; somatic obsessions, instead, could delay help-seeking because patient might be afraid of being ill and could avoid medical advice. Depressive symptoms could develop if the OCD remains untreated and make more difficult for patients to ask for help. Checking compulsions, being one of the most well-known obsessive compulsive symptoms, and overt in nature, could facilitate the process of pursuing help, while aggressive obsessions are often very ego-dystonic and disturbing for patients, who might be more prone to ask for support earlier in the course of their illness. This meta-analysis confirms the long duration of untreated illness in OCD and proposes possible factors associated with the length of DUI. Early intervention programs for OC-related illnesses are universally needed[3].

References

[1] Albert U, Barbaro F, Bramante S, Rosso G, De Ronchi D, Maina G. Duration of untreated illness and response to SRI treatment in Obsessive-Compulsive Disorder. Eur Psychiatry 2019;58:19–26. https://doi.org/10.1016/j.eurpsy.2019.01.017. [2] García-Soriano G, Rufer M, Delsignore A, Weidt S. Factors associated with non-treatment or delayed treatment seeking in OCD sufferers: a review of the literature. Psychiatry Res 2014;220:1–10. https://doi.org/10.1016/j.psychres.2014.07.009. [3] Fineberg, N.A., Dell'Osso, B., Albert, U., Maina, G., Geller, D., Carmi, L., Sireau, N., Walitza, S., Grassi, G., Pallanti, S., Hollander, E., Brakoulias, V., Menchon, J.M., Marazziti, D., Ioannidis, K., Apergis-Schoute, A., Stein, D.J., Cath, D.C., Veltman, D.J., Van Ameringen, M., Fontenelle, L.F., Shavitt, R.G., Costa, D., Diniz, J.B., Zohar, J., 2019. Early intervention for obsessive compulsive disorder: An expert consensus statement. Eur Neuropsychopharmacol 29, 549–565. https://doi.org/10.1016/j.euroneuro.2019.02.002

No conflict of interest

https://doi.org/10.1016/j.nsa.2024.104522

P2050

NEUROSCIENCE APPLIED 3 (2024) 104523

PAVLOVIAN AND NORADRENALINE-DEPENDENT MECHANISMS OF COMPULSIVE COPING BEHAVIOUR

C. Chernoff[1], A. Belin-Rauscent[1], M. Puaud[1], S.A. Torrisi[2], M. Fouyssac[1], B. Németh[1], C. Yu[1], A. Higuera-Mata[3], D. Belin[1]. [1] *University of Cambridge, Department of Psychology, Cambridge, United Kingdom;* [2] *University of Catania, Department of Biomedical and Biotechnological Sciences, Catania, Italy;* [3] *National Distance Education University, Department of Psychobiology, Madrid, Spain*

Loss of control over coping strategies initially aimed at relieving stress can result in excessive, rigid behaviours that are maintained despite adverse consequences, a hallmark feature of impulsive compulsive spectrum disorders (ICSDs) such as substance use disorder and obsessive-compulsive disorder (OCD). In schedule-induced polydipsia (SIP), food deprived rats exposed to intermittent, predictable food delivery will drink considerable amounts of water as an adjunctive stress coping response. As in humans, a subset of individuals lose control over their behaviour and develop excessive, compulsive coping manifested here as hyperdipsia. The psychological and neurobiological basis of the vulnerability to develop such compulsive coping has not been fully elucidated.

The development of SIP depends on catecholaminergic mechanisms in the nucleus accumbens (NAc)(1–3), a neurochemical mechanism shared with motor impulsivity (4), a trait that also confers vulnerability to develop hyperdipsia. Indeed, atomoxetine, a selective noradrenaline reuptake inhibitor, decreases impulsivity and prevents the development of hyperdipsia in vulnerable highly impulsive rats (5). Interestingly, the development of compulsive coping is also accompanied by transcriptional alterations in noradrenergic neurons in the locus coeruleus (6). This occurs alongside the relinquishment of behavioural control to the dopaminergic anterior dorsolateral striatum (aDLS) habit system (7), which also underlies compulsive drug use in humans and drug-seeking in highly impulsive rats (8–10). Whether the expression of compulsive coping is under noradrenergic influence or is predicted by other behavioural traits underpinned by NAc catecholamine signaling, like sign tracking (11,12), is unknown.

To address this, we first trained rats on an autoshaping paradigm prior to undergoing SIP to examine the relationship between sign-tracking, goal-tracking, and the vulnerability to develop compulsive coping. A second cohort underwent SIP until hyperdipsia emerged in vulnerable rats. We then tested the effect of chronic atomoxetine or vehicle on the expression of SIP. We used qPCR to examine the molecular signature of compulsion and atomoxetine exposure. Data were analyzed with repeated-measures ANOVAs, linear regression, and Spearman correlation. Sign-trackers acquired SIP more rapidly than goal-trackers, which mostly developed adaptive low/intermediate levels of polydipsia. Interestingly, chronic atomoxetine did not influence adaptive polydipsia, yet exacerbated hyperdipsia in compulsive rats, which is in marked contrast to its protective effect on the development of compulsivity in highly impulsive rats (5). Atomoxetine also increased functional engagement of the posterior dorsomedial striatum, a core component of the goal-directed system (13,14). Atomoxetine-induced exacerbation of hyperdipsia was also associated with gene expression changes within the NAc shell (NAcS), including a coupling between dopamine receptor and c-Fos expression. These results indicate that sign-tracking influences the development of SIP coping, but not the vulnerability to develop compulsion, as previously shown in the context of drug seeking and taking (15). Further, we show that the development of compulsivity involves alterations within the NAcS catecholamine system, which could drive such disparate effects of atomoxetine on early and well-established SIP. Together with previous results from our laboratory, these data reveal a switch in the influence of ventral striatal noradrenergic control over coping behaviour between its development and the transition to its compulsive manifestation in vulnerable individuals.

1.Moreno M, Gutiérrez-Ferre VE, Ruedas L, Campa L, Suñol C, Flores P. Poor inhibitory control and neurochemical differences in high compulsive drinker rats selected by schedule-induced polydipsia. Psychopharmacology (Berl). 2012 Jan 1;219(2):661–72. 2.Weissenborn R, Blaha CD, Winn P, Phillips AG. Schedule-induced polydipsia and the nucleus accumbens: electrochemical measurements of dopamine efflux and effects of excitotoxic lesions in the core. Behav Brain Res. 1996 Feb 1;75(1):147–58. 3.Mittleman G, Blaha CD, Phillips AG. Pituitary-adrenal and dopaminergic modulation of schedule-induced polydipsia: Behavioral and neurochemical evidence. Behav Neurosci. 1992;106(2):408–20. 4.Economidou D, Theobald DEH, Robbins TW, Everitt BJ, Dalley JW. Norepinephrine and dopamine modulate impulsivity on the five-choice serial reaction time task through opponent actions in the shell and core sub-regions of the nucleus accumbens. Neuropsychopharmacology. 2012;37(9):2057–66. 5.Ansquer S, Belin-Rauscent A, Dugast E, Duran T, Benatru I, Mar AC, et al. Atomoxetine decreases vulnerability to develop compulsivity in high impulsive rats. Biol Psychiatry. 2014 May 15;75(10):825–32. 6.Velazquez-Sanchez C, Muresan L, Marti-Prats L, Belin D. The development of compulsive coping behaviour is associated with a downregulation of Arc in a Locus Coeruleus neuronal ensemble. Neuropsychopharmacology. 2023 Mar;48(4):653–63. 7.Marti-Prats L, Giuliano C, Domi A, Puaud M, Peña-Oliver Y, Fouyssac M, et al. The development of compulsive coping behavior depends on dorsolateral striatum dopamine-dependent mechanisms. Mol Psychiatry. 2023 Nov;28(11):4666–78. 8.Belin D, Everitt BJ. Cocaine Seeking Habits Depend upon Dopamine-Dependent Serial Connectivity Linking the Ventral with the Dorsal Striatum. Neuron. 2008 Feb 7;57(3):432–41. 9.Giuliano C, Belin D, Everitt BJ. Compulsive Alcohol Seeking Results from a Failure to Disengage Dorsolateral Striatal Control over Behavior. J Neurosci. 2019 Feb 27;39(9):1744–54. 10.Vollstädt-Klein S, Wichert S, Rabinstein J, Bühler M, Klein O, Ende G, et al. Initial, habitual and compulsive alcohol use is characterized by a shift of cue processing from ventral to dorsal striatum. Addiction. 2010;105(10):1741–9. 11.Fraser KM, Janak PH. Long-lasting contribution of dopamine in the nucleus accumbens core, but not dorsal lateral striatum, to sign-tracking. Eur J Neurosci. 2017;46(4):2047–55. 12.Flagel SB, Clark JJ, Robinson TE, Mayo L, Czuj A, Willuhn I, et al. A selective role for dopamine in stimulus–reward learning. Nature. 2011 Jan;469(7328):53–7. 13.Murray JE, Belin D, Everitt BJ. Double Dissociation of the Dorsomedial and Dorsolateral Striatal Control Over the Acquisition and Performance of Cocaine Seeking. Neuropsychopharmacology. 2012 Oct;37(11):2456–66. 14.Yin HH, Ostlund SB, Knowlton BJ, Balleine BW. The role of the dorsomedial striatum in instrumental conditioning. Eur J Neurosci. 2005;22(2):513–23. 15.Belin D, Belin-Rauscent A, Everitt BJ, Dalley JW. In search of predictive endophenotypes in addiction: insights from preclinical research. Genes Brain Behav. 2016;15(1):74–88.