Schizophrenia Research 209 (2019) 278–280

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Relationship between *ANKK1 rs1800497* polymorphism, overweight and executive dysfunction in early psychosis

To the editor:

Individuals with schizophrenia have higher rates of overweight and metabolic abnormalities than the general population. The relationship between some atypical antipsychotics and weight gain has been largely documented. However, elevated weight has also been found in subjects at risk of psychosis and in drug-naïve, first-episode patients (FEP), suggesting that there may be an intrinsic metabolic risk associated with schizophrenia (Cordes et al., 2017). In addition, overweight has been described as a risk factor for developing cognitive impairment and dementia. In both community and obese samples elevated BMI has particularly been associated to executive dysfunction (Gunstad et al., 2007; Steenbergen and Colzato, 2017). Otherwise, the relationship between overweight and cognitive dysfunction in psychosis has been understudied (Bora et al., 2017).

The T allele of the *ANKK1* rs1800497 polymorphism modulates the density of D2 receptors in the striatum and has been linked to difficulties in executive function (EF) in healthy subjects (Richter et al., 2013). The only previous study examining the interaction effect of the T allele and excess weight in a non-psychotic sample (Ariza et al., 2012) found that obese T carriers performed worse than non-carriers in working memory tasks. This is therefore, the first study aiming to investigate the effect of overweight, T allele status and its interaction on EF in subjects with an early psychotic disorder.

We included 156 Caucasian outpatients attending the Early Intervention Service of University Hospital, Pere Mata Institute of Reus, Spain. The sample included 49 at-risk mental states (ARMS) and 106 recent-onset psychosis (ROP) (defined as onset of full psychotic symptoms within the last 12 months). All participants gave written informed consent and the study was approved by the Committee for Ethical Clinical Investigation of the Hospital Sant Joan of Reus. Cognitive tests for EF assessment included: The spatial and letter-number spans of the *Wechsler Memory Scale*®—3rd Ed (WMS®-III), *Parts A and B of the Trail Making Test* (TMT), the *Wisconsin Card Sorting Test* (WCST) and the *Stroop colour and word test* and were assessed by experienced psychologist blind to clinical assessments. Overweight was defined as a Body Mass Index (BMI) ≥25 according to the classification criteria of the World Health Organization. Total DNA was obtained from peripheral blood and isolated using the Gentra® PureGene reagents (Qiagen, Barcelona, Spain). The rs1800497 variant was genotyped by the SequenomiPlex® MassARRAY platform according to the manufacturer's instructions (Sequenom, San Diego, CA). The obtained genotyping rate for rs1800497 was 97.25%. Genotypes were grouped into: those with any T allele or T^+ (including TT and TC genotypes) and those with the CC homozygote genotype or T^-. Each neuropsychological test or subtest was analyzed by factorial ANCOVA. Both the group (overweight and normal weight) and allelic status (T^+ and T^-) and their interaction term were included as factors controlling for diagnostic subgroup (ROP or ARMS), age, sex, years of education, tobacco use and antipsychotic and antidepressant treatment (yes/no).

The characteristics of participants are displayed in Table 1. The 32% of participants were overweight (22% of them showed a BMI ≥30), without differences between ROP and ARMS ($\chi^2 = 0.068$; $p = 0.94$). Nearly 71% were on antipsychotic (AP) treatment. Among treated, 65.4% were on AP for <6 months (nearly 77.5% of them for <3 months). No differences in overweight rates were found between individuals treated for less or >6 months ($\chi^2 = 2.77$, $p = 0.15$). Characteristics of the sample stratified by diagnosis (ROP and ARMS) are displayed in Table S1.

As shown in Table S2, there was a significant interaction effect on the interference index of the Stroop test (see Fig. S1). Overweight T carriers performed poorly compared to non-carriers ($t = 3.21$; $p = 0.002$), whereas that difference was not found among normal weight subjects ($t = -0.88$; $p = 0.37$). The analysis was repeated including exclusively patients under AP treatment (N = 110). Controlling for chlorpromazine equivalent dose and length on AP, the group x allele interaction continued to be significant on the interference index of the Stroop test (see Fig. S2).

We failed to find an effect of overweight on performance in the different constructs within EF other than inhibitory control. The lack of inhibitory control has been related to the loss of control over eating and the inability to control excessive food intake, which may contribute to excess weight (Lavagnino et al., 2016; Stinson et al., 2018). Our results are convergent with research in obesity and binge eating disorders, where the rs1800497 SNP seemed to be not directly related to BMI itself, whereas its interaction predisposed to deficits in EF and impulsivity (Benton and Young, 2016). Together, these findings support the involvement of the *ANKK1* gene via decreased striatal D2 receptor availability (Gluskin and Mickey, 2016) in regulating prefrontal cognitive processes that in turn may contribute to overeating and maintaining overweight.

The main limitation of the study was the relatively small sample size that lacked power to detect some associations and prevented us from correcting for multiple comparisons. Sample size also limited us to conduct a separate analysis by diagnosis subgroup. However, the main findings did not change when controlling for the diagnostic subgroup. Considering the lack of previous studies, our findings might be considered exploratory and require replication.

Despite limitations, this is the first study to provide preliminary evidence for the potential contribution of the rs1800497 SNP of the *ANKK1* gene and overweight to executive dysfunction in early psychotic patients. Future studies including larger number of subjects are warranted to further investigate the effect of dopamine-related genes and other metabolic components on specific cognitive domains.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2019.05.022.

Contributions

The contributions of each author to the paper are the following: Authors Vilella and Sanchez-Gistau designed the current study. Sanchez-Gistau, Sole, Algora and Marine

https://doi.org/10.1016/j.schres.2019.05.022

Table 1
Clinical characteristics of the sample.

	Total sample (N = 156)	Normal weight (N = 106)	Overweight (N = 50)	Statistic t/χ^2
Socio-demographic variables				
Age, years (mean, SD)	23.1 (5.1)	22.8 (4.7)	24.1 (5.7)	−1.32
Sex, male (n, %)	105 (67.3)	70 (66)	35 (70)	0.24
Education years (median, IQR)	10 (9–12)	10 (8–12)	10 (10−12)	−1.08[a]
ANKK1 genotype				
T^+ allele (n, %)	49 (31)	33 (31)	16 (32)	0.09
T^- allele (n,%)	107 (69)	73 (69)	34 (68)	
Smoking				
Yes (n, %)	93 (60)	63 (88)	30 (60)	0.09
Anthropometric variables				
BMI (kg/m^2) (mean, SD)	22.7 (20.4–25.7)	21.3 (19.6–22.8)	26.6 (25.7–28.8)	**−10.06**[a,***]
Weight (kg) (mean, SD)	69.2 (13.6)	62.8 (9.5)	82.8 (11.1)	**−11.55**[***]
HR (mean, SD)	76.4 (12.5)	76.7 (12.6)	75.9 (12.4)	0.35
Systolic BP (mm Hg) (median, IQR)	112 (103−120)	113 (103–120)	112 (101−122)	−0.22[a]
Diastolic BP (mm Hg) (median, IQR)	70 (65–78)	70 (65–75)	70 (65–80)	−1.79[a]
Waist circumference (cm) (mean, SD)	82.9 (11.2)	77. 5 (6.9)	94.9 (9.3)	**−11.56**[***]
Metabolic variables				
HDL (mg/dl) (median, IQR)	52 (43–64)	55 (45–68)	49 (42–54)	**3.03**[a,**]
LDL (mg/dl) (mean, SD)	97.3 (30.7)	93.7 (29.9)	106.6 (30.9)	**−2.43**[**]
Cholesterol total (mg/dl) (mean, SD)	171.4 (37.9)	167.4 (38.2)	180.3 (36.1)	**−1.95**[*]
Triglycerides (mg/dl) (median, IQR)	85 (62–114)	76 (58–100)	105 (83–154)	**−4.32**[a,***]
Glucose (mg/dl) (median, IQR)	78 (70–85)	77 (70–83)	80 (71–87)	−1.04[a]
Treatment variables				
Antidepressant treatment (n, %)	43 (27.6)	28 (26.4)	15 (30)	0.32
Antipsychotic treatment (n, %)	110 (70.5)	72 (69.9)	38 (77.6)	0.97
Days on AP treatment (median, IQR)	76 (40–166)	69 (38–128)	85 (51–238)	−1.78
CPZE, mg/day (median, IQR)	300 (200–469)	300 (200–450)	300 (200–566)	−0.46[a]
Number of APs (median, IQR)	1 (0–1)	1 (0–1)	1 (1–1)	−1.12[a]
AP type: (n, %)				
– Risperidone, paliperidone	56 (35.8)	33 (33)	23 (46.9)	2.72
– Olanzapine, quetiapine, clozapine	38 (24.3)	29 (29)	9 (18.4)	0.96
– Aripiprazole	22 (14.1)	14 (14)	8 (16.2)	1.37
– Other	2 (1.28)	1 (1)	1 (2)	1.83

Abbreviations: BMI = body mass index; HR = heart rate; HDL = high-density lipoprotein-cholesterol; LDL = low-density lipoprotein-cholesterol; BP = blood pressure; AP = antipsychotic; CPZE = chlorpromazine equivalent day dose; t = Student's test-test; χ^2 = chi-square test.
[a] U-Mann-Whitney test.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

contributed to the acquisition of the data. Sanchez-Gistau, Martorell and Labad undertook the statistical analysis. Sanchez-Gistau wrote the first draft of the article and all other authors provided their contributions to the first draft. All authors have approved the final manuscript.

Declaration of Competing Interest

Drs. Sanchez-Gistau, Labad, Marine and Sole had received financial travel support from Otsuka, Janssen and Lumbeck. Drs Sanchez-Gistau and Labad had received honoraria for consulting and presenting from Otsuka and Janssen. The present work is unrelated to these relationships. The other authors report no financial or potential conflicts of interest.

Acknowledgments

The authors would like to acknowledge the time and effort by the subjects who participate in the study.

References

Ariza, M., Garolera, M., Jurado, M.A., Garcia-Garcia, I., Hernan, I., Sanchez-Garre, C., Vernet-Vernet, M., Sender-Palacios, M.J., Marques-Iturria, I., Pueyo, R., Segura, B., Narberhaus, A., 2012. Dopamine genes (DRD2/ANKK1-TaqA1 and DRD4-7R) and executive function: their interaction with obesity. PLoS One 7, e41482. https://doi.org/10.1371/journal.pone.0041482.

Benton, D., Young, H.A., 2016. A meta-analysis of the relationship between brain dopamine receptors and obesity: a matter of changes in behavior rather than food addiction? Int. J. Obes. 40 (Suppl. 1), S12–S21. https://doi.org/10.1038/ijo.2016.9.

Bora, E., Akdede, B.B., Alptekin, K., 2017. The relationship between cognitive impairment in schizophrenia and metabolic syndrome: a systematic review and meta-analysis. Psychol. Med. 47, 1030–1040. https://doi.org/10.1017/S0033291716003366.

Cordes, J., Bechdolf, A., Engelke, C., Kahl, K.G., Balijepalli, C., Losch, C., Klosterkotter, J., Wagner, M., Maier, W., Heinz, A., de Millas, W., Gaebel, W., Winterer, G., Janssen, B., Schmidt-Kraepelin, C., Schneider, F., Lambert, M., Juckel, G., Wobrock, T., Riedel, M., Moebus, S., 2017. Prevalence of metabolic syndrome in female and male patients at risk of psychosis. Schizophr. Res. 181, 38–42. https://doi.org/10.1016/j.schres.2016.09.012.

Gluskin, B.S., Mickey, B.J., 2016. Genetic variation and dopamine D2 receptor availability: a systematic review and meta-analysis of human in vivo molecular imaging studies. 6, e747–e748. https://doi.org/10.1038/tp.2016.22.

Gunstad, J., Paul, R.H., Cohen, R.A., Tate, D.F., Spitznagel, M.B., Gordon, E., 2007. Elevated body mass index is associated with executive dysfunction in otherwise healthy adults. Compr. Psychiatry 48, 57–61. https://doi.org/10.1016/j.comppsych.2006.05.001.

Lavagnino, L., Arnone, D., Cao, B., Soares, J.C., Selvaraj, S., 2016. Inhibitory control in obesity and binge eating disorder: a systematic review and meta-analysis of neurocognitive and neuroimaging studies. Neurosci. Biobehav. Rev. 68, 714–726. https://doi.org/10.1016/j.neubiorev.2016.06.041.

Richter, A., Richter, S., Barman, A., Soch, J., Klein, M., Assmann, A., Libeau, C., Behnisch, G., Wustenberg, T., Seidenbecher, C.I., Schott, B.H., 2013. Motivational salience and genetic variability of dopamine D2 receptor expression interact in the modulation of interference processing. Front. Hum. Neurosci. 7, 250. https://doi.org/10.3389/fnhum.2013.00250.

Steenbergen, L., Colzato, L.S., 2017. Overweight and cognitive performance: high body mass index is associated with impairment in reactive control during task switching. Front. Nutr. 4, 51. https://doi.org/10.3389/fnut.2017.00051.

Stinson, E.J., Krakoff, J., Gluck, M.E., 2018. Depressive symptoms and poorer performance on the Stroop task are associated with weight gain. Physiol. Behav. 186, 25–30. https://doi.org/10.1016/j.physbeh.2018.01.005.

Vanessa Sanchez-Gistau*
Rosa Mariné
Lourdes Martorell
Angel Cabezas
Maria José Algora
Montse Sole
Hospital Universitari Institut Pere Mata of Reus, IISPV, Universitat Rovira I Virgili and CIBERSAM, Spain
*Corresponding author at: Early Intervention Program, Hospital Universitari, Institut Pere Mata of Reus, Institut Pere Mata Road, 6-10, 43202 Reus, Spain.
E-mail address: sanchezv@peremata.com (V. Sanchez-Gistan).

Javier Labad
Department of Mental Health, Parc Taulí Hospital Universitari, Sabadell, Universitat Autonoma, I3PT and CIBERSAM, Spain

Elisabet Vilella
Hospital Universitari Institut Pere Mata of Reus, IIPSV, Universitat Rovira I Virgili and CIBERSAM, Spain

28 December 2018