Effect of the catechol-*O*-methyltransferase Val ^{158}Met polymorphism on theory of mind in obesity

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Abstract

Obesity is often accompanied with psychosocial adjustment problems, such as difficulties in social interactions and social withdrawal. A key aspect of social cognition is theory of mind, which allows inferring mental states, feelings, motivations, and beliefs of others and to use this information to predict their future behaviour. Theory of mind is highly dependent on prefrontal dopami- nergic neurotransmission, which is regulated by catechol-*O*-methyltransferase (COMT) activity. We aimed at determining whether theory of mind is altered in obesity and if this ability is modulated by COMT. Fifty patients with obesity and 47 normal-weight individuals underwent the Reading the Mind in the Eyes Test, the Wisconsin Card Sorting Test, and the Vocabulary subscale of the Wechsler Adult Intelligence Scale. The genotype for the COMT Val ^{158}Met functional polymorphism was determined for all subjects. Patients with obesity obtained significantly lower scores in the negative items of the Reading the Mind in the Eyes Test than normal-weight subjects. Further, an interaction effect was observed between group and COMT genotype. Specifically, the pres- ence of the Met allele was associated to a better identification of negative men- tal states only in patients with obesity. Our results indicate that obesity is accompanied with difficulties in theory of mind and that this ability is influ- enced by the COMT genotype.

1 INTRODUCTION AND AIMS

Obesity has been related to higher risk of psychosocial adjustment problems (Xie, Ishibashi, Lin, Peterson, & Susman, 2013). For instance, difficulties in social interac- tions and social withdrawal are commonly observed in individuals with obesity (Pitrou, Shojaei, Wazana, Gilbert, & Kovess-Masféty, 2010; Puder & Munsch, 2010; Xie et al., 2013). Social cognition is defined as a set of mental operations used to identify and interpret social signals and guide behaviour by using those signals. Difficulties in interpreting social information may lead to the engagement in conflictive interactions with others, which are often a source of social stress and negative emotions. Both acute and chronic stressors as well as negative emotions modify eating habits, often increasing the intake of highly palatable, calorically dense, foods (Dallman, 2010). This emotional eating (i.e., eating as a coping strategy in response to emotional distress) has been proposed as a contributing factor to excessive food intake and obesity (Torres & Nowson, 2007). Indeed, several studies demonstrate higher rates of eating due to emotional distress in subjects with obesity (Baños et al., 2014; Karlsson et al., 2015). Thus, identifying potentially modifiable sources of psychosocial distress, such as diffi- culties in social cognition, may provide valuable informa- tion about the development and maintenance of obesity and provide potential therapeutic targets.

A key aspect of social cognition is theory of mind, which is the ability to infer the mental states, feelings, motivations, and beliefs of others and to use this information to accurately predict their future behaviours (Bicks, Koike, Akbarian, & Morishita, 2015; Skuse & Gallagher, 2011). Although information may be gathered from different sources, eye gaze and facial expressions are common sources of information to infer what others might be feeling or planning. Theory of mind has been evaluated in eating disorders such as anorexia nervosa and bulimia. Several studies have reported impaired theory of mind in anorexic patients (Russell, Schmidt, Doherty, Young, & Tchanturia, 2009; Tapajóz Pereira de Sampaio, Soneira, Aulicino, & Allegri, 2013), whereas it seems to be preserved in patients with bulimia (DeJong et al., 2013; Tapajóz Pereira de Sampaio et al., 2013). Following a procedure similar to ours, a recent study has reported difficulties in children and adolescents with obesity in understanding others' mental states from eye gaze (Percinel, Ozbaran, Kose, Simsek, & Darcan, 2016), but data from adult population with obesity are lacking.

Converging evidence from lesion (Stuss, Gallup, & Alexander, 2001) and functional studies (Sebastian et al., 2012) demonstrates that the prefrontal cortex is a key structure for theory of mind. It is well known that the activity of the prefrontal cortex is dependent on dopa- minergic neurotransmission and dopamine has turned out to be a highly relevant neurotransmitter for theory of mind (Abu-Akel & Shamay-Tsoory, 2011). One of the regulatory mechanisms of synaptic dopamine availability in the prefrontal cortex is enzymatic breakdown by catechol-*O*-methyltransferase (COMT). Several functional polymorphisms have been described in the COMT gene, amongst which, the Val ^{158}Met polymorphism has been consistently related to variations in cognitive processes sustained by the prefrontal lobes (Caldú & Dreher, 2007; Caldú et al., 2007). Due to a missense mutation in the COMT gene, two forms of the protein arise. The enzyme containing the amino acid valine (Val) is 3 to 4 times as much active as the enzyme containing the amino acid methionine (Met); hence, the Val allele is associated to lower levels of synaptic dopamine availability in the pre- frontal lobes (Chen et al., 2004). There seems to be no association between the COMT Val ^{158}Met polymorphism and neither eating disorders, such as anorexia nervosa or bulimia nervosa (Collantoni et al., 2017), nor obesity (Kring et al., 2009; Need, Ahmadi, Spector, & Goldstein, 2006). However, alterations in dopaminergic neurotrans- mission have been described in obesity (Michaelides, Thanos, Volkow, & Wang, 2012; van Galen, Ter Horst, Booij, la Fleur, & Serlie, 2018), thus positioning COMT as an important agent in regulating dopamine-dependent cognitive functions and behaviours in this condition.

A few studies have addressed the possible effects of the COMT genotype on theory of mind, yielding variable results. In pathological samples, such as individuals with 22q11 deletion syndrome, a worse performance in theory of mind was associated to the Met allele hemizygosity (Bassett, Caluseriu, Weksberg, Young, & Chow, 2007), whereas a recent study reported a better performance associated to the Met allele in several social cognition tasks in patients with schizophrenia (Tylec, Jeleniewicz, Mortimer, Bednarska-Makaruk, & Kucharska, 2017).

Another study found an effect of several serotonin and dopamine-related polymorphisms on theory of mind only in subjects with major depression, but not in healthy controls, although no effect of the COMT Val ^{158}Met functional polymorphism was observed (Zahavi et al., 2016). In healthy subjects, the Met allele of the COMT has been related to a better performance in social cogni- tion (Lin et al., 2013), although other studies have not found any effect of the COMT Val ^{158}Met polymorphism on theory of mind (Lackner, Bowman, & Sabbagh, 2010; Xia, Wu, & Su, 2012; Zahavi et al., 2016). Although differ- ences in the samples and tasks used in these studies could contribute to explain the disparity observed in the results, it could also be that the effect of single nucleotide polymorphisms is more evident in samples with a com- promised neurotransmission (Zahavi et al., 2016).

We conducted the present study with the aim of ascer- taining whether there are differences in theory of mind capacity between adult individuals with obesity and normal-weight individuals and whether theory of mind performance is affected by the Val ^{158}Met functional polymorphism of the COMT. Recent research indicates that obesity is associated to difficulties in recognizing facial expressions of emotions and that these difficulties seem to be especially noticeable for negative emotions (Cserjési, Vermeulen, Lénárd, & Luminet, 2011; Koch & Pollatos, 2015). Thus, we hypothesize that this tendency will also apply to recognizing others' mental states, so that patients with obesity will show more pronounced dif- ficulties in identifying negative mental states as compared with positive and neutral mental states. Further, given the involvement of prefrontal dopaminergic neurotrans- mission in theory of mind, we hypothesize that the higher dopaminergic availability associated to the Met allele will favour theory of mind performance, especially in subjects in which dopaminergic basal neurotransmission is altered. Understanding the interaction between genetic and cognitive factors that contribute to the development and maintenance of obesity will provide valuable information to improve the efficacy of prevention and intervention programmes.

2 METHOD

2.1 Subjects

Ninety-seven individuals aged 16 to 40 years participated in the study. Fifty of them were classified as into the obesity group (34 women; mean age 30.4 years; *SD* 7.57), and 47 were normal-weight controls (32 women;mean age 28.8 years; *SD* 7.29). Subjects were accurately matched by age and gender. The inclusion in each group was done on the base of each participant's body mass index (BMI). Those with a BMI equal to or higher than 30 kg/m^2 were included in the obesity group, whereas those with a BMI below 25 kg/m^2 were included in the normal-weight group. Exclusion criteria included (a) the presence of any neurological or psychiatric disorder, with the possible presence of anxiety or depression being ruled out by means of the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) and the possible pathological use of alcohol and/or drugs being ruled out by means of the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1999); (b) a history of any disorder that could be related to obesity (e.g., thyroid dysfunctions); (c) presence of diabetes or hypertension; (d) BMI in the overweight range (25–29.9 kg/m^2); and (e) the pres- ence of cognitive impairment. The study was approved by the institutional ethics committee (*Comissió de Bioètica de la Universitat de Barcelona*), and the research was carried out in accordance with the Helsinki Declaration. All subjects gave written informed consent to participate in the study, and for those under 18 years of age, written informed consent was also obtained from their parents.

2.2 Genotyping

Peripheral blood samples were obtained from all subjects, and genomic DNA was extracted automatically by the MagNaPure Compact Instrument (Roche Applied Sci- ence, Barcelona, Spain), as stated by the manufacturer's protocol. The Val ^{158}Met COMT polymorphism (rs4680) was amplified by polymerase chain

reaction (PCR) containing 100 ng of genomic DNA from each subject, 0.5 μM each of forward (*5′-CTCATCACCATCGAGA TCAA-3′*) and reverse (*5′-CCAGGTCTGACAACGG GTCA-3′*) primer, 1× PCR buffer, 1.5-mM $MgCl_2$, 200 μM of dNTPs, 5% dimethyl sulfoxide, and 2.5 units of BioTaq DNA polymerase (Bioline, Ecogen, Barcelona, Spain). The PCR program was 95°C for 5 min followed by 35 cycles of 94°C for 30 s, 58°C for 30 s, and 72°C for 1 min. The 109-bp PCR product was digested with NlaIII enzyme (New England Biolabs, Izasa, Barcelona, Spain) for 90 min at 37°C, followed by 65°C heat inactivation for 20 min. Digested fragments were visualized under ultraviolet light on a 15% ethidium bromide acrylamide gel. The COMT Val allele was cleaved into two fragments of 87 and 22 bp, whereas the Met allele was cleaved into three fragments of 69, 22, and 18 bp.

2.2.1 Theory of mind assessment

To assess theory of mind capacity, participants were administered the Spanish paper version of the Reading the Mind in the Eyes Test (RME; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). Briefly, 36 black-and-white pictures of the eyes and surrounding facial area were presented together with four words, one of them correctly describing the mental state of the per- son in the picture and the other three being distractor words with the same emotional valence. Besides the global score, items were divided into positive, negative, and neutral, as described in previous studies (Harkness, Sabbagh, Jacobson, Chowdrey, & Chen, 2005). Because verbal intelligence contributes significantly to the variance in the RME performance (Peterson & Miller, 2012), the Vocabulary subtest of the Wechsler Adult Intelligence Scale was administered to all subjects. Sub- jects were also administered the Wisconsin Card Sorting Test (WCST), because it has been suggested that theory of mind is partially dependent on executive function (Perner & Lang, 1999). Finally, because theory of mind has consistently been shown to be impaired in depres- sion, we also included the depression score of the HADS as a covariate in the analysis.

2.3 Statistical analysis

Data were analysed with SPSS 21.0 software, using the SPSS multivariate general lineal model analysis with global score, positive stimuli score, negative stimuli score, and neutral stimuli score of the RME as dependent variables and group (obesity vs. normal-weight) and COMT genotype (Met carriers vs. Val homozygous) as independent variables. The Vocabulary subscale of the Wechsler Adult Intelligence Scale, the number of persev- erative responses of the WCST, and the depression score of the HADS were introduced as covariates. The signifi- cance threshold was set at $p = 0.05$ for all tests.

3 RESULTS

Demographics as well as means and standard deviations for RME, perseverative responses, vocabulary, and depression score of the HADS are shown in Table 1. There were no differences between individuals of the obe- sity group and normal-weight subjects in terms of age ($t_{95} = 1.068$, $p < 0.288$), gender ($\chi^2_1 = 0.000$, $p < 0.993$), vocabulary scores ($t_{95} = -0.308$, $p < 0.759$), number of perseverative responses of the WCST ($t_{95} = -0.231$, $p < 0.818$), nor depression score in the HADS ($t_{95} = 0.388$, $p < 0.699$). There were no differencesbetween carriers and noncarriers[1] of the Met allele in terms of age ($t_{95} = 0.52$, $p < 0.601$), gender ($\chi^2 = 2.15$, $p < 0.143$), vocabulary scores ($t_{95} = 1.30$, $p < 0.198$), num- ber of perseverative responses of the WCST ($t_{95} = 0.937$, $p < 0.351$), nor depression score of the HADS ($t_{95} = 0.354$, $p < 0.724$). A group effect was found for negative items of the RME ($F_{1, 93} = 4.448$, $p < 0.038$), with subjects in the obesity group showing significantly lower scores than normal-weight subjects. Further, an interaction effect was observed between group and COMT genotype. Specifically, the presence of the Met allele was associated to a better identification of negative mental states in subjects with obesity ($F_{1, 93} = 5.619$, $p < 0.020$). None of the statistically significant results survived correction for multiple comparisons, and results

remained essentially unchanged when covariates were removed from the analysis (group effect: $F_{1, 93} = 4.489$, $p < 0.037$; genotype × group interaction: $F_{1, 93} = 6.339$, $p < 0.014$).

4 DISCUSSION

In the present study, we assessed theory of mind in a sample of subjects with obesity and investigated whether theory of mind is under the influence of the COMT Val ^{158}Met polymorphism. Our results demonstrate that subjects with obesity show a reduced capacity to recog- nize others' negative mental states as compared with normal-weight individuals. Moreover, an interaction effect between group and COMT genotype was observed. Concretely, there was a significant effect of genotype on the group of subjects with obesity, in which the presence of the Met allele was associated to a better performance in the recognition of negative stimuli.

To the best of our knowledge, this is the first study specifically assessing theory of mind in adults with obesity. Previous studies, most of them conducted on children with obesity or on overweight children, have evaluated the identification of facial expressions of basic emotions, which is less cognitively demanding than infer- ring subtler mental states from only the eyes' surrounding facial area. These studies indicate that obesity is related to difficulties in recognizing facial expressions of basic emo- tions (Baldaro et al., 1996, 2003; Cserjési et al., 2011; Koch & Pollatos, 2015), although negative results have also been obtained (Surcinelli et al., 2007). Interestingly, some of these studies have pointed out that difficulties shown by subjects with obesity are especially remarkable in the processing of emotions of negative valence (Cserjési et al., 2011; Koch & Pollatos, 2015). The results obtained from our study reinforce this observation, because our sample of subjects with obesity only obtained lower results in the identification of negative mental states. Because quickly and accurately identifying social cues is of great value to avoid involvement in conflictive social interactions or to adequately engage in social interac- tions, difficulties in this domain may contribute to problematic social interactions and social withdrawal that are often observed in subjects with obesity (Griffiths & Page, 2008). Besides, the psychosocial stress and negative emotions arising from inadequate social interactions may be related to increases in food consumption and, eventu- ally, become a risk factor for the development and maintenance of obesity. Alternatively, it is also plausible that difficulties in the socioemotional domain are related to the frequently reported experiences of rejection by others, discrimination, and stigmatization of individuals with obesity.

Our results extend those reported in a recent study (Percinel et al., 2016) showing lower performance in the RME related to obesity in a sample of children and ado- lescents. Our results partially agree with those described by Percinel et al. (2016), because our subjects with obesity also showed a lower performance in the test. However, in our study, patients with obesity showed reduced perfor- mance only in the identification of negative stimuli. Because the study of Percinel et al. (2016) did not sepa- rate the items of the RME according to their emotional valence, it is difficult to stablish how theory of mind capacity evolves in patients with obesity from childhood to adulthood. One possibility is that the lower perfor- mance observed in adulthood for negative mental states represents the maintenance of a specific deficit already observed early in development. An alternative possibility would be that, although the identification of neutral and positive mental states improves with age, negative mental states remain as a pitfall for subjects with obesity. A precise understanding of the development of theory of mind capacity from infancy to adulthood is essential to correctly focus intervention and prevention strategies and maximize their success.

There is converging evidence from lesion (Geraci, Surian, Ferraro, & Cantagallo, 2010; Stuss et al., 2001) and functional studies (Sebastian et al., 2012) that the prefrontal cortex is an important brain region for social cognition. Recent neuroanatomical data demonstrate that people with obesity show grey matter reductions in prefrontal regions, including the ventromedial prefrontal cortex (Marqués-Iturria et al., 2013). Because the ventromedial prefrontal cortex turns out to be a key structure for affective theory of mind (Shamay-Tsoory & Aharon-Peretz, 2007; Shamay-Tsoory, Tibi-Elhanany, & Aharon-Peretz, 2006), cortical reductions in the ventromedial prefrontal cortex are an appealing neural substrate for the poorer results obtained by subjects with

obesity in affective theory of mind tasks, such as the one we have used in our study.

It is well known that prefrontal cortex function critically depends on dopaminergic neurotransmission, and several studies have addressed the issue of whether variations in dopamine-related genes affect social cognition (Gong, Liu, Li, & Zhou, 2013; Kempton et al., 2009; Lackner, Sabbagh, Hallinan, Liu, & Holden, 2012; Lin et al., 2013; Xia et al., 2012). Regarding COMT, a few studies have evaluated its impact on theory of mind, pro- viding inconsistent results (Bassett et al., 2007; Lackner et al., 2012; Xia et al., 2012). A recent study carried out in healthy subjects (Xia et al., 2012) found no association between the Val ^{158}Met polymorphism and the perfor- mance on several tasks measuring theory of mind. Our results support the notion of an effect of the Val ^{158}Met polymorphism of the COMT on theory of mind, at least in patients with obesity. It has been suggested that theory of mind depends on executive functions (Yeh, Lo, Tsai, & Tsai, 2015) and there is extensive evidence that executive functions are affected by COMT activity (Caldú et al., 2007; Joober et al., 2002; Rosa et al., 2004). Previous studies have revealed executive dysfunction in subjects with obesity (Boeka & Lokken, 2008; Gunstad et al., 2007; Lokken, Boeka, Yellumahanthi, Wesley, & Clements, 2010; Marqués-Iturria et al., 2014), although negative results have also been reported (Ariza et al., 2012). Our sample of subjects with obesity did not differ from normal-weight subjects in the number of persevera- tive responses of the WCST. In spite of the fact that the WCST only explores some, but not all, of the executive subcomponents, the absence of differences between patients with obesity and controls rises the possibility that differences in theory of mind may be independent on executive functioning.

Interestingly, in the current study, the effect of the COMT Val ^{158}Met functional polymorphism was only observed in the group of individuals with obesity. Similar results have been reported recently (Zahavi et al., 2016). Zahavi et al. (2016) reported an effect of dopamine and serotonin polymorphisms on theory of mind only in depressed subjects but not in healthy controls. As suggested by the authors, one possible explanation may be related to differences in the baseline functioning of the neural circuitry associated to theory of mind between individuals with obesity and controls. Because the effect of one single polymorphism on neurotransmission is known to be small, it is plausible that this effect becomes more evident in the context of a not fully functional neurotransmission system. Previous data have demon- strated that prefrontal dopaminergic signalling is compro- mised in patients with obesity (Michaelides et al., 2012; Volkow et al., 2008). Therefore, it could be argued that our sample size has been insufficient to detect this small effect in controls but enough to detect a larger effect in individuals with obesity.

The results of the present study should be interpreted cautiously and taking several limitations into account. Some limitations are related to the characteristics of the sample. In this sense, the small sample size for a genetic study rises the probability of reporting false positive results, but also may have hindered us from detecting small genotype effects. Still related to the sample, we included subjects with a minimum age of 16 years old in order to increase our power to detect genetic effects. Maturation of the prefrontal cortex exceeds adolescence (Gogtay et al., 2004), accomplishing its development dur- ing the first adulthood, so the inclusion in the sample of subjects with different prefrontal maturational degrees must be considered when interpreting results. Finally, in order to increase our power to detect possible COMT genotype effects, we included both men and women in the study. It has been shown that the enzymatic activity of the COMT is influenced by oestrogen levels (Jacobs & Henry Wheeler Jr Brain, n.d.; Harrison & Tunbridge, 2008), so that the study of the effects of the COMT genetic variants on theory of mind separately for men and women could be of great interest. Other limitations are related to the task we used in our study. We studied the- ory of mind based on eye gaze, which is only one of the multiple sources of social information available in social interactions. Therefore, future studies with larger homog- enous samples and a wider variety of theory of mind tasks may help confirm and extend to other modalities the putative role of the COMT Val ^{158}Met polymorphism on theory of mind.

In conclusion, we provide some evidence that obesity is accompanied with specific difficulties in theory of mind and that this capacity is influenced by the COMT genotype. Difficulties in social cognition may underlie the social adjustment problems and poor social interac- tions often observed in people with obesity and may be a contributing factor to the higher incidence of psychiat- ric disorders present in this population, especially depression. However, the fact that the causal relationship between obesity and social problems is bidirectional (Puder & Munsch, 2010; Xie et al., 2013) must be taken into account, and

longitudinal studies will be needed in order to disentangle how these two variables relate with each other. Because social competence is a determinant factor for treatment success (de Niet et al., 2011), understanding how social cognition is involved in obesity and how genetic variations contribute to interindividual differences in this cognitive domain is crucial in order to design and implement effective prevention and inter- vention programmes.

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TABLE 1 Frequencies, means, and standard deviations for sex, age, body mass index, global score, positive, negative, and neutral items of the Read the Mind in the Eyes Test, perseverative responses of the Wisconsin Card Sorting Test, and Vocabulary scores of the Wechsler Adult Intelligence Scale

	Sex (women)	Age	BMI	HADS (depression)	RME global score	RME positive items	RME negative items	RME neutral items	Perseverative responses	Vocabulary
Obesity (50)	34	30.4 (7.57)	37.8 (7.09)	1.4 (1.60)	22.6 (4.07)	5.6 (1.34)	7.1* (1.81)	9.9 (2.48)	16.9 (12.29)	43.0 (6.90)
Met/− (34)	23	29.9 (7.08)	38.0 (7.45)	1.4 (1.74)	22.8 (4.31)	5.4 (1.52)	7.7^ (1.57)	9.7 (2.56)	17.6 (11.91)	44.2 (7.10)
Val/Val (16)	11	31.5 (8.67)	37.2 (6.46)	1.4 (1.31)	22.0 (3.58)	5.9 (0.81)	5.9^ (1.71)	10.25 (2.32)	15.4 (13.32)	40.4 (7.58)
Controls (47)	32	28.8 (7.29)	21.8 (2.00)	1.3 (1.53)	23.8 (3.54)	5.7 (1.27)	7.6* (1.94)	10.5 (2.22)	17.57 (14.56)	43.4 (6.90)
Met/− (35)	27	29.9 (7.32)	21.9 (2.12)	1.2 (1.42)	23.8 (3.76)	5.7 (1.26)	7.5 (1.95)	10.6 (2.33)	18.5 (15.22)	43.4 (7.16)
Val/Val (12)	5	25.8 (6.54)	21.6 (1.69)	1.4 (1.88)	23.8 (2.98)	5.8 (1.36)	7.8 (2.01)	10.3 (1.92)	15.0 (12.67)	43.6 (6.36)
Total (97)	66	29.7 (7.44)	30.0 (9.57)	1.3 (1.56)	23.2 (3.86)	5.6 (1.30)	7.31 (1.88)	10.2 (2.36)	17.2 (13.37)	43.2 (7.13)
Met/− (69)	50	29.9 (7.15)	29.8 (9.75)	1.3 (1.57)	23.3 (4.04)	5.6 (1.30)	7.6 (1.76)	10.2 (2.47)	18.1 (13.60)	43.8 (7.09)
Val/Val (28)	16	29.0 (8.22)	30.5 (9.27	1.4 (1.55)	22.8 (3.40)	5.8 (1.06)	6.7 (2.04)	10.3 (2.12)	15.3 (12.81)	41.8 (7.14)

Note. The number of subjects in each group is shown in parentheses. Symbols * and ^ indicate statistically significant differences between means of the RME ($p < 0.05$). RME: Reading the Mind in the Eyes Test; BMI: body mass index; HADS: Hospital Anxiety and Depression Scale.