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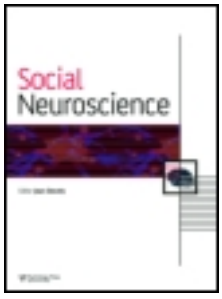

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Preliminary investigation of the influence of dopamine regulating genes on social working memory

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Preliminary investigation of the influence of dopamine regulating genes on social working memory

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Working memory (WM) refers to mental processes that enable temporary retention and manipulation of information, including information about other people ("social working memory"). Previous studies have demonstrated that nonsocial WM is supported by dopamine neurotransmission. Here, we investigated in 131 healthy adults whether dopamine is similarly involved in social WM by testing whether social and nonsocial WM are influenced by genetic variants in three genes coding for molecules regulating the availability of dopamine in the brain: catechol-*O*-methyltransferase (COMT), dopamine active transporter (DAT), and monoamine-oxidase A (MAOA). An advantage for the Met allele of *COMT* was observed in the two standard WM tasks and in the social WM task. However, the influence of *COMT* on social WM performance was not accounted for by its influence on either standard WM paradigms. There was no main effect of *DAT1* or *MAOA*, but a significant *COMT* x *DAT1* interaction on social WM performance. This study provides novel preliminary evidence of effects of genetic variants of the dopamine neurotransmitter system on social cognition. The results further suggest that the effects observed on standard WM do not explain the genetic effects on effortful social cognition.

Keywords: Working memory; Executive functions; Dopamine; Social cognition; COMT.

Working memory (WM) is the ability to maintain and manipulate information in a temporary memory buffer. Dopamine neurotransmission in the lateral prefrontal cortex (PFC) is known to be critically involved in WM processing (Levy & Goldman-Rakic, 2000; Mehta et al., 2000). Little is known about the role of dopamine in *social WM*, the ability to store and manipulate information about other people, or in other aspects of social cognition such as mentalizing, the ability to think about people's thoughts, traits, and beliefs (Skuse, 2006; Skuse & Gallagher, 2011). Mentalizing recruits the medial PFC (MPFC) (Amodio & Frith, 2006; Van Overwalle, 2009). Although the MPFC shows decreased activity during nonsocial forms of WM (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003), it was recruited in a recent task that involved social WM (Meyer, Spunt, Berkman, Taylor, & Lieberman, 2012). Based on this finding and evidence that the MPFC releases dopamine (Ceccarini

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et al., 2012; Lataster et al., 2011) and has functional connections with limbic regions highly populated with dopamine receptors (e.g., striatum; Draganski et al., 2008), we hypothesized that dopamine might uniquely affect social WM performance.

Apart from some recent evidence of dopamine release in MPFC, little is known about how dopamine affects social cognition. Previous research has mainly focused on how dopamine's role in motivation and reward may indirectly affect social interactions (Skuse, 2006; Skuse & Gallagher, 2009, 2011; Yacubian & Büchel, 2009). One study demonstrated a relationship between dopamine catabolism and altruism (Reuter, Frenzel, Walter, Markett, & Montag, 2011), another between dopamine-relevant genes and social facilitation (Walter, Markett, Montag, & Reuter, 2011). Another series of studies has investigated the relationship between dopamine and recognition and neural responses to emotional faces in adults (Blasi et al., 2009; Lelli-Chiesa et al., 2011; Soeiro-de-Souza et al., 2012; Weiss et al., 2007). Only one study has investigated mentalizing, and showed that variation of the dopamine receptor D4 gene was associated with preschoolers' understanding that other people's actions are caused by internal mental states (Lackner, Sabbagh, Hallinan, Liu, & Holden, 2012).

A number of genes are known to affect the regulation of dopamine availability in the brain, and common polymorphisms have been found to explain some interindividual variation in normal performance on WM tasks (Barnett, Xu, Heron, Goldman, & Jones, 2011; Barnett et al., 2007; Bruder et al., 2005; Caldú et al., 2007; Dumontheil et al., 2011; Goldberg et al., 2003; Mattay et al., 2003). The current study investigated the effect of single nucleotide polymorphisms (SNPs) that affect dopamine availability in the brain on performance in a WM paradigm that requires maintenance and manipulation of social information.

Genetic variation was studied in three genes that are implicated in the regulation of synaptic levels of dopamine (Meyer-Lindenberg & Weinberger, 2006). The enzymes catechol-*O*-methyltransferase (COMT) and monoamine-oxidase A (MAOA) predominantly regulate dopamine catabolism in the PFC (Berry, Juorio, & Paterson, 1994), while the dopamine active transporter (DAT) regulates dopamine reuptake in the striatum (Hall et al., 1999; Sasaki et al., 2012).

COMT is located on chromosome 22, and we genotyped the rs4680 Valine^{158}Methionine (Val^{158}Met) polymorphism, which is the most commonly studied SNP at *COMT*. The Met allele is associated with a reduction of COMT enzymatic activity (Chen et al., 2004), superior WM performance (Diaz-Asper et al., 2008; Dumontheil et al., 2011; Goldberg et al., 2003), and reduced PFC activation during executive function tasks (Dickinson & Elvevåg, 2009; Mier, Kirsch, & Meyer-Lindenberg, 2010; Tunbridge, Harrison, & Weinberger, 2006; Witte & Flöel, 2012). Note, however, that the association between rs4680 and WM performance has not always been consistently observed (e.g., Blanchard, Chamberlain, Roiser, Robbins, & Müller, 2011) and depends on the population studied and the specific paradigm used (see Barnett, Scoriels, and Munafò (2008) for meta-analysis, and Dickinson and Elvevåg (2009) and Witte and Flöel (2012) for reviews). In addition, results vary regarding whether additive (intermediary performance of Val/Met), Val dominant or Met dominant models best fit the WM performance measures or neuroimaging data (e.g., Dumontheil et al., 2011; Goldberg et al., 2003).

MAOA is located on chromosome X, and we genotyped the rs1137070 C/T substitution in exon 14 (position 337/470). Rs1137070 is associated with visuospatial WM (VSWM) performance in children (Rommelse et al., 2008) and indirectly with VSWM brain activity (via linkage disequilibrium with rs6609257, Ziermans et al., 2012). *DAT1* is located on chromosome 5, and we investigated the rs27072 C/T substitution in the 3′-untranslated region of exon 15 (position 2317). The T-allele is linked to the 9-repeat variant of the commonly studied variable number of tandem repeats (VNTR) on *DAT1* (Brookes et al., 2006; Laucht et al., 2007). This variant is associated with lower DAT activity and therefore higher levels of striatal dopamine (Pinsonneault et al., 2011) and superior WM performance in children (Stollstorff et al., 2010).

In the current study, participants performed two standard WM paradigms: a backwards digit span task and a VSWM task, as well as a social WM task adapted from the paradigm used by Meyer et al. (2012). This social WM task was designed to parallel the format of standard WM paradigms as much as possible, requiring both maintenance and manipulation of social information over a delay (Meyer et al., 2012). We chose this task for the following reasons: performance on the social WM task is associated with activation of both domain general WM regions and parts of the social brain (Meyer et al., 2012); the sensitivity to social WM load in the MPFC in particular is correlated with self-reported measure of perspective taking; and performance on the task is not at

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ceiling and is sensitive to load. The two standard WM tasks were included to assess whether observed genetic effects were specific to social WM or mediated by genetic effects on WM abilities more generally.

We predicted that genetic variation at *COMT* (and potentially *MAOA*), which are modulators of prefrontal levels of dopamine, but not at *DAT1*, which is expressed in the striatum, would affect performance on the two standard WM tasks. Specifically, we predicted better WM performance would be associated with the Met *COMT* variant. We also tested the hypothesis that performance on the social WM task would be affected by rs4680 at *COMT*, and that this effect would not be fully mediated by the effect of rs4680 on standard WM. Additive effects of variations at *DAT1* and *COMT* have been observed in neuroimaging (but not behavioral) data on the N-back WM task, with lower activations (interpreted as "more focused") in the left dorsolateral PFC associated with increasing numbers of Met alleles at *COMT* and of 10 repeat alleles at *DAT1* (Bertolino et al., 2006; Caldú et al., 2007). Only one study has investigated and reported an interaction between *COMT* and *MAOA* variants in a WM task, and this effect was only observed in male children (Barnett et al., 2011), and no study has reported interactions between *DAT* x *MAOA* variants and WM measures. On this basis, we further investigated possible interactions between *DAT1* and *COMT* variants only, with a prediction of poorer performance associated with the T allele (linked to the 9-repeat) at *DAT1* and the Val allele at *COMT* in combination.

METHODS

Participants and genetic analysis

We recruited 161 healthy adult participants (81 males) via University College London (UCL) volunteer databases. Participants were genotyped for the A/G substitution at rs4680 (*COMT*), the C/T substitution at rs27072 (*DAT1*), and the C/T substitution at rs1137070 (*MAOA*) (see Supplemental Data). After exclusions based on ethnicity and genotyping, analyses included 131 participants for *COMT*, 132 participants for *DAT1* (*SLC6A3)*, 96 participants for *MAOA*, and 130 participants for *COMT* x *DAT1* (see Supplemental Data for a justification of the different sample size). The less frequent allele groups were combined for the analyses involving *DAT1* and *MAOA* (Table 1). The study was approved by UCL Research Ethics Committee, and all participants gave written informed consent.

Participants were individually tested in a quiet room on a battery of tests, which included the WM tasks and the vocabulary subtest of the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999). Males and females, and the genotype groups, did not significantly differ in terms of age, verbal IQ, or ethnicity, and the distribution of sex did not differ between genotype groups (see Supplemental Data).

Although our sample was relatively small for a genetic association study, it is similar to some other studies investigating performance on computerized tests and *COMT* genotype (e.g., $N = 104$ in Reuter, Montag, Peters, Kocher, and Kiefer (2009); and $N = 140$ in Deuker et al. (2013)).

TABLE 1

Participant demographics. Mean age, verbal IQ and distribution of ethnicity and sex are presented for the three genotypes. Note that the section describing the sex distribution is based on those participants included in the COMT analysis ($N = 131$)

	N	*Age Mean (SD)*	*IQ Mean (SD)*	*Ethnicity Caucasian/Non-Caucasian*	*Sex Female/male*
Sex					
Female	67	25.9 (3.3)	113.1 (13.1)	42/25	–
Male	64	27.0 (4.4)	113.1 (12.4)	47/17	–
Total	131	26.4 (3.9)	113.1 (12.7)	89/42	–
COMT					
Met/Met	38	25.2 (3.2)	113.6 (12.0)	30/8	15/23
Met/Val	59	26.7 (3.9)	112.5 (13.4)	39/20	34/25
Val/Val	34	27.3 (4.3)	113.7 (12.5)	20/14	18/16
DAT1					
C/C	96	26.4 (4.2)	112.7 (12.2)	65/31	49/47
C/T or T/T	36	26.4 (3.2)	114.6 (14.1)	25/11	19/17
MAOA					
C/C or C	61	26.1 (3.8)	117.0 (10.5)	58/3	28/33
C/T, T/T or T	35	27.1 (4.5)	115.8 (11.6)	31/4	18/17

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Behavioral assessment

Participants were tested on three WM tasks in this order: (1) a social trait-ranking WM task (Meyer et al., 2012), (2) a VSWM grid task (Dumontheil et al., 2011); and (3) a backwards digit span task. The social trait-ranking WM task and VSWM were computer-based and developed in MatLab with experimental stimuli designed in Cogent graphic (http://www.vislab.ucl.ac.uk/cogent_graphics.php). Two additional computerized tasks, not described here, were performed by the participants between the first two WM tasks. The testing session ended with the completion of the vocabulary subtest of the WASI (Wechsler, 1999) and collection of the saliva sample and took in total approximately 1 h.

Backwards digits span task

The backwards digit span task measures verbal WM for numerical information. Participants were presented with sequences of digits of increasing load, which they had to repeat in the reverse order. There was a maximum of four trials at loads 3, 4, and 5 and two trials at load 7. Correct reversal of three out of four trials was required to start the next load level. The score was the total number of correct reversals, out of a total of 14.

Visuospatial WM task

The VSWM task measures spatial WM for visually presented stimuli, and was adapted from the Dot Matrix test of the Automated WM Assessment (Alloway, 2007). The task required participants to remember and replicate the order and location of sequences of dots presented one by one in a four by four grid. Each dot was presented for 600 ms, with a 300 ms interval between dots. Each sequence of dots was followed by a short delay (1.5 s), after which participants reproduced the sequence using a computer mouse. Trials varied in load depending on the number of dots in a sequence (between three and eight). There were four trials of each load condition and correct reversal of three trials was required to start the next load level. The score was the total number of correct sequence reproduction, out of a total of 24. Reaction time (RT) was recorded from the beginning of the response phase to the last response and divided by the number of dots in the trial.

Social trait-ranking WM task

The social trait-ranking WM task is a variant of a WM task that uses social stimuli (Meyer et al., 2012). Prior to the study, participants completed a questionnaire in which they named and rated 10 friends on 10 predefined personality traits (e.g., funny, clever, stubborn), using a rating scale from 0 to 100. Forty stimuli were generated by combining two or three names (load 2 or 3, equally distributed), for which ratings varied by at least five points on a given personality trait. On each trial, participants were first presented with a list of names, followed by a personality trait (e.g., "happy"). During a delay period, participants were asked to order, in a decreasing manner, in their head, the names on the list according to how much the personality trait applied to each of the names (i.e., the happiest friend is at the top of the list) (see Figure 1). We then collected a measure of participants' WM manipulation by presenting a question such as "Second happy? Jane", which required a yes/no response using a right/left index finger key press. Participants were asked to answer as quickly and accurately as possible. Measures of accuracy (consistency between questionnaire and responses in the task) and RT (response time to the final question) were calculated, and we investigated both *average accuracy* and *RT*, and the effect of load on accuracy and RT (*difference in accuracy* or *RT* between load 3 and load 2 trials). The social WM task is a recently developed paradigm (Meyer et al., 2012). As increased recruitment of regions of the social brain has been observed with increased WM load both during the delay period and in response to the probe (i.e., the question), we did not have specific predictions regarding whether task performance would be associated with genetic variation in a load-sensitive manner, or whether accuracy or RTs to the probe would be more sensitive to genetic variation. This study is therefore exploratory in nature, and the number of tests performed limits the strengths of the results, but the primary motivation behind our study was to go beyond using standard WM measures and to extend research into the domain of social cognition.

Statistical analyses

Statistical analyses were carried out in SPSS (IBM Corp., 2011). We first tested the correlation between the different WM measures using partial correlations

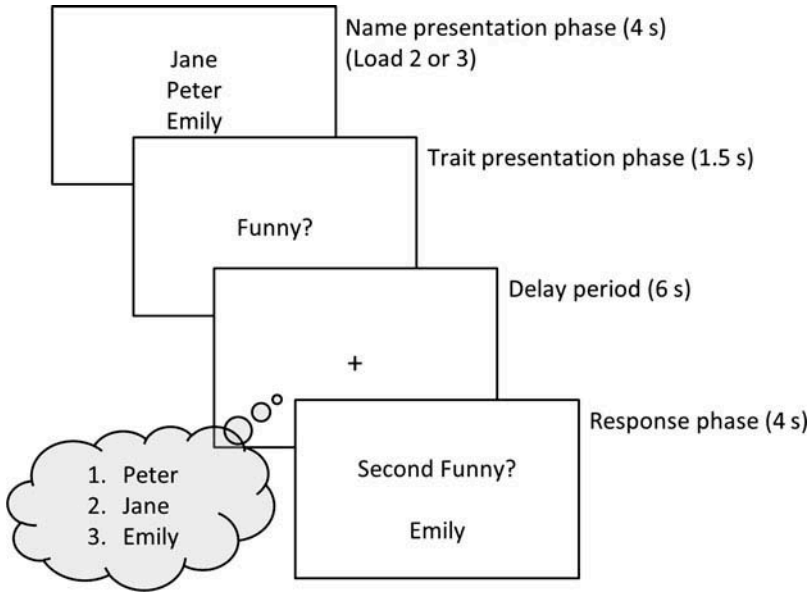

Figure 1. Social trait-ranking WM paradigm. Schematic description of the four phases of a load 3 trial of the social trait-ranking WM task, including timings.

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controlling for age and sex. Significant effects were further investigated in male and female participants separately, using partial correlations controlling for age, to assess whether the observed pattern was consistent across sex.

In the genetic analyses, we modeled the effect of the three SNPs on WM performance using multiple regression analyses. This approach enabled us to investigate the proportion of variance accounted for by genetic variation beyond age and sex effects alone, and in the case of social WM, beyond an association between genetic variation and standard WM performance. Previous findings in the literature vary regarding whether additive (intermediary performance of Val/Met), Val dominant or Met dominant models best fit the WM performance measures or neuroimaging data (e.g., Dumontheil et al., 2011; Goldberg et al., 2003). We therefore explored genetic effects of *COMT* using both an additive effect model (coded as 0: Met/Met, 1: Val/Met, 2: Val/Val) (Model 1), a Met dominant model (0: Met carriers, 1: Val/Val) (Model 2), and a Val dominant model (0: Met/Met, 1: Val carriers) (Model 3). All analyses were hierarchical regressions. In a first block, we included age and sex as covariates. In a second block, the main effect of genotype was entered as a predictor. Significant improvements to the model associated with the inclusion of genetic predictors in the second block are reported as a change in R^2. Significant effects of genotype were further investigated in male and female participants separately, using hierarchical regressions in which age was entered first, and genotype second, to assess whether the observed pattern was consistent across sex groups.

The analysis of the effect of *COMT* on social WM was followed up using regression analyses investigating whether the effect of rs4680 on social WM was accounted for by the effect of the SNP on standard WM. Hierarchical regression analyses were performed, starting from model 3, which included age, sex, and *COMT* Val dominant genotype as predictors, and adding in a second block either of the three measures of standard WM performance (backwards digit score, VSWM score, VSWM RT) as predictors. The R^2 change associated with the inclusion of standard WM scores, and the effect of the inclusion of standard WM scores on the role of *COMT* genotype as a predictor were evaluated.

Gene by gene interactions between *DAT1* and *COMT* were investigated using the additive model of *COMT* for standard WM measures, and the Val dominant model of *COMT* for the social WM measures, which were the models that associated most strongly with performance on either paradigm when investigated alone. Hierarchical regression analyses were performed. Age and sex were entered in the first block, *COMT* and *DAT1* genotypes were entered in a second block, and the interaction between *COMT* and *DAT1* was entered in a third block. *MAOA* x *COMT* interactions were not investigated because of the smaller sample size selected for *MAOA* analysis. Note that given the exploratory nature of this study, the statistics

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of the analyses reported in this paper were not Bonferroni-corrected for multiple comparisons.

RESULTS

Correlation between WM tasks

Total scores on the two standard WM paradigms were highly correlated (controlling for age and sex), indicating that participants who performed well on one standard WM task also performed well on the other (Table 2). Social WM performance was also significantly correlated with performance on the standard WM tasks (Table 2). High VSWM scores were associated with fewer errors on the social WM task, while backwards digit span performance correlated significantly with the load-dependent measure of social WM RT (a similar trend was observed for the VSWM task, $p < .1$) (Table 2). This effect appeared to be driven by a nonsignificant link between high backwards digit score and faster social WM RT in load 2 trials ($r = -.140$, n.s.) but not in load 3 trials ($r = .001$, n.s.). Note that although the correlation did not necessarily reach significance, the significant correlations described above showed consistent patterns when male and female participants were considered separately in partial correlations controlling for age (Table 2).

To summarize, partial correlation analyses showed that, independent of the genetic effects, performance on the standard WM tasks was highly correlated, whereas correlations between standard WM and social WM performance were much lower.

Genetic effects on standard WM tasks performance

Multiple regression analyses were performed to assess the impact of the three genes (*COMT, DAT1*, and *MAOA*) on VSWM and backwards digit span performance. The effects of *COMT*, the main gene of interest, are reported in Table 3. No main effects were observed for *DAT1* or *MAOA*; there was also no significant *DAT1* x *COMT* interaction on either standard WM measure (all *p*s > .05).

Backwards digit span task

Performance on the backwards digit span task was significantly predicted by an additive effect of *COMT*, which explained 3.2% of the variance (Table 3, Model 1). Higher scores were associated with a greater number of Met alleles (Figure 2A).

Visuospatial WM

Both the additive and the Val dominant model of *COMT* significantly explained variance in VSWM performance. The additive effect presented the best fit accounting for 5.7% of the variance in VSWM performance (Table 3, Model 1; Figure 2B). Higher VSWM scores were associated with a greater number of Met alleles.

There was no significant association between *COMT* and RT in the VSWM task (all *p*s > .5 for the effects of *COMT* in Models 1, 2, 3).

To summarize, the Met allele was found to be advantageous for performance on both standard WM tasks.

Genetic effects on the social trait-ranking WM task

Similar analyses were performed on social WM task performance. Again, there was a main effect of *COMT*, but no main effect of either *DAT1* or *MAOA*. For this measure we observed an interaction between *COMT* and *DAT1*.

TABLE 2

Partial correlations between performance on the three WM paradigms, controlling for age and sex. Significant effects are indicated in bold, and significance values are reported as *: $p < .05$, **: $p < .01$, ***: $p < .001$

	Standard WM		*Social WM*			
	VSWM RT	*Backwards digits*	*Average errors*	*Difference errors*	*Average RT*	*Difference RT*
VSWM	**−.210*[a]**	**.507***[b]**	**−.179*[c]**	−.062	−.030	.169
VSWM RT		−.092	.141	−.078	.037	−.074
Backwards digits			−.063	−.129	−.069	**.185*[d]**

Notes: [a]Partial correlation significant in female ($r = -.352$**) but not male participants ($r = -.115$).
[b]Partial correlation significant both in female ($r = .623$***) and male participants ($r = .376$**).
[c]Partial correlation does not reach significance when females ($r = -.155$) and males ($r = -.209$) are considered separately.
[d]Partial correlation significant in male ($r = .271$*) but not female participants ($r = .121$).

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TABLE 3

COMT genotype effects on WM performance. Synthesis of the results of multiple regression analyses performed on the WM measures to identify significant effects of *COMT* genotype. Models 1, 2, and 3 test for additive, Met dominant, and Val dominant effects of *COMT* genotype, respectively. Model improvements (ΔR^2) are relative to a model that used age and sex only as predictors of WM performance. For each model, the total R^2, ΔR^2, and standardized regression coefficients (betas) for each regressor are provided. Significant effects are indicated in bold, and significance values are reported as *: $p \leq .05$, **: $p < .01$.

	VSWM	*Backwards digit*	*Social WM av. RT*
Model 1: Age, sex, COMT additive effect			
R^2	**.072***	.037	**.064***
ΔR^2	**.057****	**.032***	.006
Age	−.046	−.034	**.220***
Sex	.051	−.024	−.064
COMT	**−.247**[a]**	**−.183*[c]**	.082
Model 2: Age, Sex, Met dominant effect			
R^2	.041	.022	.059
ΔR^2	.026	.017	.001
Age	−.077	−.055	**.244****
Sex	.078	−.005	−.077
COMT Met dom.	−.162	−.131	−.038
Model 3: Age, Sex, Val dominant effect			
R^2	**.070***	.032	**.085***
ΔR^2	**.055****	.027	**.028***
Age	−.047	−.037	**.200***
Sex	.041	−.030	−.044
COMT Val dom.	**−.243**[b]**	−.170	**.173*[d]**

Notes: [a]Effect possibly driven more by males ($\beta_{COMT} = -.331$**) than females ($\beta_{COMT} = -.157$)
[b]Effect similar in females ($\beta_{COMT} = -.253$*) and males ($\beta_{COMT} = -.231$)
[c]Effect possibly driven more by females ($\beta_{COMT} = -.207$) than males ($\beta_{COMT} = -.151$)
[d]Effect possibly driven more by females ($\beta_{COMT} = .216$) than males ($\beta_{COMT} = .134$)

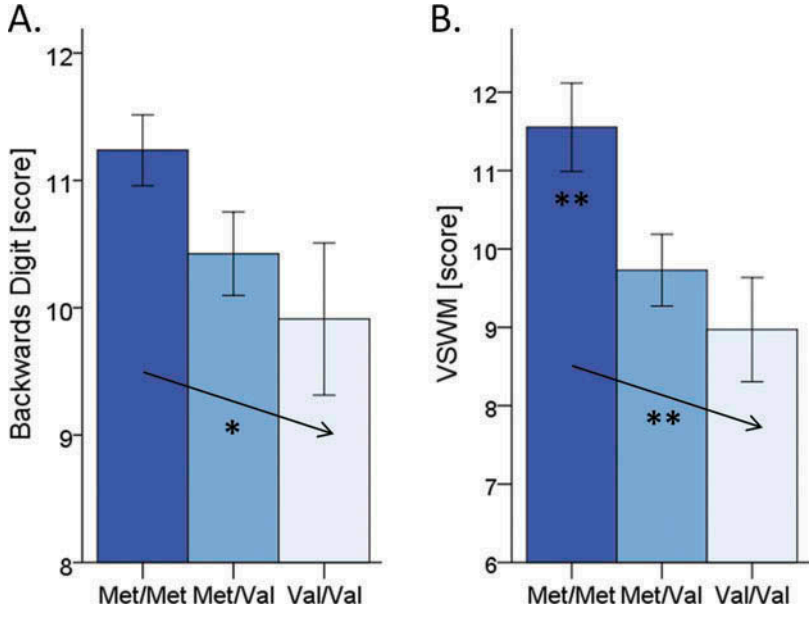

Figure 2. Genetic effects on the backwards digit span and VSWM tasks. (A) Mean (±SE) backwards digit span score plotted as a function of *COMT* genotype. Increasing number of Val allele significantly predicted poorer backwards digit task performance (additive effect of rs4680). (B) Mean (±SE) VSWM score plotted as a function of *COMT* genotype. Increasing number of Val allele significantly predicted poorer VSWM task performance (additive effect of rs4680). There was also a significant effect when using a Val dominance model of the genotype effect. (* indicates significance at $p < .05$, ** at $p < .001$).

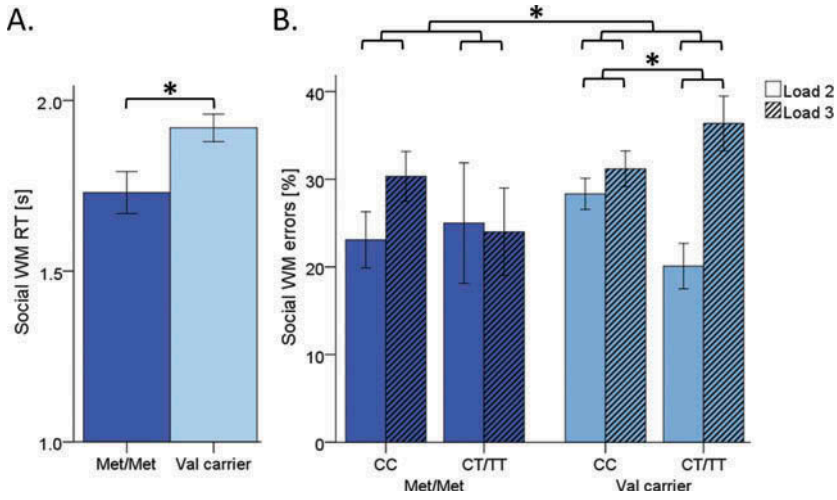

Figure 3. Genetic effects on the social trait ranking WM task. (A) Mean (±SE) social WM average RT plotted as a function of *COMT* genotype with Val dominance. Val carriers were slower than Met/Met participants. (B) Although errors on the social WM task were not predicted by *COMT* or *DAT1* genotypes separately, there was a significant interaction between *COMT* with Val dominance and *DAT1* genotype on the load effect on errors committed on the task. The bar chart illustrates the mean (±SE) social WM percentage errors at loads 2 and 3 plotted as a function of *COMT* genotype with Val dominance and *DAT1* genotype. Follow-up tests showed there was a significant effect of *DAT1* genotype in the Val carriers only, with the effect of load on errors greater in C/T or T/T Val carriers than C/C Val carriers (* indicates significance at $p < .05$).

Effect of COMT genotype on social WM performance

There was no significant association between *COMT* and accuracy on the social WM task (all *p*s > .18 for the effects of *COMT* genotype in Models 1, 2, 3). However *COMT* genotype, modeled with Val allele dominance (comparing Val-allele carriers to Met/Met individuals), significantly explained some of the observed variability in RT (Table 3, Model 3). The effect of the Val allele significantly explained 2.8% of the variance in average RT (Table 3, Model 3; Figure 3A), with lower RTs (better performance) observed in Met/Met participants compared with Val carriers.

To summarize, the social WM task also showed a benefit for the Met allele, but only in terms of RT, not accuracy.

Independence of COMT effects on social and standard WM tasks

We investigated whether the effect of *COMT* on social WM was driven by its effect on standard WM performance by adding VSWM score, VSWM RT, or backwards digits span score as predictors of the average RT measure on the social WM task (Table 4). Standard WM performance did not significantly account for variance in average RT. In addition,

TABLE 4
Social WM performance (average RT) as a function of *COMT* genotype and standard WM performance. Model improvements (ΔR^2) are relative to Model 3 (Table 3) which included sex, age, and the Val dominant model of *COMT* as predictors of average RT

	Social WM average RT		
R^2	**.087***	**.085***	**.086***
ΔR^2	.002	<.001	.001
Age	**−.198***	**.200***	**.198***
Sex	−.045	−.044	−.042
COMT Val dom.	.166[a]	.176[a]	.172[a]
Backwards digit	−.041	–	–
VSWM	–	.011	–
VSWM RT	–	–	.026

Notes: For each model, the total R^2, ΔR^2, and standardized regression coefficients (betas) for each regressor are provided. Significant effects are indicated in bold, and significance values are reported as: *$p < .05$.
[a]The effect of *COMT* Val dominant becomes a trend in all three multiple regressions (respectively $p = .065$, $p = .055$, and $p = .055$).

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entering VSWM or backwards digit span measures as regressors had little influence on the effect of *COMT* on average RT (Table 4). In summary, the effect of *COMT* on the social WM performance appears to be independent of standard WM.

Gene x gene interaction in the social WM task

We used the *COMT* Val dominant model, since this was the model that showed effects both in the VSWM and social WM tasks, to explore a potential *DAT1* × *COMT* interaction in the social WM task. A significant *DAT1* × *COMT* interaction accounted for 4.5% of the variance in the load-dependent measure of percentage error (i.e., the difference in percentage error between load 3 and load 2) (β = 0.418, p = .014). Together *COMT, DAT1*, and their interaction significantly explained 7.0% of the variation in the difference in percentage error on the social WM task (p = .027) beyond the effects of age and sex. Note, however, that one of the groups in this gene x gene interaction had a low N (Met/Met: CC, N = 28, CT or TT, N = 10; Val/Val: CC, N = 67, CT or TT, N = 25).

Follow-up multiple regression analyses indicated that within *COMT* Met/Met participants, there was no effect of *DAT1* genotype on the difference in percentage error between loads 3 and 2 (β = −0.165, p = .330). However, there was an effect of *DAT1* genotype in Val carriers (β = 0.303, p = .003), with a larger detrimental effect of load in the T carriers than C homozygotes (Figure 3B). Thus overall, the T allele of *DAT1* and the Val variant of *COMT* were together associated with a greater detrimental effect of increasing load on the percentage error in the social WM task.

Note that including participants' backwards digit span score, VSWM score, or VSWM RT as predictors did not affect the finding of an interaction between *DAT1* and *COMT* genotypes on the difference in social WM percentage error. Furthermore, none of these measures significantly predicted the difference in social WM percentage error (all βs < .135, ps > 0.13).

To summarize the results, the Met allele was broadly associated with better VSWM and backwards digit scores, and faster average RT in the social WM task. An interaction between *DAT1* and *COMT* variants was observed, with a greater impact of load on social WM percentage errors in carriers of at least one Val allele at *COMT* and at least one T allele at *DAT1*. The genetic associations with social WM task performance were not mediated by genetic effects on the standard WM tasks. Note however that these results would not survive correction for multiple comparisons, and will need to be replicated.

DISCUSSION

Common genetic variants permit the study of the role of neurotransmitters in cognition. We investigated the correlation between three common SNPs (in *COMT, DAT1*, and *MAOA*) and interindividual variability in performance on three WM paradigms: visuospatial, verbal, and social WM. Our aim was to gain insight into the role of dopamine neurotransmission in social WM and the extent to which this is independent of its role in standard WM.

VARIATION AT *COMT* AND STANDARD WM CAPACITY

Consistent with some previous studies (Diaz-Asper et al., 2008; Dumontheil et al., 2011; Goldberg et al., 2003; Mattay et al., 2003), we found a main effect of C*OMT* genotype on performance in both standard WM tasks (stronger in the VSWM task), with superior performance associated with the Met allele (Figure 2A and B). The fact that some studies have not found this association (Barnett et al., 2008; Blanchard et al., 2011) may be due to differences in the paradigms used. For example, the N-back task (Blanchard et al., 2011) implements a fixed maximum WM load (e.g., 3-back). In contrast, the VSWM and backwards digit span tests used here assess participants' maximum WM capacity, and may therefore be more sensitive to interindividual differences in WM and more appropriate to the study of genetic associations.

No association was observed between *DAT1* or *MAOA* variants and performance in the standard WM tasks. Although MAOA plays a role in frontal dopamine degradation (Berry et al., 1994), there is little evidence of an effect of *MAOA* variants on behavioral measures of WM (although, see Enge, Fleischhauer, Lesch, Reif, & Strobel, 2011). It has been suggested that neuroimaging measures may be more sensitive to the effect of *MAOA* polymorphisms (Hariri & Weinberger, 2003; Ziermans et al., 2012). DAT density is 10 times lower in the PFC than in the striatum, making DAT a greater determinant of striatal rather than PFC functioning (Hall et al., 1999; Sasaki et al., 2012). WM improvements in response to training may be more sensitive to the effect of *DAT1* polymorphisms than WM measures at a single timepoint (Brehmer et al., 2009; Söderqvist et al., 2012).

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Although the T allele of the SNP studied here is linked to the 9-repeat variant of the more commonly studied VNTR on *DAT1* (Brookes et al., 2006; Laucht et al., 2007), the SNP may be more weakly associated with DAT activity than the VNTR.

No genetic associations were observed with RT in the VSWM task. In contrast, studies using the N-back task have observed effects of *COMT* genotype on both accuracy and RT (Goldberg et al., 2003; Mattay et al., 2003). In the VSWM task used in the current study, the time needed to retrieve and reproduce accurately the sequence of dots may be in part affected by WM capacity. However, RT is likely to be less sensitive to individual differences in WM capacity than the total score, which is the only measure considered in the original Dot Matrix test (Alloway, 2007; Dumontheil et al., 2011).

ASSOCIATION BETWEEN *COMT* AND *DAT1* VARIANTS AND SOCIAL WM PERFORMANCE

Little is known about the role of dopamine in mentalizing (Skuse, 2006; Skuse & Gallagher, 2011). Only one study has shown that variation of the dopamine receptor D4 gene was associated with mentalizing in preschoolers (Lackner et al., 2012). Here we chose to focus on one aspect of social cognition, social WM, which relates to the ability to evaluate and manipulate social information held in WM, and used a paradigm introduced in a recent functional magnetic resonance imaging (fMRI) study (Meyer et al., 2012). Although this task only measures one particular aspect of mentalizing, and further work will be needed to extend our results to other aspects, we chose it for the following reasons: performance on the social WM task is associated with activation of both domain general WM regions and parts of the social brain (Meyer et al., 2012); the sensitivity to social WM load in the medial PFC in particular is correlated with self-reported measure of perspective taking; performance on the task is not at ceiling, which is important for the investigation of individual differences, and task performance is sensitive to load. This task was therefore considered a good first step to extend the findings of association between dopamine, COMT, and WM to the social domain. Two genetic associations were observed in the social WM task.

First, Met/Met individuals were faster than Val carriers, suggesting that, as with the standard WM tasks, there is a benefit of the Met allele of *COMT* on social WM (Figure 3A). Although this effect was observed for RT only and not for accuracy, it is unlikely to be driven by an association between variation at *COMT* and motor response speed for two reasons: (1) no association was observed between *COMT* and VSWM RT; (2) the association between *COMT* and social WM RT remained when controlling for individual differences in VSWM RT. The fMRI study by Meyer et al. (2012) showed load-dependent activation in a broad network of lateral and medial frontoparietal networks during the social WM task over both delay and probe phases. This suggests that WM-related processing occurred over both phases of the task. Since RTs to the probe in the social WM task are sensitive to the WM load (Meyer et al., 2012), they are likely to reflect social WM processes.

In line with the finding discussed above, a study by Reuter et al. (2009) found an effect of *COMT* on RT with Met/Met individuals responding faster to a lexical decision task. In their study, the Val^{158}Met polymorphism was found to explain between 9% and 14.5% of the variance in RT. Both the present and Reuter et al.'s studies required participants to respond to words presented on the screen, still, the tasks participants had to do were quite different. In the current paradigm, the RT corresponded to the time participants took to read three words in the probe question (e.g., "Second funny? Rebecca") and assess the correct answer by considering information stored in WM before pressing the response button. In the lexical decision task used by Reuter et al. (2009), participants were asked to judge whether the presented word was a real German word. Note that the effect of *COMT* genotype in the study by Reuter et al. (2009) was not affected by lexical priming; the authors therefore suggest that their finding may reflect a more domain general association between *COMT* and executive functions.

The paradigm used in the current study differs from previous WM studies of COMT in that it required participants to maintain and manipulate information of a social nature. As mentioned above, little research has investigated the role of dopamine in mentalizing, however two lines of evidence have related COMT variability to social–emotional processing more broadly. First, carriers of the Met allele have been found to show increased levels of anxiety and avoidance behaviors (see Montag, Jurkiewicz, and Reuter (2012) for review). Second, two recent studies have found that Met-allele carriers behave in a more conformist manner than carriers of at least one Val-allele (Deuker et al., 2013; Falk, Way, & Jasinska, 2012). These latter findings have been taken to suggest that Met carriers may be more likely to seek social approval by conforming in a group setting and may therefore be more sensitive to cues that signal

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social reward or punishment (Deuker et al., 2013). Two explanations for higher social conformity observed in Met carriers are highlighted by Deuker et al. (2013); both relate to the role of COMT in emotional processing. First, it has been suggested that the elevated levels of anxiety observed in Met carriers (Montag et al., 2012) may predispose them to seek approval by their social group and thus exhibit greater conformity (Deuker et al., 2013). Second, it has been suggested that disagreeing with one's social group is more unpleasant and causes greater conflict in carriers of the Met allele (Deuker et al., 2013), which may be linked to the fact that Met carriers may be more sensitive to intrinsic signals as supported by findings of increased sensitivity to pain in these individuals (Zubieta et al., 2003). In addition, a recent fMRI study of group conformity found that homozygous Met-allele carriers showed increased anterior cingulate cortex activity in trials where the majority of the group was incorrect. The authors speculate that this may be due to a subjectively perceived higher degree of, or greater sensitivity to, conflict in Met carriers, which has been observed in behavioral studies (Deuker et al., 2013). Of note, this seemingly increased sensitivity to one's social status within the group observed in Met carriers may be in line with the current finding of increased performance (faster RTs) in Met carriers in the social WM task, which requires speeded access and manipulation of social information and judgment of character traits in the participants' own social group.

Although our sample size was relatively small for this test, the second genetic association was a significant interaction between *COMT* and *DAT1* on the load-dependent accuracy measure of the social WM task. In combination, the Val allele at *COMT* and T allele at *DAT1* were associated with poorer performance in load 3 compared to load 2 trials (Figure 3B). Additive effects of *COMT* and *DAT1* polymorphisms on brain activation in the PFC, but not performance, have been observed on standard WM tasks (Bertolino et al., 2006; Caldú et al., 2007). This suggests that social WM performance may be more sensitive to the interplay between regions expressing *DAT1* and those expressing *COMT*.

While only the additive model of *COMT* effects was significant for the backwards digit span task, indicating a linear increase in span with an increasing number of Met allele, the VSWM finding was observed with both additive and Val dominant models, and the social WM genetic associations were observed with a Val dominant model, i.e., with better performance observed in carriers of two Met alleles. A variety of approaches have been used in the literature (e.g., Val dominant model in Barnett et al. (2008); homozygotes comparison or additive effects in Mier et al. (2010)), and a variety of patterns of genetic effects have been reported (Mier et al., 2010; Witte & Flöel, 2012). Although the effect of rs4680 at the enzymatic level is likely to be additive, the proposed inverted U-shape of PFC functioning as a function of dopamine level (Meyer-Lindenberg & Weinberger, 2006) might transform the enzymatic additive level into a variety of pattern of Val/Met performance at the level of brain activity or performance.

INDEPENDENCE OF EXECUTIVE AND SOCIAL COGNITION COMPONENTS OF SOCIAL WM

Importantly, both genetic associations between dopamine regulating SNPs and social WM remained when standard WM measures were covaried out, suggesting an independent effect of these SNPs on social WM processing. These results therefore provide novel preliminary evidence that executive and social cognitive components of the social WM task recruit parallel, and at least partially independent, cognitive systems (Mitchell, 2008), each dependent on dopamine neurotransmission (or neutrotransmission of other catecholamines that are degraded by *COMT*).

One limitation of the current study is that the social WM paradigm differed from the two standard WM tasks. Including a matched nonsocial WM control condition with similar demands in terms of maintenance over a delay and reordering of verbal information would be beneficial. The current paradigm is not able to distinguish which particular aspects of the task, beyond the social nature of the information being manipulated, may be differentially sensitive to variation in COMT compared with the standard WM tasks. Potential differences between the tasks include the need for mentalizing, the maintenance of socially salient information (names of friends) or providing an answer to a probe question rather than a reproduction of a memorized or reordered sequence stored in WM. It is notable that the two standard WM tasks also themselves differed in a number of ways, including the nature of the stimuli (verbal vs. visuospatial), mode of presentation (auditory vs. computer-based), mode of response (verbal vs. mouse response), and WM demands (maintenance and manipulation vs. maintenance only). Despite these differences, scores on these two tasks showed similar associations with COMT genotype. The social WM task used in this study is a recently developed paradigm (Meyer et al., 2012), and the relationship between performance on

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this task and other measures of social cognition and mentalizing remains to be investigated.

The findings of independent effects of dopamine-related genetic variants on social and standard WM measures extend findings from fMRI studies that have shown simultaneous recruitment of both executive and social brain networks during tasks requiring both executive functioning and social cognition (Dumontheil, Küster, Apperly, & Blakemore, 2010; Meyer et al., 2012). COMT is expressed not only in the lateral parts of the parietal cortex and PFC (Chen et al., 2004) that support WM (Curtis & D'Esposito, 2003; Petrides, 2005), but also throughout the cortex, including the MPFC and temporal regions (Hong, Shu-Leong, Tao, & Lap-Ping, 1998; Lloyd, Davidson, & Hornykiewicz, 1975) recruited during social cognition tasks (Van Overwalle, 2009). The additional influence of DAT on social WM performance may indirectly suggest an involvement of subcortical regions where DAT shows high concentration (Ciliax et al., 1999).

Of note, an association between midbrain dopamine uptake and activity in both medial and lateral PFC during a 0-back task has previously been found to be modulated by *COMT* rs4680 (Meyer-Lindenberg et al., 2005). In addition, a recent study showed that genetic variants of the D2 dopamine receptor affect the association between DAT binding in the striatum and connectivity within the default mode network, including the MPFC (Sambataro et al., 2013; see also Dang, Donde, Madison, O'Neil, and Jagust (2012) for an association between striatal dopamine and MPFC deactivation). Finally, it should be noted that the fMRI study that employed the social WM task found load-sensitive activity in the striatum (globus pallidus) in addition to the social brain regions and standard frontoparietal WM network (Meyer et al., 2012). This, together with the current findings, provides independent support for involvement of DAT-expressing striatal regions in social WM, although our results are preliminary. Our sample was relatively small for a genetic association study and the results would not survive correction for multiple comparisons. The findings should therefore be interpreted with caution and will need to be replicated. However, this study is novel in its investigation of dopaminergic effects on social cognition in adults, and thus generates hypotheses that can be tested with larger samples.

CONCLUSION

Social WM is related to keeping track of and navigating one's social environment. It has been proposed that the cognitive demands of large social networks might explain the increased neocortex size in humans compared with other primates ("social brain hypothesis" (Dunbar, 1998)). Improving our understanding of the role of neurotransmitter systems in social cognition contributes to our understanding of interindividual variations in social cognitive abilities in the normal population, and may inform our understanding of disorders characterized by impaired WM and social cognitive deficits (Diamond, 2007; Meyer-Lindenberg & Weinberger, 2006; Skuse, 2006).

SUPPLEMENTAL DATA

Supplemental data for this article can be accessed here. http://dx.doi.org/10.1080/17470919.2014.925503

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