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The influence of COMT rs4680 on functional connectivity in healthy adults: A systematic review

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ABSTRACT

The aim of this systematic review was to qualitatively synthesise the available research that investigated the influence of COMT genotype at SNP rs4680 on both task-based and resting-state connectivity in healthy adults. Thirty-five studies were identified that met inclusion criteria. Of the included studies, 20 studies reported resting-state findings and 16 studies reported task-based findings (emotion processing, memory, working memory, reward-based learning, and executive function). Studies were highly heterogeneous but an overall trend towards an association of the Val allele with greater resting-state connectivity and the Met allele with greater task-based connectivity is reported. A possible interpretation of current findings is discussed, whereby the Val allele is associated with improved cognitive flexibility allowing integration of novel relevant stimuli, and the Met allele allows improved sustained attention and targeted neural processing, particularly between limbic regions and prefrontal cortex. The most promising brain regions implicated in a COMT genotype influence on functional connectivity include prefrontal regions, amygdala and hippocampus.

Introduction

Catechol-*O*-methyltransferase (COMT) is an enzyme that catalyses the transfer of a methyl group from S-adenosylmethionine to any catechol containing molecule, this is an important step in the degradation of families of molecules such as the catecholamines (dopamine, epinephrine and norepinephrine (Guldberg & Marsden, 1975; Weinshilboum *et al.*, 1999)) and the catecholestrogens (Ball *et al.*, 1972). The COMT gene includes a number of single nucleotide polymorphisms (SNPs), the most commonly studied being rs4680. COMT SNP rs4680 is nonsynonymous with a guanine to adenine substitution in the DNA nucleotide sequence resulting in a valine (Val) to methionine (Met) amino acid substitution. This amino acid substitution has functional significance because the presence of the Met amino acid results in a protein that has greater thermo-instability which results in ~fourfold decrease in enzymatic activity (Lachman *et al.*, 1996; Chen *et al.*, 2004a). This proposed mechanism of action on central nervous system function has led to rs4680 being the most extensively studied SNP of the COMT gene.

There is an increasing understanding of the biological mechanisms by which COMT can bring about changes in central nervous system function. COMT is present as a membrane-bound (MB-COMT) and soluble form (S-COMT), with MB-COMT having a higher substrate affinity and S-COMT, which is distributed throughout the cytoplasm, having higher catalytic activity (Assicot & Bohuon, 1971; Lotta *et al.*, 1995; Mannisto & Kaakkola, 1999). Notably, it was postulated that the variation in enzymatic activity due to change in amino acid sequence, caused by SNP rs4680, influenced levels of dopamine in prefrontal cortex (PFC). It was presumed that the increased metabolism of dopamine was via MB-COMT because it could access synaptic dopamine (Gogos *et al.*, 1998; Egan *et al.*, 2001; Matsumoto *et al.*, 2003; Chen *et al.*, 2011). However, it has recently been shown that rs4680 genotype was associated with changes in levels of S-COMT, but not MB-COMT, in human cortex (Chen *et al.*, 2004a; Parkin *et al.*, 2018). As S-COMT is in the cytoplasm, where it would not have ready access to synaptic dopamine, the alternative mechanisms of action of COMT need to be considered as a potential way COMT genotype could be related to cortical activity and cognition.

S-COMT is important in the metabolism of catecholestrogens which can regulate gene expression via estrogen response elements (Klinge, 2001; Parkin *et al.*, 2018). It has also been shown that the rs4680 genotype is associated with variation in levels of expression of the human cortical muscarinic M1 receptors (CHRM1; Dean & Scarr, 2016). Notably, CHRM1 is known to be important in cognition (Melancon *et al.*, 2013; Nathan *et al.*, 2013) including attentional set-shifting (Chen *et al.*, 2004b). Therefore, it is possible that COMT genotype may be associated with levels of cognition by mechanism other than causing changes in dopamine metabolism. This would particularly be the case in the absence of high levels of estrogen because under such conditions, the catecholestrogens would be more potent in regulating gene expression.

Focussing on COMT genotype and central nervous system function, it is significant that in healthy adult samples, free of psychiatric or neurological disorders, the Met allele has been associated with a small but significant performance increase on tasks of executive function (Barnett *et al.*, 2007) and episodic memory retrieval (de Frias *et al.*, 2004; Bertolino *et al.*, 2006), whilst the Val allele may be advantageous for emotion processing (Mier *et al.*, 2010). The advantage of the Met allele for cognitive function and the Val allele for emotion processing has been described as a trade-off whereby each allele offers specific environmental advantage, hence both are maintained in the population (Goldman *et al.*, 2005). However, results are not always consistent and some studies have found opposing effects (Tsuchimine *et al.*, 2013; Matsuzaka *et al.*, 2017) or no behavioural effect of COMT rs4680 (Schott *et al.*, 2006; Barnett *et al.*, 2008; Dennis *et al.*, 2010). Indeed, one study supported an effect of COMT rs4680 on cogntion only in males and post-menopausal females (Papaleo *et al.*, 2015). This effect could be due to the effects of COMT mediated changes in catecholestrogen levels having an increased impact on gene expression in the presence of low estrogen levels (Parkin *et al.*, 2018).

COMT rs4680 has also been associated with task-activated differences in functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) response, producing a complex picture (Mier *et al.*, 2010; Witte & Flöel, 2012). Increased activation has been associated with the Val allele in the presence of reduced task performance in studies of executive function (Egan *et al.*, 2001; Mattay

et al., 2003). Similarly, the Met allele has been associated with improved memory performance and reduced activation in the PFC, but increased activation in the hippocampus (Bertolino *et al.*, 2006). During emotion processing tasks, greater activation in the ventrolateral PFC, hippocampus and limbic regions has been associated with the Met allele (Smolka *et al.*, 2005; Drabant *et al.*, 2006), and a working memory task with emotional distraction produced greater activation in Val carriers in PFC and limbic regions (Bishop *et al.*, 2006). Reduced performance and increased PFC activation associated with the Val allele has been explained as reduced neural efficiency due to reduced signal-to-noise ratio (Egan *et al.*, 2001; Mier *et al.*, 2010). Further, it has been proposed that the Met allele confers cognitive stability which is advantageous for tasks requiring sustained attention (Bilder *et al.*, 2004), and that the Val allele is advantageous for tasks requiring flexibility of processing (Krugel *et al.*, 2009).

Considering the hypothesis that COMT rs4680 is involved in regulating PFC dopamine and hence cognitive function, it is notable that BOLD response differences have been found in regions outside the PFC, such as the hippocampus (Drabant *et al.*, 2006), and ventral striatum (Tunbridge *et al.*, 2012). Investigating the effect of COMT genotype on functional connectivity will assist in understanding its influence on brain function and could further elucidate the theories of neural efficiency and cognitive stability versus flexibility. Both resting-state and task-based studies will contribute to this understanding given that hub regions exist across states reflecting dynamic neural architecture (Smith *et al.*, 2009; Cole *et al.*, 2016; Ito *et al.*, 2017). Numerous resting-state networks have been identified with good test-retest reliability and validity across individuals (Damoiseaux *et al.*, 2006; Shehzad *et al.*, 2009), and the individual variability in these functional networks has been linked to behavioural differences (Vaidya & Gordon, 2013). The current systematic review aims to qualitatively synthesise the available research that has investigated the influence of COMT rs4680 on both task-based and resting-state functional connectivity in healthy adults. Consolidation of these findings will assist identification of neural networks and associated cognitive processes consistently influenced by COMT genotype and inform future targeted investigation.

Method

Search protocol

The current review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher *et al.*, 2009) and pre-registered with the international prospective register of systematic reviews; PROSPERO (CRD42018107734). The following databases were searched for relevant literature; PubMed, Scopus, Web of Science, Academic Search Complete, and CINAHL. Search terms comprised: (fMRI OR MRI OR "magnetic resonance imaging" OR MEG OR magnetoencephalography OR EEG OR electroencephalography) AND (catechol-o-methyltransferase OR COMT OR "catechol o methyltransferase") AND ("resting state" OR connectivity OR "functional connectivity"). Searches were conducted from 1 January 1990 until 12 November 2018, with the earliest identified relevant article published in 2006 (Bertolino *et al.*, 2006). Additional literature was sourced from the reference lists of included articles which identified one earlier study in 2006 (Schott *et al.*, 2006).

Study selection

Database searches, title and abstract screening, and full text screening was conducted independently by two authors (KM and SG), with any discrepancies resolved collaboratively according to criteria. Empirical studies that met the following criteria were include in the review: (1) the study was published in English language; (2) included a sample of healthy adult humans; (3) reported resting-state or task-based functional connectivity; (4) reported a main effect of COMT rs4680 on functional connectivity. Studies were excluded that: (1) used child or adolescent samples, under 18 years of age; (2) reported findings where the effects of COMT rs4680 independently could not be determined; (3) reported only functional activation or structural findings; (4) healthy group comprised siblings of a group with psychopathology; (5) studies only reporting a mediation effect of COMT rs4680 on an outcome of interest other than functional connectivity; (6) reviews, book chapters, meeting proceedings, or poster abstracts.

Data extraction and grouping of studies

Data extraction was conducted by KM and for each study included: (1) sample characteristics; sample size, age, gender, ethnicity, handedness, genotype distribution and grouping; (2) task details if applicable; (3) neuroimaging modality; (4) method of functional connectivity analysis; (4) rationale for seed region selection, if applicable; (5) network/s and/or regions of interest investigated; (6) key finding: COMT rs4680 effect on functional connectivity (see Table 1, and additional details in Supplementary Material.). Studies were grouped into resting-state and task-based studies, and further grouped by resting-state studies that: (1) analysed whole-brain functional connectivity separated into those that did and did not use seed-based analyses; (2) investigated default mode network (DMN); and (3) other resting-state networks. Task-based studies were grouped by: (1) emotion processing; (2) memory; (3) working memory; (4) reward-based tasks; and (5) executive function.

Evaluation of study quality and risk of bias

Studies were evaluated for sample and neuroimaging procedure and analysis. Samples were assessed for: (1) sample size, age and gender distribution, genotype group distribution; (2) reporting of exclusion criteria, ethnicity, handedness, Hardy-Weinberg equilibrium, significant differences in age and gender distribution across genotype groups. Neuroimaging procedure and analysis was assessed for: (1) eyes open or closed during resting-state; (2) method for defining network and/or seed region selection (e.g. based on previous research or current study); (3) pre-processing parameters; and (4) whether analysis controlled for age, gender, intelligence quotient, or other variables.

Results

Database searches identified 252 articles (PubMed = 55, Scopus = 63, Web of Science = 97, EBSCOhost (Academic Search Complete and CINAHL) = 37), resulting in 109 articles after duplicates were removed. Following title, abstract and full-text screening a total of 35 articles remained for inclusion in the current review (see Figure 1). Of the 35 included studies, 20 studies reported resting-state findings

(whole-brain analysis = 13, DMN = 4, other resting-state networks = 4), with one study conducting both whole-brain analysis and analysis restricted to ROIs of the DMN (Liu *et al.*, 2010). 16 studies reported task-based findings (emotion processing = 4, memory = 3, working memory = 3, reward-based = 4, executive function = 2), one study probed both reward and emotion processing (Klucken *et al.*, 2015), and one study reporting both resting-state and task-based findings (Elton *et al.*, 2017). All identified studies utilised fMRI to assess functional connectivity except for one study that used resting-state electroencephalogram (EEG; Lee *et al.*, 2011). No studies were found that used magnetoencephalogram. Five of the included studies also investigated patient groups, four of which reported results independently for healthy participants. The remaining study by Gong *et al.* (2017) reported no significant main effect of COMT rs4680 across a group including healthy participants and those with a diagnosis of major depressive disorder which is noted where applicable.

Figure 1. here

Study quality and risk of bias

Issues regarding comparability across studies, including; eyes open/eyes closed conditions, sample characteristics, and lack of power are covered under "Limitations and future directions*"*. Notably, there were seven studies with samples greater than two hundred (see Figure 2), and six of these studies investigated the same sample of Chinese Han participants (Tian *et al.*, 2013; Wang *et al.*, 2015a; Zhang *et al.*, 2015; Zhao *et al.*, 2015; Li *et al.*, 2016; Xu *et al.*, 2016). These studies all reported resting-state findings and found either increased connectivity with the Val allele or no significant effect of COMT rs4680. The remaining large independent study also investigated a Chinese sample and utilised EEG in their functional connectivity investigation (Lee *et al.*, 2011). Generalisability of findings from Chinese samples to Caucasian samples and vice versa may be problematic as some studies have shown differences in the direction of COMT rs4680 effects in different ethnic samples (Lee & Prescott, 2014), for example, the Met allele has been associated with improved cognitive performance in European Caucasians (Aguilera *et al.*, 2008), and the Val allele has been associated with improved cognitive

performance in Chinese samples (Yeh *et al.*, 2009; Wang *et al.*, 2013). Additionally, a recent study found differences in resting-state connectivity between those with European and non-European ancestry, authors suggesting this may be driven by differences in head and brain morphology which are carried through resting-state MRI processing pipelines (Altmann & Mourao-Miranda, 2019). Further details of quality and bias evaluation can be found in Supplementary Material.

Figure 2. here

Resting-state studies

Whole brain

To aid comparison of findings, studies that assessed functional connectivity across the whole brain were initially separated into those that used seed-based analysis and those that used analysis without seed region selection.

Seed-based analyses

Six studies used seed-based analyses, which involves the selection of an a-priori seed region from which BOLD time-course data is extracted and used as a regressor in correlational analysis (Cole *et al.*, 2010). Seeds were placed across several frontal cortical sites: ventromedial PFC, anterior medial PFC, dorsolateral PFC, ventrolateral PFC, orbitofrontal cortex, dorsal anterior cingulate cortex, and subgenual anterior cingulate cortex. Seeds were chosen for reasons including involvement in DMN, network intersection, and task association. Other seed regions included: posterior cingulate cortex (part of DMN), ventral striatum (fronto-striatal dopaminergic circuity), primary visual area (DMN negative control), and bilateral amygdala (framing effect). Two of these six studies found no effect of COMT rs4680 on functional connectivity, three found increased connectivity with the Val allele, and one found increased connectivity in heterozygotes compared to Val homozygotes without the inclusion of Met homozygotes. A schematic representation of these seed-based analyses findings within the PFC is shown in Figure 3.A.

In a sample of 57, Liu *et al.* (2010) conducted whole brain correlational analysis using two seed regions from within the DMN; ventromedial PFC and

posterior cingulate cortex, and striatal and primary visual area seed regions chosen due to being outside the DMN. Differences in functional connectivity were compared between heterozygotes and Val homozygotes only. Heterozygotes had stronger connectivity than Val homozygotes between the ventromedial PFC seed and the anterior medial PFC, posterior cingulate cortex/retrosplenial, and right inferior temporal cortex, and also the posterior cingulate cortex seed with anterior medial PFC. There were no differences found with the striatal or primary visual area seeds, leading the authors to suggest that a COMT rs4680 effect on functional connectivity is restricted to PFC regions. Wang and colleagues (2015a) also found no main effect of COMT with ventral striatum seed regions in their whole-brain resting-state analysis in a sample of 266 comparing Val homozygotes to Met carriers.

Two studies with female only samples looked at effects of COMT rs4680 on whole-brain resting-state functional connectivity. Favaro *et al.* (2013) used PFC seeds (dorsolateral, ventrolateral, and ventromedial) in a context of executive functioning and found no significant differences with COMT rs4680 in their sample of 30. Baeken *et al.* (2014) investigated a sample of 61 using a seed in the subgenual anterior cingulate cortex, chosen due to its role in emotion processing (Drevets *et al.*, 2008). Val carriers had significantly stronger functional connectivity between the subgenual anterior cingulate cortex and the left parahippocampal gyrus and the right inferior frontal gyrus. Met carriers had stronger functional connectivity between the subgenual anterior cingulate cortex and the left middle frontal gyrus. In considering these results, it should be noted that these two studies did not control for the potential confound of cycling estrogen levels in their female only samples.

Gao *et al.* (2016) focussed on positive functional connectivity using seed regions in the orbitofrontal cortex, dorsal anterior cingulate cortex, ventromedial PFC, and bilateral amygdala in a sample of 98. These regions were chosen due to a previously demonstrated role in the framing effect (De Martino *et al.*, 2006), and may be involved in a negative-emotion processing bias previously associated with the Met allele (Williams *et al.*, 2010). Val homozygotes had increased connectivity compared to Met carriers with each seed region, including: right orbitofrontal cortex seed with bilateral amygdala, bilateral dorsal anterior cingulate cortex, right lateral orbitofrontal cortex, and right inferior frontal gyrus; dorsal anterior cingulate cortex seed with left and right lateral orbitofrontal cortex, bilateral dorsolateral PFC, and

cerebellum; ventromedial PFC seed with caudate, inferior temporal gyrus, Cuneus, superior temporal gyrus, and dorsomedial PFC; left amygdala seed with precuneus; and right amygdala with left and right lateral orbitofrontal cortex, and precuneus. Connectivity between these regions mediated the relationship between COMT rs4680 and task performance. In contrast to resting-state analysis; during emotion processing tasks the Met allele has been associated with increased connectivity between the amygdala and orbitofrontal cortex, and negativity bias (Drabant *et al.*, 2006; Rasch *et al.*, 2010).

Meyer *et al.* (2016) investigated a sample of 106 using a seed region within the anterior medial PFC, chosen due to its role as an intersection of the task activated executive control network and DMN. Connectivity increased with the number of Val alleles between the anterior medial PFC and left ventrolateral PFC, and the left dorsolateral PFC and bilateral parahippocampal gyrus.

Other analyses

Three studies have used global functional connectivity density mapping to analyse differences in functional connectivity with COMT rs4680. This method does not require seed regions and is a measure of the number of statistically significant functional connections at a given voxel (Tomasi & Volkow, 2011). These analyses are restricted to grey matter regions that have a signal to noise ratio of > 50% (Tomasi & Volkow, 2010). None of these studies found an effect of COMT rs4680 on global functional connectivity density after correcting for multiple comparisons, in samples of 258 (Tian *et al.*, 2013), 265 (Li *et al.*, 2016), and 85, including 50 with diagnosis of major depressive disorder (Gong *et al.*, 2017).

Two studies used eigenvector centrality mapping to assess functional connectivity differences with COMT rs4680. Eigenvector centrality does not require ROI selection and considers a voxel's degree of connectivity and weights its centrality by taking into account the centrality of the voxels to which it is connected (Lohmann *et al.*, 2010). In a sample of 99, Markett *et al.* (2016) found greater eigenvector centrality in Val homozygotes compared to heterozygotes within the medial temporal subsystem of the DMN; including clusters within the angular gyri, the inferior parietal lobules, and middle temporal gyri, and a cluster within the dorsomedial prefrontal subsystem of the DMN. Conversely. Met carriers had

increased eigenvector centrality compared to Val homozygotes in the somatomotor network, comprising pre and postcentral gyri and paracentral lobule. There were no differences found between heterozygotes and Met homozygotes. Zhang *et al.* (2015) found Val homozygotes demonstrated significantly higher eigenvector centrality in the left parahippocampal cortex than Met carriers in their sample of 287.

Wang *et al.* (2018) used degree centrality in their investigation of functional connectivity in a sample of 56. This method assesses the total number of significant BOLD time-course correlations with a given voxel ($r > 0.6$), and is distinct from eigenvector centrality as it does not weight functional connections according to the degree each voxel is itself functionally connected (Lohmann *et al.*, 2010). Carriers of the Met allele had higher degree centrality in the left hippocampus and left amygdala, compared to Val homozygotes. Similarly, within the DMN, Liu *et al.* (2010) found heterozygotes (carriers of one Met allele) to have greater degrees of connectivity compared to Val homozygotes in the ventromedial PFC, anterior medial PFC, and left superior frontal cortex in their sample of 57.

Only one study to date has used a method other than fMRI to assess differences in functional connectivity according to COMT rs4680. Lee *et al.* (2011) studied resting-state EEG of 254 participants and found a dose-dependent trend of the Val allele with greater connectivity between multiple pairs in delta and theta frequencies. These connection-frequency pairs were predominately in frontal areas and included connections to left temporal and parietal areas. Only one significant connection-frequency pair was not inclusive of frontal regions and was between the left temporal and parietal area, overall results tended towards left lateralisation.

Default Mode Network (DMN)

The DMN is a defined network of resting-state function which is reliably present during passive conditions and thought to be involved in self-generated cognition (Andrews-Hanna, 2012; Spreng, 2012). This network has been described as medial temporal and medial prefrontal subsystems with shared nodes for integration including the posterior cingulate cortex (Buckner *et al.*, 2008). Although many resting-state studies consider the DMN, only four have investigated COMT rs4680 connectivity differences restricted to this network and two of these studies

has participants with eyes open (Dang *et al.*, 2013; Damoiseaux *et al.*, 2016). Damoiseaux *et al.* (2016) looked at correlations between activity in anterior and posterior hippocampal regions and DMN regions including; medial PFC, posterior cingulate/retrosplenial cortex, bilateral lateral parietal and bilateral parahippocampal gyrus in a sample of 132. Functional connectivity between the posterior hippocampus and the posterior cingulate/retrosplenial cortex was significantly greater in both heterozygotes and Met homozygotes when compared to Val homozygotes.

In a sample of 15, Dang *et al.* (2013) used a posterior cingulate cortex seed to define the DMN which included; medial PFC, posterior cingulate, lateral parietal, and left superior temporal cortices. Heterozygotes were found to have greater functional connectivity of the medial PFC with the rest of the DMN, than either Val homozygotes or Met homozygotes. Also defining the DMN with a posterior cingulate cortex seed, Jang *et al.* (2012) demonstrated Val homozygotes to have stronger DMN connectivity in the left medial frontal gyrus, bilateral superior frontal gyri, and cerebellum compared to Met carriers in a sample of 23. Finally, in a sample of 57, Liu *et al.* (2010) analysed differences in functional connectivity between 13 ROIs of the DMN between two groups; Val homozygotes and heterozygotes. Overall, heterozygotes had greater mean connectivity of the DMN compared to Val homozygotes and greater degrees of connectivity in the ventromedial PFC, anterior medial PFC, and left superior frontal cortex. Increased connectivities in heterozygotes were predominately between the prefrontal regions and posterior cingulate cortex/retrosplenial and found both within the prefrontal lobules, and between the prefrontal lobules and other areas. Conversely, Val homozygotes exhibited increased connectivity compared to heterozygotes between the left inferior temporal cortex and bilateral parahippocampal gyrus, and the left lateral parietal cortex and the cerebellar tonsils (Liu *et al.*, 2010).

The heterogeneity of these four studies precludes drawing conclusions regarding COMT rs4680 influence on functional connectivity of the DMN. For example, increased connectivity between the left lateral parietal cortex and the cerebellar tonsils in Val homozygotes (Liu *et al.*, 2010) suggests some consistency with increased DMN connectivity in the cerebellum found by Jang *et al.* (2012), however these groups compared Val homozygotes with heterozygotes and Val

homozygotes with Met homozygotes, respectively. Further, it is not clear whether Dang and colleagues (2013) had participants with eyes open or closed in their notably small sample of 15. In a large sample of 132, Damoiseaux *et al.* (2016) had participants with eyes-open and found increased connectivity in heterozygotes and Met homozygotes compared to Val homozygotes, however, used hippocampal seeds rather than posterior cingulate cortex seeds. Whilst, Jang *et al.* (2012) found Val homozygotes to have the strongest DMN connectivity in multiple areas with participant's eyes closed.

Other resting-state networks

More recently, studies have investigated neural networks involved in specific functions such as attention, task control, and sensorimotor processes during resting-state (Smith *et al.*, 2009; Power *et al.*, 2011). Tunbridge *et al.* (2013) investigated the effect of COMT rs4680 on the executive control network at rest in 55 individuals. The executive control network was identified with independent component analysis and included bilateral frontal regions (anterior cingulate cortex, anterior insula, frontal pole, inferior and middle frontal gyri), caudate head, areas of the middle temporal gyrus and superior parietal lobule. Comparisons were made between homozygote groups, with Val homozygotes showing greater functional connectivity between the ventrolateral PFC (left insula and inferior frontal gyrus) and the rest of the executive control network.

Using functional connectivity density mapping to identify connectivity hubs (Tomasi & Volkow, 2010; 2011), Tian *et al.* (2013) investigated three ROIs within resting-state networks, including: primary visual cortex in visual network, posterior cingulate cortex in DMN, and right anterior insula in salience network. In the sample of 258 there was no main effect of COMT rs4680 on functional connectivity density for any of these ROIs, however, there were interaction effects with dopamine D_2 receptor genotype. Looking at 11 resting-state networks identified with independent components analysis, Zhao *et al.* (2015) found that compared to Met carriers, Val homozygotes had greater intra-network connectivity in the right dorsolateral PFC of the right dorsal attention network, and the right dorsolateral PFC of the right frontoparietal network in their sample of 250. Using a dorsal anterior cingulate

cortex seed region, Xu *et al.* (2016) defined the salience network and found no significant main effect of COMT in a sample of 280, consistent with no COMT rs4680 effect on functional connectivity density of the salience network found by Tian *et al.* (2013).

More recently, Elton *et al.* (2017) looked resting-state functional connectivity in 13 large scale functional networks comprising 264 coordinates in 86 individuals. This study differed from most other included studies because a fixation cross was used rather than eyes closed. There was no main effect of COMT rs4680 on strength of functional connectivity, however, there were numerous COMT rs4680 differences in functional connectivity when split by gender. This could be due to the age of the sample (18-40 years) as it has been suggested that COMT rs4680 does not affect cognitive function in females prior to menopause, possibly due to high estrogen (Papaleo *et al.*, 2015). Males and females exhibited opposing results for which allele was associated with increased or decreased functional connectivity between the 13 resting-state networks, resulting in a U-shaped pattern. Greater positive functional connectivity correlated with stronger U-shaped COMT by sex effect, and similarly negative functional connectivity was correlated with an inverted-U pattern of COMT by sex effect.

Figure 3. here

Figure 4. here

Task-based studies

Various methods were used to investigate functional connectivity during the tasks-based studies, including; BOLD time-course correlation, psychophysiological interaction analysis, dynamic causal modelling, structural equation modelling, and cluster granger analysis. Each method has strengths and weaknesses and investigates a distinct connectivity context (O'Reilly *et al.*, 2012), hence comparison of results across differing analysis methods should engender caution. Further, most of the included studies describe "stronger" or "greater" connectivity or coupling and only two reported whether the relationship between regions was positive or negative. A summary of overall findings by sample size and task type is provided in Figure 5.

Figure 5. here

Emotion processing

To date, four studies have used fMRI to investigate how COMT rs4680 affects functional connectivity during tasks with an emotion processing component. Drabant *et al.* (2006) investigated effective connectivity of 44 individuals during a corticolimbic reactivity task, involving the matching of fearful and angry facial expressions. Functional connectivity between three reference regions (bilateral hippocampus, right ventrolateral PFC, and right amygdala), and all other regions activated by the task was compared between two COMT rs4680 homozygote groups. Met homozygotes had greater coupling between; the ventrolateral PFC reference region and the parahippocampal gyrus and bilateral fusiform gyrus; the bilateral hippocampus reference region and the ventrolateral PFC and orbitofrontal cortex; the right amygdala reference region and the bilateral orbitofrontal cortex and ventrolateral PFC. There were no other significant findings, including no significant findings for Val/Val > Met/Met contrasts.

Rasch *et al.* (2010) also used affective stimuli including emotionally positive, neutral and negatively valanced pictures in a sample of 56. Using psychophysiological interaction analysis (Friston *et al.*, 1997), functional connectivity during negative/unpleasant versus neutral conditions was investigated with a right amygdala seed region. Similar to Drabant *et al.* (2006), the Met allele was associated with greater connectivity from the right amygdala to the right orbitofrontal cortex, and this was demonstrated in a dose dependent manner with the inclusion of a heterozygous group. Connectivity from the right amygdala to multiple regions in the left hemisphere also increased with the number of Met alleles, including middle temporal gyrus, caudate tail, posterior cingulate cortex, and right cerebellum.

In a sample of 91, Surguladze *et al.* (2012) used dynamic displays of facial emotion including; fear, anger, sadness and happiness to investigate emotion processing. The emotion processing circuit identified included; bilateral fusiform/inferior occipital regions, right superior temporal gyrus/superior temporal sulcus, bilateral inferior/middle PFC and the right amygdala. Strength of effective

connectivity was compared between COMT heterozygotes and homozygote groups using a "total degree" measure; defined as the total number of significant Granger-causalities (Granger, 1969; Sato *et al.*, 2010) between regions of interest within the emotion-processing circuit. Contrasting with the previous two studies, total effective connectivity during the "fearful" condition increased with the number of Val alleles. The authors suggest this contradictory finding may be due to differences in the precise location of PFC regions identified in the emotion processing circuit compared to the two prior studies.

Utilising an appetitive conditioning paradigm, which probed both emotion and reward processing, Klucken *et al.* (2015) investigated effective connectivity, using psychophysiological interaction analysis with amygdala and midbrain as seed regions in a sample of 80. Similar to the studies by Drabant *et al.* (2006) and Rasch *et al.* (2010); Met homozygotes exhibited increased coupling with the amygdala compared to Val homozygotes, this time with the ventromedial PFC. There were no group differences with the midbrain seed region. The authors suggest the greater coupling between the amygdala and ventromedial PFC in Met homozygotes may reflect an inhibitory effect of the ventromedial PFC on the amygdala, however whether the connectivity was positive or negative was unclear. Regions that showed increased connectivity with the Met allele during emotion processing contrast with similar regions that had increased connectivity with the Val allele during resting-state (Gao *et al.*, 2016; Meyer *et al.*, 2016). A schematic representation of this is shown in Figure 3.B.

Memory

A role for COMT rs4680 has been demonstrated in studies using memory paradigms such as declarative memory and working memory, with the Met allele often associated with better performance (e.g. de Frias *et al.*, 2004; Bruder *et al.*, 2005). The following three studies looked at the role of COMT rs4680 in functional connectivity during episodic, recognition, and associative memory processes. Using an episodic memory paradigm, Schott *et al.* (2006) looked specifically at successful memory encoding in 49 individuals. Psychophysiological interaction analysis revealed stronger coupling in Met homozygotes compared to Val homozygotes

between seed regions in the left hippocampus and bilateral PFC; heterozygotes exhibited intermediate connectivity. Despite no effect of COMT on memory performance in this study, authors suggested that the greater coupling facilitates information transfer between the PFC and hippocampus (Schott *et al.*, 2006).

Bertolino *et al.* (2006) studied coupling between the hippocampal formation and ventrolateral PFC during a recognition memory task in 27 individuals. During retrieval, strength of connectivity between the hippocampal formation and ventrolateral PFC increased with the number of Val alleles. Consistent with prior studies looking at COMT rs4680 in memory processes; increased behavioural accuracy (which correlated with reduced connectivity) was found in Met carriers. Conversely, Schott *et al.* (2006) found no COMT rs4680 association with task performance. Further differing from Schott et al., Bertolino and colleagues found a negative relationship between task related activation of the hippocampal formation and ventrolateral PFC associated with the Met allele, possibly related to task paradigm differences and contributing to divergent findings.

Dennis *et al.* (2010) investigated functional connectivity during a relational memory task, which involved face-scene pairings using medial temporal lobe seed regions in 22 individuals. There was no difference in memory performance found between homozygote groups. Met homozygotes had stronger connectivity than Val homozygotes between the medial temporal lobe and PFC regions: During successful encoding these PFC regions included; right orbitofrontal cortex, right dorsolateral PFC, and left ventromedial PFC, somewhat consistent with Schott *et al.* (2006) described above. During successful retrieval PFC regions included; right dorsomedial PFC, right anterior cingulate cortex, and right superior PFC. Within the medial temporal lobe, however, Val homozygotes exhibited greater connectivity. Despite no performance difference they suggest that the COMT rs4680 genotype differentially influences the neural processes involved in the behavioural outcome (Dennis *et al.*, 2010).

Working memory

The influence of COMT rs4680 on connectivity during working memory has been assessed by three studies using differing analysis methods and regions of

interest. In a sample of 75 undertaking a low-load working memory task, Sambataro *et al.* (2009) used independent components analysis and identified three components: (1) A prefrontal-parietal component, predominately in the left hemisphere, within which connectivity of the left dorsolateral PFC with the rest of the network increased with the number of Val alleles, whilst Met homozygotes showed greatest connectivity of the left ventrolateral PFC; (2) A medial frontal cortex component, within which Met homozygotes exhibited the greatest connectivity in the frontopolar cortex and Val homozygotes exhibiting the greatest connectivity in the medial superior frontal gyrus; (3) A superior parietal cortex component, within which Val homozygotes exhibited the greatest connectivity in the left inferior parietal lobule. Notably, this study found that within one task-activated component, increased connectivity was associated with both alleles but in different regions.

In 46 individuals undertaking a task requiring maintenance and/or manipulation of numbers, Tan *et al.* (2012) investigated effective connectivity using dynamic causal modelling which allows estimation of strength and direction (Friston *et al.*, 2003). Regions of interest were voxels that were robustly engaged during the task and included; dorsolateral PFC, parietal and subcortical regions (thalamus during maintenance, and striatum during manipulation). Connection from dorsolateral PFC to parietal cortex during maintenance exhibited stronger excitatory effective connectivity in Met carriers compared to Val homozygotes, contrasting with decreased connectivity in Met carriers in similar regions found by (Sambataro *et al.*, 2009). Met carriers also had stronger inhibitory effective connectivity from the dorsolateral PFC to striatum at manipulation phase compared to Val homozygotes.

Finally, in 28 individuals undertaking a visual-spatial working memory task, Kondo *et al.* (2015) investigated effective connectivity between regions defined using structural equation modelling. The resulting ROIs included; medial frontal gyrus, inferior frontal gyrus, anterior cingulate cortex, and right inferior parietal lobule. Met carriers had greater effective connectivity from the anterior cingulate cortex to the medial frontal gyrus compared to Val homozygotes during encoding, which was positively correlated with recognition accuracy.

Reward-based tasks

COMT rs4680 has previously been associated with reward processing and reward-related learning through modulation of both cortical and striatal activation (Tunbridge *et al.*, 2012). Four studies were found that included reward processing in their task paradigm. In a sample of 44, Schmack *et al.* (2008) activated reward areas of the brain using a monetary incentive delay task and investigated effective connectivity using psychophysiological interaction analysis. Seed regions were those that exhibited a task-based effect of rs4680 and included the right temporal pole and ventral striatum and connectivity between these regions in both directions was analysed. No significant effect of COMT rs4680 during loss anticipation, gain anticipation or task performance was found. Krugel *et al.* (2009) used psychophysiological interaction analysis to assess coupling between PFC and left ventral striatal seed regions during flexible reward-based learning in 26 individuals. The task involved learning to make the most profitable choice among four options. Greater change in connectivity between the PFC and striatum, depending on learning rate, was found for Val homozygotes compared to Met homozygotes. Val homozygotes also outperformed Met homozygotes suggesting this was due to a PFC mediated striatal response. The association between greater coupling and high dynamic learning rate supported an advantage of the Val allele in rapidly and flexibly adapting to changing contingencies.

Investigating appetitive conditioning, which included an emotion and reward-based learning component, Klucken *et al.* (2015) found increased coupling of the amygdala and ventromedial PFC in Met homozygotes compared to Val homozygotes in 80 individuals. The authors suggest that increased connectivity from the amygdala to the ventromedial PFC may indicate inhibited learning during the conditioning paradigm in Met homozygotes. This explanation is consistent with the hypothesised advantage of the Val allele for flexibility in integration of relevant information; between right amygdala and orbitofrontal cortex in an emotion processing context (Drabant *et al.*, 2006; Rasch *et al.*, 2010) and between PFC and striatum in reward-based learning (Krugel *et al.*, 2009).

In a different type of investigation, Elton *et al.* (2017) looked at functional connectivity flexibility in 86 individuals. Functional connectivity flexibility was defined as the extent of reorganisation between states and calculated as the Euclidean distance between each pair of correlation matrices. A delay discounting task was

used, requiring the choice between smaller-immediate or larger-delayed rewards. Correlation matrices included the four tasks decision types (want, don't want, sooner, later) and resting-state. Met homozygotes exhibited greater connectivity flexibility in three of the 13 functional networks identified, independent of gender, including; fronto-parietal task control, lateral sensorimotor and medial sensorimotor networks. COMT genotype by sex interaction effects were found for numerous other networks.

Executive function tasks

PFC dependent tasks probing executive functions have previously demonstrated an effect of COMT rs4680 on neural activation and performance (e.g. Egan *et al.*, 2001; Malhotra *et al.*, 2002). Two studies were found that investigated the influence of COMT rs4680 on connectivity during executive function tasks. Prata *et al.* (2009) investigated a verbal fluency task requiring participants to generate a word that starts with a presented letter. The seed region was the area of peak activation; the right frontal operculum/anterior insula. Findings failed to survive correction for multiple comparisons and no task performance differences were found in the sample of 48.

Using a Stroop paradigm in a sample of 45, Jaspar *et al.* (2016) investigated functional connectivity during response inhibition; a critical component of executive function. Similar to Prata *et al.* (2009), a seed region in the right inferior frontal operculum was used. Val carriers had greater positive functional connectivity from the right inferior frontal operculum to both the right cingulate gyrus and right superior temporal gyrus, compared to Met homozygotes. Also reported was a greater positive association of activity in the inferior frontal operculum and the right superior frontal gyrus, left mid-cingulate gyrus, left medial temporal gyrus/superior temporal gyrus, and negative connectivity with the left lingual gyrus in Val homozygotes compared to Met carriers. These regions have previously been implicated in the Stoop paradigm (Laird *et al.*, 2005; Polk *et al.*, 2008). Further, task performance was better in Met homozygotes compared to Val carriers, the authors suggesting this indicated less susceptibility to interference.

Figure 6. here

Table 1. here

Discussion

Summary

Due to the heterogeneity of the literature, no definitive conclusions can be drawn regarding the influence of COMT SNP rs4680 on functional connectivity, however some trends have emerged. Overall, this review suggests an association between the Val allele and increased functional connectivity during resting-state. Trends within the literature also suggest an advantage of the Val allele in cognitive flexibility; allowing integration of dynamically changing contingencies. Conversely, the Met allele tends to be associated with increased connectivity during emotion processing, and potentially other tasks including memory and working memory, between limbic regions (predominately hippocampus and amygdala) and PFC. This suggests a potential advantage of the Met allele in sustained processing and attention.

PFC

There was a tendency towards increased resting-state connectivity with the Val allele (Figure 4), however, within PFC whole-brain resting-state functional connectivity analysis has produced some inconsistent findings (see Figure 3.A). For example, using ventromedial PFC seeds one study found Val homozygotes to have increased connectivity with the dorsomedial PFC compared to Met carriers (Gao *et al.*, 2016), and another study found heterozygotes to have increased connectivity with the anterior medial PFC compared to Val homozygotes (Liu *et al.*, 2010). Notably the study that found increased connectivity with heterozygotes did not include Met homozygotes in analyses thereby reducing power. Favaro *et al.* (2013) found no difference in connectivity between dorsolateral PFC, ventrolateral PFC, and ventromedial PFC in young-adult females, although this is unsurprising if the effect of COMT rs4680 is only present in post-menopausal females and males as reported by Papaleo *et al.* (2015). Whole-brain analysis has also shown the right inferior frontal gyrus to have greater connectivity in Val homozygotes with seeds

from the subgenual anterior cingulate cortex (Baeken *et al.*, 2014) and orbitofrontal cortex (Gao *et al.*, 2016).

The influence of COMT rs4680 on the degree of connectedness of nodes within the PFC is unclear. This has been measured with various centrality analyses yielding mixed results; Val homozygotes have shown greater eigenvector centrality of the dorsomedial PFC compared to Met carriers (Markett *et al.*, 2016), while heterozygotes have shown increased degree centrality of the ventromedial PFC, anterior medial PFC, and left superior frontal cortex compared to Val homozygotes (Liu *et al.*, 2010). The only EEG study in this literature supported PFC as the primary region of COMT rs4680 effect; the analysis found multiple connection-frequency pairs (delta-theta) in the frontal areas, demonstrating dose-dependent increased connectivity with the Val allele, these extended to the left temporal and left parietal areas (Lee *et al.*, 2011).

With analysis restricted to the DMN, the medial PFC has shown greater connectivity in heterozygotes with the rest of the DMN, although in a small sample of 15 (Dang *et al.*, 2013) and in a larger sample ($N = 132$) Damoiseaux *et al.* (2016) found no effect of COMT rs4680 on connectivity between medial PFC and hippocampus. Again in a small sample ($N = 23$), DMN connectivity was greater in Val homozygotes in the left medial frontal gyrus, and bilateral superior frontal gyrus (Jang *et al.*, 2012), but in a larger sample ($N = 57$), Liu *et al.* (2010) found increased connectivity in heterozygotes between frontal regions and the posterior cingulate cortex compared to Val homozygotes.

Connectivity during emotion processing most commonly demonstrated increases with the Met allele between PFC regions (including; ventrolateral PFC, orbitofrontal cortex, and ventromedial PFC) and both amygdala and hippocampal regions (Drabant *et al.*, 2006; Rasch *et al.*, 2010; Klucken *et al.*, 2015). Although one study found that overall total effective connectivity of the emotion processing circuit increased with the number of Val alleles (Surguladze *et al.*, 2012). During memory tasks, connectivity findings between PFC regions and the hippocampus have been inconsistent, although three studies found group differences, which allele confers increased or decreased connectivity is not clear. These conflicting findings seemed to depend whether task performance differed. For example, during both

encoding and retrieval, the Met allele was associated with reduced connectivity and increased task accuracy (Bertolino *et al.*, 2006), and increased connectivity and no task-performance difference (Schott *et al.*, 2006; Dennis *et al.*, 2010).

Comparability of functional connectivity findings during working memory tasks may also be confounded by task performance. PFC to parietal connectivity was found to increase with the number of Val alleles (Sambataro *et al.*, 2009), exhibit stronger excitatory connectivity in Met carriers (Tan *et al.*, 2012), and not differ in the only study reporting an effect of COMT rs4680 on task-performance (Kondo *et al.*, 2015). During reward-based tasks, PFC exhibited greater change in connectivity with the left ventral striatum associated with increased learning rate in Val homozygotes (Krugel *et al.*, 2009), and greater connectivity between ventromedial PFC and amygdala in Met homozygotes (Klucken *et al.*, 2015). The reward-based studies used heterogeneous task-paradigms such that an overall conclusion cannot be drawn, e.g. Met homozygotes had greater connectivity in a task with an emotion processing component (Klucken *et al.*, 2015), whilst Val homozygotes exhibited higher dynamic learning rate (Krugel *et al.*, 2009).

Overall, current evidence points to an association between the Val allele and greater resting-state connectivity of PFC regions, particularly medial (Jang *et al.*, 2012; Gao *et al.*, 2016; Markett *et al.*, 2016) and lateral PFC regions (Meyer *et al.*, 2016), however with some contradiction (Liu *et al.*, 2010). In contrast, PFC connectivity during emotion processing tasks shows an association between the Met allele and increased connectivity with limbic regions (Drabant *et al.*, 2006; Rasch *et al.*, 2010; Klucken *et al.*, 2015), also during memory tasks where task-performance did not differ (Schott *et al.*, 2006; Dennis *et al.*, 2010). Other task performance findings cannot be compared due to heterogeneity of task paradigms and performance differences which appear to confound connectivity findings (see Figure 6).

Anterior and Posterior Cingulate Cortex

Resting-state connectivity analysis identified regions of the anterior cingulate cortex with increased connectivities associated with the Val allele, including the subgenual anterior cingulate cortex (Baeken *et al.*, 2014) and dorsal anterior

cingulate cortex (Gao *et al.*, 2016), although Baeken *et al.* (2014) also reported an increased connectivity in Met carriers between the subgenual anterior cingulate cortex and the left medial frontal gyrus in their young adult female only sample. Task-based findings showed some consistency; during successful memory retrieval, Met homozygotes had increased connectivity between medial temporal lobe and right anterior cingulate cortex (Dennis *et al.*, 2010). Similarly, a working memory task showed greater connectivity between dorsal anterior cingulate cortex and medial frontal gyrus in Met carriers during encoding (Kondo *et al.*, 2015). Regarding the posterior cingulate cortex; during resting-state, connectivity with anterior medial PFC (Liu *et al.*, 2010) and posterior hippocampus (Damoiseaux *et al.*, 2016) was increased in heterozygotes and Met carriers, respectively. Similarly during emotion processing, connectivity between the right amygdala and left posterior cingulate cortex increased with Met alleles (Rasch *et al.*, 2010), suggesting connectivity of the posterior cingulate cortex may increase with the presence of the Met allele during both task and resting-state.

Limbic regions

Functional connectivity of the right amygdala with the orbitofrontal cortex was greater in Val homozygotes during resting-state (Gao *et al.*, 2016) and greater in Met carriers during emotion processing (Drabant *et al.*, 2006; Rasch *et al.*, 2010). Similarly, Met homozygotes had greater connectivity between the right amygdala and ventromedial PFC during appetitive conditioning (Klucken *et al.*, 2015). Resting-state centrality analyses have been inconsistent in limbic regions and shown left lateralised COMT rs4680 effects; Met carriers exhibited increased degree centrality of the left amygdala and left hippocampus (Wang *et al.*, 2018) and Val homozygotes showed greater eigenvector centrality than Met carriers in the left hippocampal cortex (Zhang *et al.*, 2015), although it should be noted these methods differ and eigenvector centrality weights connections where degree centrality does not.

During resting-state, hippocampal regions have shown greater connectivity with the anterior medial PFC in Val carriers (Meyer *et al.*, 2016) and during emotion processing; greater connectivity with ventrolateral PFC in Met homozygotes

(Drabant *et al.*, 2006). During memory tasks, findings are inconsistent; the Met allele was associated with increased connectivity of hippocampal regions in the absence of task-performance differences (Schott *et al.*, 2006; Dennis *et al.*, 2010), and when the Met allele was associated with increased memory retrieval accuracy this group exhibited decreased connectivity (Bertolino *et al.*, 2006). Overall, greater inter-regional connectivity of limbic regions tended to be associated with the Val allele during resting-state (Gao *et al.*, 2016; Meyer *et al.*, 2016), and the Met allele during task performance (Drabant *et al.*, 2006; Rasch *et al.*, 2010; Klucken *et al.*, 2015), see Figure 3.B.

Temporal and parietal cortices

Resting-state studies have primarily demonstrated the Val allele to have increased functional connectivity between PFC and temporal regions. Regions included; between ventromedial PFC and inferior and superior temporal gyri (Gao *et al.*, 2016), and EEG resting-state connectivity between left PFC regions and both the left temporal and left parietal cortices, including one connection-frequency pair between the temporal and parietal areas (Lee *et al.*, 2011). However, one study found increased connectivity in heterozygotes from the ventromedial PFC to the right inferior temporal cortex (Liu *et al.*, 2010). Val homozygotes have demonstrated greater eigenvector centrality within the inferior parietal lobule and medial temporal gyrus (Markett *et al.*, 2016).

During a low-load working memory task, Sambataro *et al.* (2010) found increased connectivity of the left inferior parietal lobule with a superior parietal cortex component in Val homozygotes. Conversely, also during a working-memory task although with greater maintenance requirement, excitatory connectivity from dorsolateral PFC to parietal cortex during maintenance was stronger in Met carriers (Tan *et al.*, 2012). Overall, a trend towards increased connectivity in temporal and parietal cortices with the Val allele during resting-state seems to be emerging (Lee *et al.*, 2011; Gao *et al.*, 2016; Markett *et al.*, 2016), although the converse has been found (Liu *et al.*, 2010). Findings appear to support those in other brain regions, tending towards greater resting-state connectivity with the Val allele, and greater task-based connectivity with the Met allele.

Cognitive flexibility versus targeted and sustained signalling

One interpretation of the current findings is that the effect of COMT rs4680 on functional connectivity is nuanced, dynamic and specific to inter-regional circuits. Indeed, global functional connectivity density results of three studies have shown no difference with COMT rs4680 during resting-state (Tian *et al.*, 2013; Li *et al.*, 2016; Gong *et al.*, 2017), suggesting a global measure is insufficient. The trend towards greater resting-state functional connectivity with the Val allele, and greater task-based connectivity with the Met allele could support a role for COMT rs4680 in cognitive flexibility, with the Met allele being advantageous for targeted and sustained signalling, improving task-performance. This would be consistent with past report of the Met allele conferring greater cognitive control and attention (Bilder *et al.*, 2004). It has previously been suggested that the Val allele is associated with cognitive inefficiency, whereby greater neural activation is required to produce a task-specific signal. (Egan *et al.*, 2001; Mier *et al.*, 2010). This need for greater task-specific signal with the Val allele combined with the current review's suggestion that the Val allele is associated with greater resting-state connectivity suggests that further exploration of COMT genotype influence utilising dynamic functional connectivity methods may be useful (see Hutchison *et al.*, 2013).

During emotion processing, greater overall connectivity was associated with the Val allele (Surguladze *et al.*, 2012), contrasting with consistent findings of increased connectivity with the Met allele between limbic regions and PFC regions (Drabant *et al.*, 2006; Rasch *et al.*, 2010; Klucken *et al.*, 2015). One interpretation is that the Val allele may produce a more dynamically connected emotion processing circuitry, the greater number of active connections perhaps facilitating integration of novel relevant stimuli. Conversely, the Met allele appears to allow more targeted processing. Connectivity between the amygdala and orbitofrontal cortex during resting-state was reduced in Met carriers and associated with susceptibility to negative-framing effect, indicating reduced ability to regulate emotion to cognitively reappraise (Miu & Crișan, 2011; Gao *et al.*, 2016). During emotion processing, greater connectivity in Met carriers between the right amygdala and orbitofrontal cortex was correlated with lower scores on a novelty seeking measure suggesting

temperamental rigidity and regimentation (Cloninger *et al.*, 1993; Drabant *et al.*, 2006), and in the study by Rasch *et al.* (2010) was correlated with less perceived difference between negative and neutral pictures. Together, these findings support a role for the Met allele in greater rigidity and inflexibility in integration of affectively relevant information in this circuit (Bilder *et al.*, 2004; Smolka *et al.*, 2005).

In a study that investigated connectivity flexibility by quantifying the degree of network reorganisation between cognitive states (resting-state and four task decision types), the Met allele exhibited greater network reorganisation (Elton *et al.*, 2017). While not precluding other interpretations, this could support an association of the Met allele with more targeted processing due to the increased requirement for reorganisation of network connectivity between states. Together, results of this review lend support to theories of increased task-specific signalling and less "noise" with the Met allele due to greater task-based connectivity, and increased resting-state connectivity and hence potentially cognitive flexibility with the Val allele (Bilder *et al.*, 2004).

The Val allele

Overall, the Val allele was more often associated with greater resting-state functional connectivity compared to the Met allele (see Figure 4). Regions of greater connectivity were predominately within PFC, but also included areas such as; parietal and temporal regions, amygdala, hippocampus, caudate, cuneus, and cerebellum. Instances where the Val allele was associated with lower resting-state connectivity were few and these conflicting findings emerged when analysis was restricted to the DMN (Liu *et al.*, 2010; Damoiseaux *et al.*, 2016) or utilised connectivity centrality analyses (Liu *et al.*, 2010; Markett *et al.*, 2016; Wang *et al.*, 2018). Conversely, during task-based studies it was relatively rare for the Val allele to be associated with increased connectivity compared to the Met allele, except when task performance differences potentially compromised comparability (Bertolino *et al.*, 2006; Krugel *et al.*, 2009; Jaspar *et al.*, 2016).

The Met allele

During resting-state, instances where the Met allele exhibited increased connectivity were less common than with the Val allele, and generally comprised centrality measures and analyses involving the DMN (see Figure 4). Findings for the DMN were complicated by two out of four included studies having participants with eyes open. Additionally, one DMN region; the posterior cingulate cortex, has shown increased connectivity in Met carriers during both resting-state (Liu *et al.*, 2010; Damoiseaux *et al.*, 2016) and task-based studies (Rasch *et al.*, 2010) possibly contributing to heterogenous findings when analyses is restricted to this network. Regarding task-based findings (see Figure 6), the most consistent data presented in this review was the association of greater connectivity with the Met allele during emotion processing between limbic (amygdala and hippocampus) and PFC regions (Drabant *et al.*, 2006; Rasch *et al.*, 2010; Klucken *et al.*, 2015). Connectivity between limbic regions and PFC was also stronger with the Met allele during memory-task studies, when performance differences were not present (Schott *et al.*, 2006; Dennis *et al.*, 2010).

Limitations and future directions

Of the included studies there were no direct replications: studies used different seed-regions with different rationale, different networks and methods for defining networks, heterogeneous task-paradigms, and various analyses probing differing connectivity characteristics. This heterogeneity compromises comparability, for example, differing regions across studies such as the precise location within regions such as PFC and hippocampus can impact connectivity results (Pezawas *et al.*, 2005; Sambataro *et al.*, 2009). Additionally, two resting-state studies had participants with eyes open (Damoiseaux *et al.*, 2016; Elton *et al.*, 2017) and one had participants "relax and think of nothing in particular" and did not report eyes open or closed (Dang *et al.*, 2013). This complicates comparison with eyes-closed studies as differences in reliability and consistency in resting-state networks across conditions of eyes open, closed, or fixated have been reported (e.g. Patriat *et al.*, 2013; Wang *et al.*, 2015b). This heterogeneity across the studies included in this review, and small numbers within each category of analysis type or task, prevented

quantitative analysis. Hence this review is only able to provide a qualitative overview and comment on trends apparent in the literature to date.

Lack of replication is not a unique issue and is a problem across neuroimaging literature driven by underpowered studies, differing methods, analysis, and task-paradigms (Poldrack *et al.*, 2017). Indeed, many of the included studies (5 resting-state and 9 task-based) were underpowered with samples less than the recommended minimum 20 per cell (Simmons *et al.*, 2011). Based on past literature, it was shown that a single group sample of 28.5 was required for an fMRI study to have 80% power to detect an effect of ~ 0.75 or larger (Poldrack *et al.*, 2017). Specifically in imaging genetics, small sample sizes are highly prone to type I and type II errors. Carter *et al.* (2017) suggest that with unknown effect sizes and limitations in collecting large imaging samples, independent replication of imaging genetics studies is required before conclusions can be drawn. The movement towards open-data sharing initiatives such as The Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) consortium (http://enigma.ini.usc.edu/), may help overcome some of these difficulties, allowing replication studies with much larger datasets, improving integrity, consistency and reproducibility. Further, single SNP association studies are potentially confounded by genotype at other SNPs, for example, studies have shown that when rs4680 is combined in a hapblock with another functional COMT SNP (rs4818), the effect on COMT expression is increased, and rs4818 may account for greater functional variation than rs4680 (Nackley *et al.*, 2006; Roussos *et al.*, 2008)

Although possible associations were drawn from this literature, it is notable that the six studies with the largest sample sizes (over 200) were from the same participant group. Further, it is important to note that whilst significant findings are discussed, seven out of 20 resting-state studies reported null findings (35%). Four of these seven studies were from large samples and despite these samples comprising the same participants, these null findings raise the possibility that smaller underpowered studies are reporting type I error. Sample characteristics may also influence findings of the included studies. Gender has shown an effect with COMT rs4680 (Elton *et al.*, 2017), one study showing that COMT rs4680 influenced cognition in males but only in females post-menopause (Papaleo *et al.*, 2015). This review included two resting-state studies with young-adult female-only samples, one

of which found no effect of COMT rs4680 (Baeken *et al.*, 2014), and one which found significant differences but was likely underpowered with three unequal groups totalling 30 (Favaro *et al.*, 2013).

Another possible confound in comparing studies in this review is sample ethnicity. Asian and Caucasian samples are known to differ in their COMT rs4680 distribution (Palmatier *et al.*, 1999; DeMille *et al.*, 2002) and all included studies with Asian samples combined heterozygotes with Met homozygotes to equalise group sizes. Notably, only seven included studies had group/cell sizes greater than 100 and these studies all utilised Chinese samples combining heterozygotes with Met homozygotes, four finding no main effect of COMT rs4680. Additional potential confounds when generalising COMT rs4680 effect on connectivity between Chinese and Caucasian samples are noted in *"*Study quality and risk of bias*"*.

Finally, given that fMRI is an indirect measure of neural activity, investigation of the influence of COMT rs4680 on functional connectivity, which appears to be dynamic and nuanced, would benefit from converging evidence from EEG and/or MEG. These methods allow millisecond temporal resolution and provide information on the contribution of distinct frequencies in functional connectivity, allowing transient synchronisation of neuronal systems to be observed (Uhlhaas *et al.*, 2017). Taking advantage of neural frequency data by utilising EEG/MEG may help clarify the current contradictory findings of inter-regional connectivity versus connectivity centrality measures.

6. Conclusions

The heterogeneity of the current literature prevents conclusions being drawn and replication of findings is necessary, however, trends have emerged. The influence of the COMT gene on cognitive flexibility versus targeted and sustained signalling appears to be a promising avenue for future investigation. COMT genotype appears to differentially influence strength of connectivity during resting-state and task-based contexts, hence, studies investigating both resting-state and task paradigms will help clarify the influence of COMT genotype on brain function and cognition. Further, the inclusion of additional SNPs of the COMT gene, such as rs4818, which has been shown to affect cognition, would increase robustness and

reliability of findings. The most consistently implicated brain-regions, during both resting-state and emotion processing, include amygdala and hippocampal regions, coupled with multiple PFC regions including, orbitofrontal cortex, ventromedial PFC, ventrolateral PFC, dorsolateral PFC, anterior medial PFC.

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Author contributions:

KM and SLR prepared the research question and search protocol, KM and SG conducted searches and screened articles independently. KM prepared the initial manuscript and all authors including SG, WW, BD, and SLR revised and contributed to the final manuscript.

Appendix A: Supplementary material

List of abbreviations:

COMT	catechol-*O*-methyltransferase
SNP	single nucleotide polymorphism
Val	valine
Met	methionine
MB-COMT	membrane bound catechol-*O*-methyltransferase

S-COMT	soluble catechol-*O*-methyltransferase
PFC	prefrontal cortex
CHRM1	cortical muscarinic M1 receptor
ROI	region of interest
DMN	default mode network

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Figure Captions

Figure 1. PRISMA flow chart

Figure 2. Overall sample sizes of studies with finding of greater connectivity for the COMT genotypes, including: VV & Val carriers (Val homozygotes and heterozygotes compared to Met carriers and Met homozygotes, respectively; n = 16), MM & Met carriers (Met homozygotes and heterozygote compared to Val carriers and Val homozygotes respectively, n = 15), VM (heterozygotes compared to homozygotes), and Not sig. (studies that found no significant effect).

Figure 3. A: Functional connectivity within the PFC during resting state; blue = V/V greater than Met carriers (Baeken et al., 2014; Gao et al., 2016; Meyer et al., 2016), red = V/V lower compared to V/M (Liu et al., 2010), green = seeds with no significant connectivity in young females (Favaro et al., 2015). B: Emotion processing and limbic connectivity: Red = Met allele associated with greater functional connectivity during emotion processing task (Drabant et al., 2006; Klucken et al. 2015; Rasch et al., 2010). Blue = Val allele associated with greater resting-state connectivity in similar regions (Gao et al., 2016; Meyer et al., 2016). Regions include; amygdala (Amy), hippocampus (HC), parahippocampal gyrus (PHG), posterior cingulate cortex (PCC), orbitofrontal cortex (OFC), ventrolateral PFC (vlPFC), anterior medial PFC (amPFC).

Figure 4. Overall number of resting-state studies that reported results of greater connectivity for each COMT allele, including those that investigated interregional connectivity and all analyses (including overall connectivity and centrality measures).
Note. Analysis method and comparison group varied by study.

Figure 5. Overall sample sizes of studies with finding of greater connectivity for the COMT genotypes (VV & Val carriers, MM & Met carriers, VM (heterozygotes) and Not sig. (studies that found no significant effect)) across the different task types.

Figure 6. Overall number of task-based studies that reported results of greater connectivity for each COMT allele, separated by task type. TP = task performance (possible confound).
Note. Analysis method and comparison group varied by study.

Resting state					
Authors	**Sample characteristics**	**Genotype groups and distribution**	**Functional connectivity analysis**	**Seed region/s & network**	**Key findings**
Whole brain seed-based analysis					
Liu et al. (2010)	N = 57 Age mean = 24.7 ± 3.6 Gender (M/F): 29/28 Ethnicity/origin: NR, China	V/V = 31 V/M = 26	Modality: fMRI Analysis: rsfMRI, BOLD time-course correlation	Seeds: vmPFC and PCC (part of DMN). Striatal and PVA (outside DMN)	V/M > V/V: vmPFC – amPFC, PCC, retrosplenial, right ITC; PCC – amPFC.
Favaro et al. (2013)	N = 30 Age mean = 25.8 ± 6.7 Gender (M/F): female only Ethnicity/origin: White	Distribution did not differ from larger sample (V/V = 34, V/M = 68, M/M = 38; $\chi^2 = 3.45$, p = 0.18)	Modality: fMRI Analysis: rsfMRI, BOLD time-course correlation	Seeds: dlPFC, vlPFC, and vmPFC: involved in executive function	No significant differences found.
Baeken et al. (2014)	N = 61 Age mean = 21.8 ± 2.5 Gender (M/F): female only Ethnicity/origin: Caucasian	V/V = 14 V/M = 37 M/M = 10	Modality: fMRI Analysis: rsfMRI, BOLD time-course correlation	Seed: sgACC: modulation of emotion behaviour	Val carriers > M/M: sgACC – left PHG; sgACC – right IFG. Met carriers > V/V: sgACC – left MFG.

Wang et al. (2015)	N = 266 Age mean = 22.7 (range: 18-31) Gender (M/F): 120/146 Ethnicity/origin: Chinese Han	V/V = 130 Met carriers = 136	Modality: fMRI Analysis: rsfMRI, BOLD time-course correlation	Seed: Ventral striatum: part of fronto-striatal dopaminergic circuitry	No COMT main effect.
Gao et al. (2016)	N = [a]98 of 111 Age mean = 21.8 ± 1.9 Gender (M/F): 71/40 Ethnicity/origin: Chinese Han	V/V = 47 Met carriers = 51	Modality: fMRI Analysis: rsFC: positive connectivity only	Seeds: OFC, dACC, vmPFC, and bilateral amygdala: involved in the framing effect	V/V > Met carriers: OFC – bilateral amygdala, bilateral dACC, rlOFC, rIFG; dACC - bilateral lOFC, bilateral dlPFC, left cerebellum; vmPFC – right caudate, ITG, cuneus, STG, dmPFC; left amygdala – precuneus; right amygdala – bilateral lOFC, precuneus.
Meyer et al. (2016)	N = 106 Age mean = 24 ± 2.6 Gender (M/F): 49/57 Ethnicity/origin: NR, Austria	V/V = 24 V/M = 59 M/M = 23	Modality: fMRI Analysis: rsfMRI, BOLD time-course correlation	amPFC: intersection of ECN and DMN	V/V > V/M > M/M: amPFC - left vlPFC, left dlPFC, and bilateral PHG.
Whole brain – other analyses					

Lee et al. (2011)	N = 254 Age range = 19-21 Gender (M/F): female only Ethnicity/origin: Chinese	V/V = 136 V/M = 104 M/M = 14	Modality: EEG Analysis: 38 channel pairs across 6 frequency bands.	Whole brain analysis using 38 channel pairs across 6 frequency bands	V/V > V/M > M/M: Delta: F7-T3; F7-C3 Theta: F3-F4; F7–T3, F7–C3, F7–P3, F3–C3, F3–F7, F4–F8.
Zhang et al. (2015)	N = 287 Age mean = 22.7 ± 2.5 Gender (M/F): 132/155 Ethnicity/origin: Chinese Han	V/V = 137 Met carriers = 150	Modality: fMRI Analysis: Eigenvector centrality (EC)	Whole brain	V/V > Met carriers: EC in the left PHG
Markett et al. (2016)	N = [a]99 of 107 Age mean = 22.9 ± 5.3 Gender (M/F): 37/70 Ethnicity/origin: NR, Germany	V/V = 24 V/M = 50 M/M = 25	Modality: fMRI Analysis: Eigenvector centrality (EC)	Whole brain	V/V > Met carriers: EC within the medial temporal and dorsomedial prefrontal subsystems of DMN (angular gyri, IPL, MTG). Met carriers > V/V: EC within the somatomotor network (pre and postcentral gyri and paracentral lobule).

Li, Liu, Xu, Jiang, and Yu (2016)	N = 265 Age mean = 22.8 (range: 18-29) Gender (M/F): 120/145 Ethnicity/origin: Chinese Han	V/V = 129 Met carriers = 136	Modality: fMRI Analysis: gFCD	Whole brain	No COMT main effect.
Gong et al. (2017)	N = 85 (including 50 MDD) Age mean = V/V: 43.1 ± 11.4; Met carriers 42.0 ± 11.6 Gender (M/F): 19/16 Ethnicity/origin: NR, China	V/V = 42 Met carriers = 43	Modality: fMRI Analysis: gFCD	Whole brain	No COMT main effect.
Wang et al. (2018)	N = 56 Age mean = 25.7 ± 6.4 Gender (M/F): 25/31 Ethnicity/origin: Chinese	V/V = 34 Met carriers = 21	Modality: fMRI Analysis: DC	Whole brain	Met carriers > V/V: DC in left hippocampus and left amygdala.
Default mode network					
Liu et al. (2010)	N = 57 Age mean = 24.7 ± 3.6 Gender (M/F): 29/28	V/V = 31 V/M = 26	Modality: fMRI	13 ROIs of DMN	V/M > V/V: Mean connectivity of DMN.

	Ethnicity/origin: NR, China		Analysis: BOLD time-course correlation		Left SFC – amPFC, vmPFC, PCC, left ITC; amPFC – PCC; vmPFC – retrosplenial, right ITC; right ITC – retrosplenial.
Jang et al. (2012)	N = 23 Age mean = V/V: 22.5 ± 3.2; Met carriers 25.0 ± 3.7 Gender (M/F): 15/8 Ethnicity/origin: NR, Korea	V/V = 8 Met carriers = 15	Modality: fMRI Analysis: BOLD time-course correlation	Seed: PCC of DMN, with whole brain	V/V > Met carriers: PCC – left MFG, bilateral SFG, cerebellum.
Dang, O'Neil, and Jagust (2013)	N = 15 Age mean = 25.3 ± 2.8 Gender (M/F): 8/7 Ethnicity/origin: NR, USA	V/V = 6 V/M = 4 M/M = 5	Modality: fMRI Analysis: BOLD time-course correlation	Defined DMN with PCC seed. Functional connectivity between the medial PFC and the whole DMN	V/M > V/V & M/M: Within medial PFC.
Damoiseaux, Viviano, Yuan, and Raz (2016)	N = [a]132 of 167 Age mean = 49.1 ± 18.0 Gender (M/F): 60/107 Ethnicity/origin: NR, USA	V/V = 38 V/M = 68 M/M = 26	Modality: fMRI Analysis: BOLD time-course correlation	Anterior and posterior hippocampal regions and DMN, including 8 ROIs	M/M > V/M > V/V: Posterior hippocampus – PCC/retrosplenial (independent of age).

Other resting state networks					
Tunbridge, Farrell, Harrison, and Mackay (2013)	N = 55 Age mean = V/V: 23.3 ± 3.8; M/M: 23.6 ± 7.1 Gender (M/F): male only Ethnicity/origin: NR, UK	V/V = 27 M/M = 28	Modality: fMRI Analysis: BOLD time-course correlations	ECN identified with ICA	V/V > M/M: vlPFC (left insula and IFG) - ECN.
Tian, Qin, Liu, Jiang, and Yu (2013)	N = 258 Age mean = V/V: 22.9 ± 2.5; Met carriers: 22.7 ± 2.3 Gender (M/F): 141/117 Ethnicity/origin: Chinese Han	V/V = 126 Met carriers = 132	Modality: fMRI Analysis: rsFC, lFCD and gFCD	Whole brain, local and gFCD and rsFC with seed regions: primary visual cortex, PCC, right anterior insula.	No COMT main effect.
Zhao et al. (2015)	N = 250 Age mean = 22.7 ± 2.4 Gender (M/F): 115/135 Ethnicity/origin: Chinese Han	V/V = 120 Met carriers = 130	Modality: fMRI Analysis: ICA	11 components including: anterior and posterior DMN, salience network, bilateral dorsal attention networks, dorsal and ventral sensorimotor networks, bilateral frontoparietal networks, visual network and auditory network.	V/V > Met carriers: Intra-network connectivity: right DLPFC of the right dorsal attention network, right DLPFC of the right frontoparietal network.

Xu, Qin, Liu, Jiang, and Yu (2016)	N = [a]280 of 323 Age mean = 22.7 ± 2.5 Gender (M/F): 157/166 Ethnicity/origin: Chinese Han	V/V = 135 Met carriers = 145	Modality: fMRI Analysis: BOLD time-course correlations	Seed region: right dACC (that showed significant COMT x DRD2 interaction effects on GMV) with whole brain – identified salience network.	No COMT main effect.
Elton, Smith, Parrish, and Boettiger (2017)	N = [a]86 of 93 Age mean = 25.9 (range: 18-40) Gender (M/F): 45/48 Ethnicity/origin: NR, USA	V/V = 20 V/M = 45 M/M = 21	Modality: fMRI Analysis: BOLD time-course correlation. 264 x 264 correlation matrix.	ROIs comprised 264 functionally important nodes within 13 functional networks; auditory, cerebellar, cingulo-opercular task control, DMN, dorsal attention, fronto-parietal task control, memory retrieval, salience, lateral sensorimotor, medial sensorimotor, subcortical, ventral attention, visual.	No COMT main effect. COMT x gender interactions found.
Task-based					
Authors	**Sample Characteristics**	**Genotype Distribution**	**Task**	**Functional connectivity analysis**	**Seed region/s & network**	**Key findings**
Emotion processing					
Drabant, Hariri, Meyer-	N = [a]44 of 101	V/V = 20 M/M = 24	Cortico-limbic reactivity task:	Modality: fMRI	Seed regions: hippocampus,	M/M > V/V: vlPFC – PHG, bilateral fusiform

Lindenberg, and et al. (2006)	Age mean = 30.3 ± 9.1 Gender (M/F): 51/50 Ethnicity/origin: White		matching fearful and angry facial expressions	Analysis: BOLD time course correlation	vlPFC, and amygdala With: all other voxels significantly activated by the task	gyrus; bilateral hippocampus – vlPFC, OFC, right amygdala – bilateral OFC, vlPFC.
Rasch et al. (2010)	N = [a]56 of 57 Age mean = 24.1 ± 0.6 Gender (M/F): 15/41 Ethnicity/origin: NR, Switzerland	V/V = 11 V/M = 31 M/M = 14	Aversive stimuli: rating emotional valence and arousal of positive, neutral and negative stimuli	Modality: fMRI Analysis: PPI	Seed region: right amygdala With: whole brain	M/M > V/M > V/V: Right amygdala – right OFC, MTG, caudate tail, PCC, right cerebellum.
Surguladze et al. (2012)	N = 91 Age mean = 32.5 ± 9 Gender (M/F): 46/45 Ethnicity/origin: Caucasian	V/V = 20 V/M = 41 M/M = 29	Facial emotion processing: fear, anger, sadness, happiness	Modality: fMRI Analysis: Cluster Granger analysis "Total degree" measure of effective connectivity.	Emotional processing circuit comprising; bilateral fusiform/inferior occipital regions, right STG/superior temporal sulcus, bilateral	V/V > V/M & M/M: Total effective connectivity in the fearful condition only.

					inferior/middle PFC, right amygdala.	
Klucken et al. (2015)	N = [a]80 of 100 Age mean = 25.3 ± 4.7 Gender (M/F): 49/51 Ethnicity/origin: Caucasian	V/V = 20 V/M = 41 M/M = 19	Appetitive conditioning: erotic pictures (reward processing and emotion regulation)	Modality: fMRI Analysis: PPI	Seed regions: amygdala and midbrain With: whole brain	M/M > V/V Bilateral amygdala – vmPFC.
Memory						
Schott et al. (2006)	N = [a]49 of 51 Age range = 18-31 Gender (M/F): 16/35 Ethnicity/origin: NR, Germany	V/V = 17 V/M = 17 M/M = 15	Encoding and retrieval of 20 words: deep and shallow processing conditions	Modality: fMRI Analysis: PPI	Seed region: left anterior hippocampus With: frontal lobes	M/M > V/M > V/V: Left anterior hippocampus – frontal lobes.
Bertolino et al. (2006)	N = 27 Age mean = 28.7 ± 5.6 Gender (M/F): 12/15 Ethnicity/origin: Caucasian	V/V = 9 V/M = 9 M/M = 9	Recognition memory: encoding and retrieval of complex scenes	Modality: fMRI Analysis: BOLD time-course correlation	Seed region: HF With: vlPFC using parietal control region and whole brain	V/V > V/M > M/M: Retrieval: HF – vlPFC Reduced connectivity associated with increased behavioural accuracy.

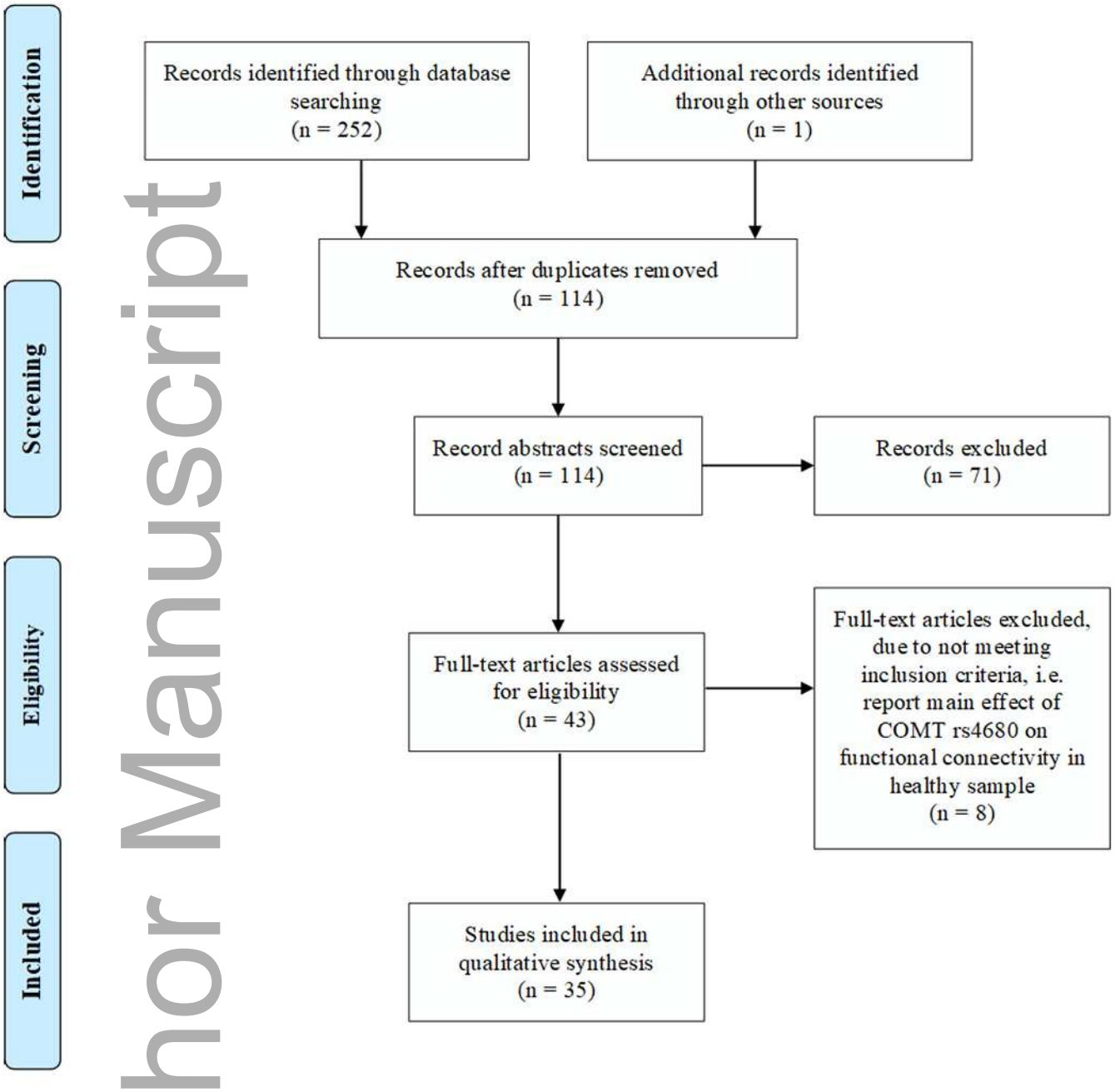
Dennis et al. (2010)	N = 22 Age mean = VV: 20.5 ± 3.6; M/M: 24.6 ± 7.7 Gender (M/F): 11/11 Ethnicity/origin: NR, USA	V/V = 11 M/M = 11	Relational memory: face-scene pairing	Modality: fMRI Analysis: BOLD time-course correlation	Seed region: left MTL for successful encoding and right MTL for successful retrieval With: whole brain	M/M > V/V: Encoding: MTL – right OFC, right dlPFC, bilateral vmPFC. Retrieval: right dmPFC, right ACC, right superior PFC. V/V > M/M: Connectivity within the MTL: Encoding: right rhinal cortex, anterior PHG, left hippocampus and left PHG Retrieval: left hippocampus/PHG, bilateral rhinal cortex, anterior PHG.
Working memory						
Sambataro et al. (2009)	N = 75 Age mean = V/V: 42.9 ± 15.1; V/M: 45.8 ± 19.4; M/M: 38.5 ± 16.9 Gender (M/F): 36/39 Ethnicity/origin: Caucasian	V/V = 20 V/M = 31 M/M = 24	1-back task: low load WM	Modality: fMRI Analysis: BOLD time-course correlation and ICA	Component of interest A (COI-A): prefrontal-parietal network predominately in the left hemisphere. COI-B: medial frontal cortex component.	V/V>V/M>M/M: COI-A: dlPFC M/M > V/M & V/V: COI-A: vlPFC M/M > V/M & V/V: COI-B: Frontopolar cortex. V/V > V/M & M/M: COI-B: Medial. V/V > V/M & M/M:

					COI-C: superior posterior parietal cortex	COI-C: left IPL.
Tan et al. (2012)	N = 46 Age mean = 32.0 ± 9.6 Gender (M/F): 26/20 Ethnicity/origin: European	V/V = 23 Met carriers = 23	Event-related WM task: maintenance or manipulation of numerical information	Modality: fMRI Analysis: Dynamic causal modelling	ROIs: left DLPFC, parietal cortex and subcortical brain region engaged by task	Met carriers > V/V: Maintenance: prefrontal-to-parietal excitatory effective connectivity. Manipulation phase: prefrontal-to-striatal inhibitory effective connectivity.
Kondo, Nomura, and Kashino (2015)	N = 28 Age mean = V/V: 23.7 ± 2.4; Met carriers: 22.9 ± 2.9 Gender (M/F): 12/16 Ethnicity/origin: Japanese	V/V = 14 Met carriers = 14	WM task: visual spatial encoding and delayed retrieval	Modality: fMRI Analysis: BOLD time-course correlation. SEM	ROIs: MFG, IFG, ACC, and IPL in right hemisphere.	Met carriers > V/V: Encoding: ACC – MFG (positively correlated with recognition accuracy).
Reward-based						
Schmack et al. (2008)	N = 44 Age mean = 38.7 ± 10.0	V/V = 10 V/M = 24 M/M = 10	Monetary incentive delay task	Modality: fMRI Analysis: PPI	Right temporal pole seed region to ventral striatum	Trend only: M/M > V/M > V/V: Right temporal pole – ventral striatum.

	Gender (M/F): 35/9 Ethnicity/origin: NR, Germany					
Krugel, Biele, Mohr, Li, and Heekeren (2009)	N = 26 Age mean = V/V: 25.7 ± 2.9; M/M: 25.2 ± 3.3 Gender (M/F): 17/9 Ethnicity/origin: NR, Germany	V/V = 12 M/M = 14	Probabilistic object reversal task: flexible reward-based learning	Modality: fMRI Analysis: PPI	Coupling between seed regions (determined by task activation) in the left ventral striatum and PFC	V/V > M/M: Greater change in effective connectivity: PFC – striatum, depending on task learning rate.
Klucken et al. (2015) See emotion processing						
Elton, Smith, Parrish, and Boettiger (2017)	N = [a]86 of 93 Age mean = 25.9 (range: 18-40) Gender (M/F): 45/48 Ethnicity/origin: NR, USA	V/V = 20 V/M = 45 M/M = 21	Delayed discounting task: smaller immediate and larger delayed reward	Modality: fMRI Analysis: BOLD time-course correlation	ROIs comprised 264 nodes within 13 functional networks; auditory, cerebellar, cingulo-opercular task control, DMN, dorsal attention, fronto-parietal task control, memory	M/M > V/M > V/V: FP, SML, and SMM networks (independent of gender).

					retrieval, salience, lateral sensorimotor, medial sensorimotor, subcortical, ventral attention, visual.	
Executive function						
Prata et al. (2009)	N = 48 Age mean = 34.1 ± 10.7 Gender (M/F): 23/25 Ethnicity/origin: Caucasian (90%), UK	V/V = 13 V/M = 20 M/M = 15	Verbal fluency: generating (word beginning with presented letter) and repetition	Modality: fMRI Analysis: BOLD time-course correlation	Right frontal operculum/anterior insula seed	Trend only: M/M > V/V Right frontal operculum – dorsal and ventral left anterior insula/frontal operculum.
Jaspar et al. (2016)	N = 45 Age mean = V/V: 21.1 ± 2.3; V/M: 22.3 ± 2.9; M/M: 21.3 ± 2.4 Gender (M/F): 20/25 Ethnicity/origin: Caucasian	V/V = 15 V/M = 15 M/M = 15	Stroop: congruent or incongruent word and colour	Modality: fMRI Analysis: PPI	Right IFop seed – whole brain, during reactive control condition.	Val carriers > M/M: Right IFop – right cingulate, right STG. Right IFop – rSFG, left mid-cingulate gyrus, left MTG, left lingual gyrus (negative).

Note. [a]after exclusions due to unavailable genotype and/or imaging data; M/F: male/female; V/V: Val/Val; V/M: Val/Met; M/M: Met/Met; fMRI: functional magnetic resonance imaging; EEG: electroencephalography; NR: not reported; MDD: major depressive disorder; WM: working memory; rsfMRI: resting state functional magnetic resonance imaging; rsFC: resting state functional connectivity; sgACC: subgenual anterior cingulate cortex; IFG: inferior frontal gyrus; MFG; medial frontal gyrus; SFG: superior frontal gyrus; HF: hippocampal formation; vlPFC; ventrolateral prefrontal cortex; vmPFC: ventral medial prefrontal cortex; dmPFC: dorsomedial prefrontal cortex; amPFC: anterior medial prefrontal cortex; PCC: posterior cingulate cortex; PVA: primary visual area; SFC: superior frontal cortex; ITC: inferior temporal cortex; MTL: medial temporal lobe; vlPFC: ventrolateral prefrontal cortex; dlPFC: dorsolateral prefrontal cortex; PHG: parahippocampal gyrus; OFC: orbitofrontal cortex; IFop: inferior frontal operculum; STG: superior temporal gyrus; NAcc: nucleus accumbens; IPL: inferior parietal lobule; DMN: Default network/default mode network; ECN: executive control network; ROI: region of interest; PPI: psychophysiological interaction analysis



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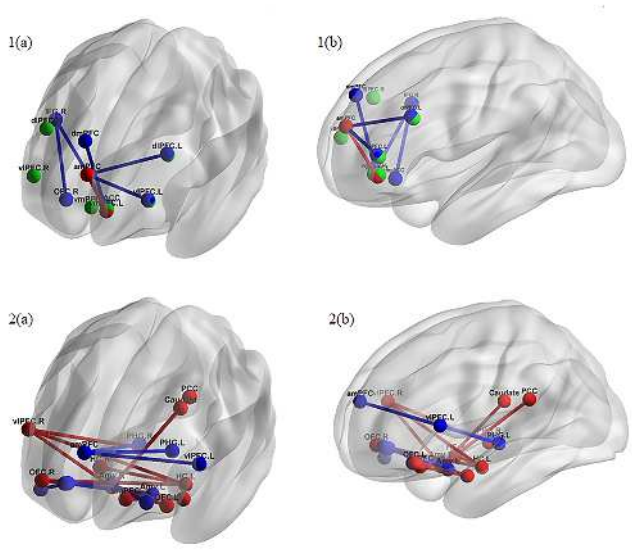

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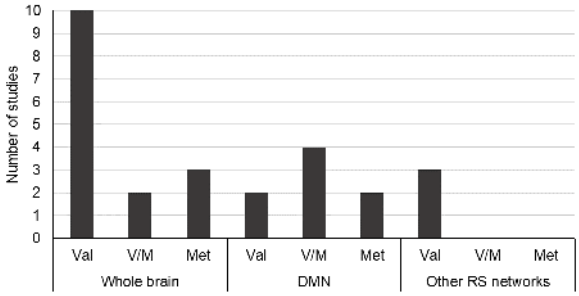

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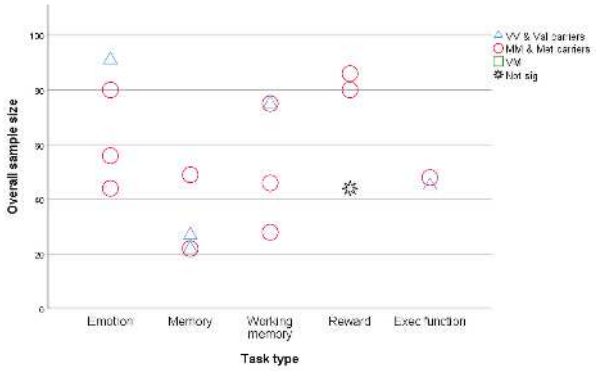

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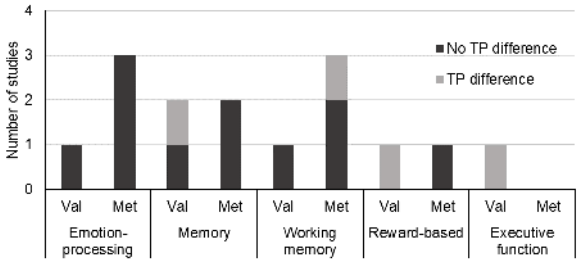

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