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# Brain predictive coding processes are associated to COMT gene Val158Met polymorphism

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ABSTRACT

Predicting events in the ever-changing environment is a fundamental survival function intrinsic to the physiology of sensory systems, whose efficiency varies among the population. Even though it is established that a major source of such variations is genetic heritage, there are no studies tracking down auditory predicting processes to genetic mutations. Thus, we examined the neurophysiological responses to deviant stimuli recorded with magnetoencephalography (MEG) in 108 healthy participants carrying different variants of Val158Met single-nucleotide polymorphism (SNP) within the catechol-O-methyltransferase (COMT) gene, responsible for the majority of catecholamines degradation in the prefrontal cortex. Our results showed significant amplitude enhancement of prediction error responses originating from the inferior frontal gyrus, superior and middle temporal cortices in heterozygous genotype carriers (Val/Met) vs homozygous (Val/Val and Met/Met) carriers. Integrating neurophysiology and genetics, this study shows how the neural mechanisms underlying optimal deviant detection vary according to the gene-determined cathecolamine levels in the brain.

## 1. Introduction

Predicting the sensory environment is a fundamental human and animal function, with significant individual variations that presumably depend on the tangled interplay between neurophysiology, genetics and biology (Friston, 2012; Parras et al., 2017). On a neurophysiological level, it is well-known that auditory predictions for sound environment are formed automatically in the supratemporal cortex and updated when errors are detected (Näätänen et al, 1978; Näätänen et al, 2007). These sensory processes have been tracked down with neurophysiological methods, giving rise to discrete neural events, namely the components of the event related potential/field (ERF/P). Indeed, when a deviant stimulus is presented inserted in a sequence of coherent ones, the brain produces a negative response called mismatch negativity (MMN), which is usually followed by a positive component named P3a. These events occur in a short time-window with a latency of about 100 to 350 ms from the onset of the deviant stimulus and are largely automatic and pre-attentive (Näätänen et al, 1978). Such components have been widely studied and provided several insights on how the brain detects and adapts to environmental irregularities (Näätänen et al, 2007). Indeed, MMN has been repeatedly connected to the predictive coding theory (PCT), which states that the brain is a constant generator of mental models of the environment that are progressively updated and refined on the basis of their match and mismatch with the external stimuli Friston (2012). Over the last decades, PCT has been successfully connected to the auditory domain and recently has been even adapted and explained in light of the peculiar and complex case of articulated music (Friston, 2012). According to the PCT perspective, MMN has been considered an iconic evidence of the brain's ability to make predictions of the upcoming events and automatically detect deviations from such predictions. Moreover, since MMN occurs also when the participants do not pay attention to the deviant stimulation, this ERF/P component is particularly suitable to study the brain predictive processes which are not mediated by the conscious elaboration of the environmental scene and that we aimed to investigate in the current work.

On an anatomical level, the originating brain sources of MMN have been especially located within the Heschl's and superior temporal gyri, with a predominance of the right hemisphere (Garrido et al., 2009; Jemel et al., 2002). However, further studies supported the existence of a functionally distinct and superordinate MMN generator in the frontal lobe Deouell (2007) which has been associated with the triggering of an involuntary attention switching process upon potentially critical unattended events in the acoustic environment (Giard et al., 1990; Näätänen et al., 2007; Rinne et al., 2000). Along this line, several studies explored the connections between MMN and more complex cogni-

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tive abilities such as high-level attentive and memory processes and the correspondent individual differences among the population. For example, previous research reported relationships between MMN amplitude and working memory (WM) (Bonetti et al., 2018) and sensory memory (Cheour, Leppänen, and Kraus, 2000). Furthermore, in a clinical review, Näätänen and colleagues (2012) proposed MMN as a privileged brain response to index a variety of pathological states as well as individual differences related to healthy and impaired cognitive functioning.

Notably, even though it is established that genetic heritage is a major source of such individual variations in cognitive processes, there are no studies tracking down the brain's auditory predictive processes to genetic mutations. Along this line, a great possibility comes from the recent advances in molecular and imaging genetics which opened up new opportunities to study the origins of the variations of auditory processing and cognitive functions among individuals. For instance, by combining the genetic variations of candidate selected genes with functional brain data broader insights may be achieved on the mechanisms regulating auditory predictive processing in the human brain. In this light, a key candidate gene implicated in both physiological (Berryhill et al., 2013; Garcia-Garcia et al., 2017) and pathological (de Diego-Balaguer et al., 2016; Hosák et al., 2007) neural conditions is COMT (Egan et al., 2001; Mier et al., 2010), a gene coding for the catechol-O-methyltransferase enzyme which is responsible for the majority of catecholamines degradation in the prefrontal cortex (PFC) (Chen et al., 2004; Käenmäki et al., 2010; Matsumoto et al., 2003; Meyer-Lindenberg et al., 2005). Specifically, Val158Met (rs4680) is a common coding single-nucleotide polymorphism (SNP) involving the substitution of guanine (G) with adenosin (A) in the exon three of the gene that leads to a change in the amino acid located at position 158 of the codon. When G is not altered, a valine residual is coded in position 158 (G or Val allele). However, when it is mutated, valine is replaced by the evolutionarily more recent methionine (A or Met allele). Thus, three different COMT genotypes can be found within the population: Val/Val (A/A), Val/Met (A/G) and Met/Met (G/G) (Frank and Fossella, 2011; Männistö & Kaakkola, 1999; Meyer-Lindenberg et al., 2005). Notably, such change significantly affects enzyme activity and therefore the levels of prefrontal extracellular dopamine (Männistö, & Kaakkola, 1999). Specifically, the Val/Val version of the COMT enzyme breaks down dopamine with a degradation rate 40% faster than the Met/Met version (Chen et al., 2004; Lotta et al., 1995). Consequently, neurotransmitter is available at the synapses for extremely short periods in the case of Val/Val carriers, whereas it is preserved intact for a longer period in the case of Met/Met carriers (Berryhill et al., 2013). The availability of neurotransmitter at the synapse largely influences neuronal activity, with both shortness and overplus of neurotransmitter undermining neuronal communication Tritsch and Sabatini (2012). In this regard, it has been suggested that an optimal dopamine availability seems to be maintained by the enzyme resulting from the heterozygous genotype Val/Met (Htun et al., 2014; Schacht, 2016).

With regards to brain functioning, dopamine levels have been shown to be indissolubly related to brain activity (Kähköen et al., 2002; Tritsch & Sabatini, 2012), and especially to PFC. Here, a large consensus has been established around the "inverted U-shaped" theory, stating that PFC requires an optimal, balanced level of dopamine and that higher or lower levels could result in impaired prefrontal mechanisms (Htun et al., 2014; Papenberg et al., 2020; Stewart and Plenz, 2006). Indeed, imbalanced dopamine levels have been linked to impairments in cognitive functions such as working memory, decision-making Rogers (2011) and attention Nieoullon (2002) as well as various neurological Chaudhuri and Schapira (2009) and neuropsychiatric disorders Arnsten (1998). Modest effects of Val158Met variant have been reported for several of these conditions (Bertolino et al. 2006; Eisenberg et al., 1999; Hong et al., 2015; Williams, 2007; Williams-Gray et al., 2008), and have been explained in the framework of the inverted U-shaped hypothesis (Saville et al., 2014; Schacht, 2016; Zhang et al., 2016).

The interplay between COMT, dopamine and PFC has been highlighted by a positron emission tomography (PET) study which has supported the "U-shaped" model (Meyer-Lindenberg et al., 2005). In this light, the more frontal generators of the neural responses to deviant stimuli may represent an excellent opportunity to better understand the impact of COMT genetic variation on brain activity. Along this line, a previous electroencephalography (EEG) study revealed an association between patients with 22q11 Deletion Syndrome (22q11DS) hemizygous for the Met allele and a reduction of the MMN amplitude compared to both Val hemizygous carriers and healthy controls. Interestingly, the reduction affected the PFC channels, normally reporting the maximum MMN amplitude values (Baker et al. 2005). Another EEG study conducted on patients with schizophrenia (Horikoshi et al., 2019) showed that COMT Met carriers presented a slightly more marked MMN but only along few selected channels. However, even though these studies reported interesting results, they only involved small clinical populations and EEG. Further, although the EEG is a valuable tool, it usually presents a lower signal-to-noise-ratio and a less precise reconstruction of the neural sources of the recorded signal than magnetoencephalography (MEG) Baillet (2017). Moreover, these studies focused on the differences between the MMNs recorded in Val/Val and Met carriers and therefore did not investigate the relationship between the suggested optimal dopamine level of the heterozygous genotype Val/Met (Htun et al., 2014; Schacht, 2016) and MMN responses. The findings regarding the Val158Met variant reported in the literature provide a highly incoherent picture, with a higher cognitive performance either for the Val homozygotes or for the Met homozygotes. In most studies, the position of Val/Met carriers was ambiguous, being sometimes included in the Met carriers' group, and in the others in the Val carriers' group. Instead, what is consistent is that they happen to be always in the better performing group. On the top of this, converging evidence from studies on both animals (Arnsten, 1998; Arnsten and Goldman-Rakic, 1990; Zahrt et al., 1997) and humans (Cools and D'Esposito, 2011; Gjedde et al., 2010), suggests that the relationship between prefrontal cognitive functions and DA levels can be explained in the framework of the inverted U-shaped hypothesis and that COMT Val158Met can exert a modulatory effect accordingly. Hence, based on prior findings and on the consolidated inverted U-shaped dopamine hypothesis, in the present study we adopted a grouping strategy that could best describe the balanced dopamine levels of the heterozygote carriers of COMT Val158Met.

Thus, for the first time to our knowledge, we investigated the relationship between COMT genetic variation (contrasting heterozygous genotype Val/Met to homozygote genotypes Val/Val and Met/Met) and neural responses to deviant sounds in a healthy population. Specifically, using the combination of MEG and magnetic resonance imaging (MRI) in 108 participants, we hypothesized to observe an enhancement of the MMN and P3a frontal vs temporal generator strength in participants with COMT Val158Met heterozygote genotype (Val/Met) vs homozygote genotype (Val/Val and Met/Met).

## 2. Results

### 2.1. Sample Characteristics

The observed distribution of the different alleles in our sample was: Met/Met = 31(28.7%); Val/Met = 58(53.7%); Val/Val = 19(17.6%), coherently with the allele frequencies reported in previous studies (Frank and Fossella, 2011). According to ANOVAs and $X^2$ tests, there were no significant differences among participants with respect to their COMT genotype, for age, sex, and handedness (**Table 1**).

### 2.2. COMT and neural responses to deviants

A 1000 permutation Monte Carlo simulation (MCS) was undertaken on the neural responses indexing deviant detection, obtained subtracting the neural response to standard stimuli from the neural response

**Table 1**
Demographic data of the participants illustrated according to their COMT genetic variation. The data of all the participants (n=108) prior to their subdivision based on genotype are reported under "Whole sample"; those of the Val/Val and Met/Met carriers are reported under the column "COMT homozygotes", whereas those of the Val/Met carriers are reported under "COMT heterozygotes". The last column reports the statistics from the contrast between the data of the homozygotes vs heterozygotes.

| Information | Whole sample | COMT homozygotes (Met/Met and Val/Val) | COMT heterozygotes (Val/Met) | Homozygotes vs heterozygotes |
|---|---|---|---|---|
| Participants | N 108 | N 50 | N 58 | |
| Age | M 28.41, SE .771 | M 28.58, SE 1.16 | M 28.26, SE 1.05 | $p^{T} > 0.05$ |
| Sex | M(N47, 43.5%), F(N61, 56.5%) | M(N21, 42%), F(N29, 58%) | M(N26, 44.8%), F(N32, 55.2%) | $p\ ^{\chi 2} > 0.05$ |
| Handedness | A(1), L(6), R(101) | L(2), R(48) | A(1), L(4), R(53) | $p\ ^{\chi 2} > 0.05$ |

$^{T}$ = Independent samples Student t-test
$^{\chi 2}$ = Chi-squared ($\chi^2$) test

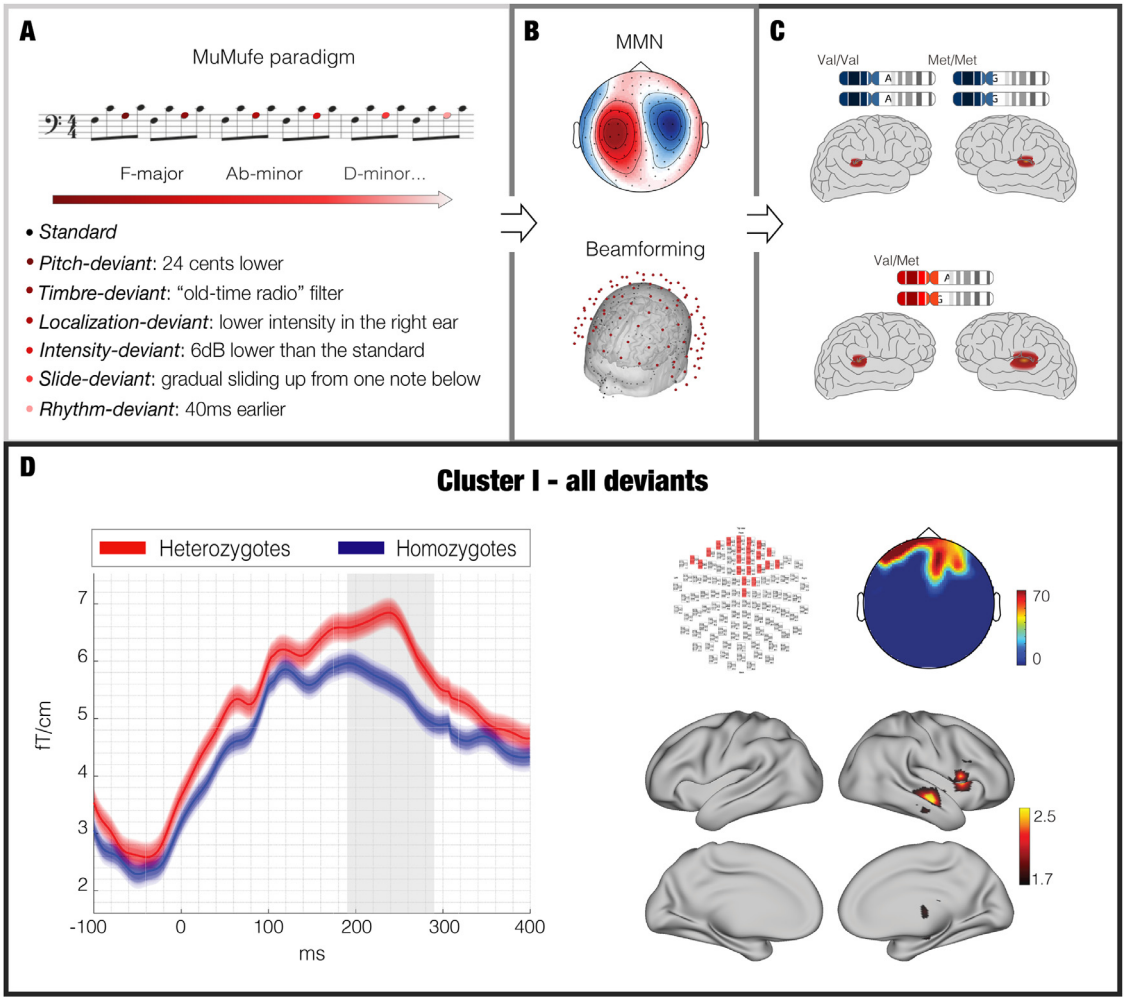


**Fig. 1.** Overview of the analysis pipeline and main results
**A –** During MEG recordings, participants were presented with the musical multifeature paradigm (MuMUFE) while watching a silent movie. This paradigm allowed us to obtain the neural responses to deviant sound stimulations. **B -** MEG data has been collected, pre-processed and beamformed into source space. **C –** Participants have been divided according to their COMT genetic variation into two groups: homozygotes (Val/Val and Met/Met) and heterozygotes (Val/Met). **D –** Representation of the main significant cluster emerged by contrasting COMT heterozygous vs homozygous participants. The left figure shows the waveforms associated to the two experimental groups (shaded areas represent standard errors), while the right images provide a spatial depiction of the MEG channels and brain sources where the neural signal differed between the homozygous and heterozygous groups.

to deviant stimuli and averaging over all the six sound deviants. As depicted in Fig. 1**D**, the analysis revealed a single significant frontal cluster ($p < 0.001$, $k = 260$, time range from the onset of the deviants: 0.19–0.29 s) where the neural amplitude was stronger for participants presenting the COMT heterozygote genotype (Val/Met) compared to homozygous genotype (Val/Val; Met/Met). Specific channels and time points are reported in Table 2. A 2D map illustrating the spatial location and name of the MEG channels is provided in Figure S2. Additionally, the MCS conducted on single deviants identified several significant fronto-temporal clusters of channels. These differences were consistent across all deviants of the paradigm, peaking for pitch, slide and timbre, and are reported in Table 3 and **Table ST1** and illustrated in Fig. 2. Conversely, as expected the other direction of the contrast (COMT homozygotes vs heterozygotes) did not return any significant cluster for slide, timbre, rhythm, localization and intensity. In this case, we obtained a very small cluster for pitch only ($k = 6$; $p < .001$).

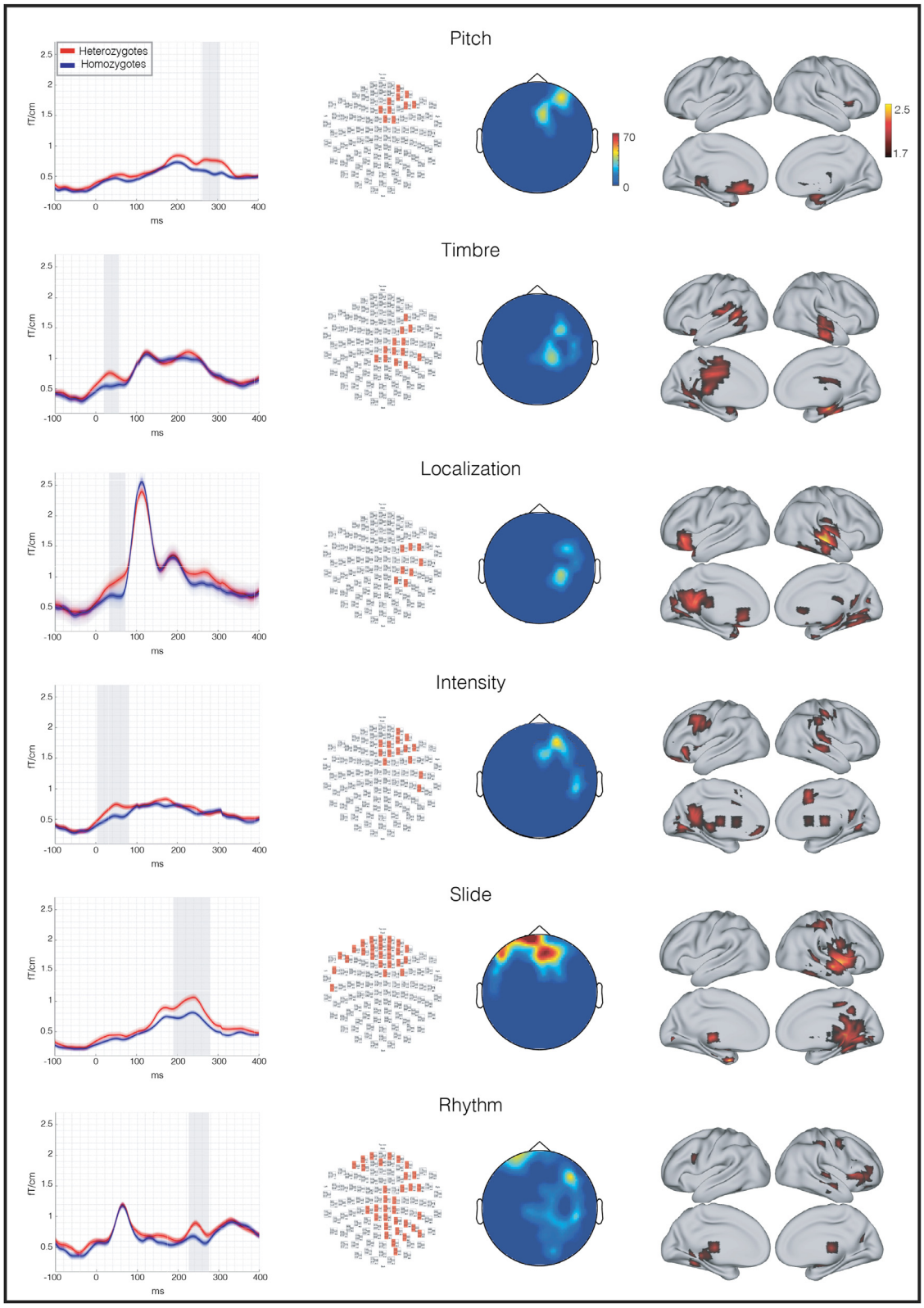


**Fig. 2.** Neural responses to all deviants depicted according to the COMT polymorphism groups

Waveforms, MEG channels maps, topoplots and brain sources of the neural response indexing deviant detection. The Figure illustrates all deviants depicted according to the COMT polymorphism groups in both MEG sensor and source spaces. Specifically, waveform images show the timeseries of the main significant cluster obtained contrasting the MEG sensor data of COMT heterozygotes vs homozygotes (shaded areas represent standard errors), while MEG channels maps, topoplots and source reconstruction plots report the spatial extent of those significant clusters, in MEG sensor and source space, respectively. With regards to topoplots, colorbars show the temporal extent (in ms) of the significant clusters, while source reconstruction plots colorbars illustrate the t-values of the contrasts.

**Table 2**
Significant channels and time-points of the cluster outputted by MCS on contrasts between the neural response indexing deviant detection of COMT heterozygous vs homozygous individuals.

| MEG channels | Time (ms) |
|---|---|
| 942 + 943 | 200 – 260 |
| 822 + 823 | 207 – 230 |
| 522 + 523 | 210 – 270 |
| 812 + 813 | 210 – 270 |
| 912 + 913 | 210 – 256 |
| 922 + 923 | 213 – 256 |
| 512 + 513 | 220 – 273 |
| 1022 + 1023 | 223 – 283 |
| 1222 + 1223 | 226 – 260 |
| 312 + 313 | 230 – 280 |
| 1212 + 1213 | 230 – 273 |
| 1232 + 1233 | 230 – 276 |
| 1012 + 1013 | 233 – 263 |
| 1032 + 1033 | 233 – 283 |
| 622 + 623 | 236 – 266 |
| 1042 + 1043 | 236 – 260 |
| 932 + 933 | 236 – 276 |
| 122 + 123 | 243 – 293 |
| 342 + 343 | 243 – 246 |
| 722 + 723 | 250 – 250 |
| 1112 + 1113 | 263 – 270 |
| 1242 + 1243 | 270 – 280 |

**Table 3**
Significant clusters outputted by MCS on contrasts between the neural response indexing deviant detection of COMT heterozygous vs homozygous individuals. In this case, the analysis has been conducted independently for each of the six deviants. *k* refers to the spatio-temporal extent of the cluster (e.g. the overall number of channels and time-points forming the cluster).

| Deviant | k | MC simulations *p* |
|---|---|---|
| Intensity | 85 | < .001 |
| | 25 | |
| | 12 | |
| Location | 53 | < .001 |
| | 22 | |
| | 17 | |
| | 15 | |
| | 14 | |
| Pitch | 84 | < .001 |
| | 35 | |
| | 14 | |
| Rhythm | 164 | < .001 |
| Slide | 263 | < .001 |
| | 39 | |
| Timbre | 82 | < .001 |
| | 70 | |
| | 26 | |
| | 15 | |
| | 15 | |

Furthermore, to provide readers with a more complete overview of the relationship between COMT Val158Met polymorphism and neural response indexing deviant detection, we have reported the neural waveforms grouped along the three genotypes (Val/Val; Val/Met; Met/Met) (**Figure S1**), showing no significant differences between Val/Val and Met/Met.

**Table 4**
Spatial coordinates, labels, t-values and hemisphere describing the significant brain sources obtained by contrasting the COMT heterologous vs homozygous groups.

| *Brain region* | *Hemisphere* | *T-stat* | *MNI coordinates* | | |
|---|---|---|---|---|---|
| | | | x | y | z |
| *Temporal Sup* | R | 2,41 | 50 | -14 | -8 |
| *Thalamus* | L | 2,13 | -6 | -22 | 8 |
| *Insula* | R | 2,07 | 42 | -14 | -8 |
| *Front Inf Ope* | R | 2,02 | 42 | 10 | 8 |
| *Insula* | R | 1,99 | 34 | 10 | 8 |
| *Temporal Mid* | R | 1,94 | 50 | -14 | -16 |
| *Front Inf Ope* | R | 1,87 | 50 | 10 | 8 |
| *Temporal Mid* | R | 1,75 | 50 | -22 | -8 |
| *Temporal Sup* | R | 1,73 | 58 | -14 | -8 |
| *Putamen* | R | 1,71 | 26 | 2 | 8 |

### 2.3. Source localized activity

We reconstructed the brain sources of the MEG signal in the significant time-windows emerged from the previous MEG sensor analysis. To this aim, we used a beamforming approach and computed a general linear model (GLM) for each source reconstructed brain voxel and time-point. At the end, we corrected for multiple comparison with a cluster-based permutation test (Hunt et al., 2012). As depicted in **Fig. 1D**, this analysis showed a stronger brain activity for Val158Met heterozygote vs homozygous participants mainly localised in the inferior frontal gyrus, and superior and middle temporal cortex. Source results for each of the six deviants are illustrated in **Fig. 2**, while detailed statistical results for both averaged and single deviants concerning each brain voxel are reported in **Table 4** and **Table ST2**.

## 3. Discussion

In this study, we aimed to assess whether auditory brain predictive processes could be tracked down to genetic mutations by investigating the relationship between different COMT genotypes and neural responses to deviant simulations. Our results showed a significant amplitude enhancement of such neural responses along the frontal MEG sensors in COMT heterozygous vs homozygous participants. Indeed, source reconstruction analysis located the neural sources concerning this difference especially within inferior frontal gyrus and superior and middle temporal cortex. Additionally, our results showed that the heterozygous vs homozygous group presented stronger neural responses to all deviants, even if such stronger neural responses occurred during different time-windows for the six deviants of the paradigm. Notably, we did not observe any difference in terms of brain responses to deviants between COMT Val/Val and Met/Met. This adds strength to our hypothesis that the neural responses to deviants are modulated by COMT heterozygous vs homozygous genotype.

The COMT polymorphism plays a crucial role in modulating catecholamine flux and dopamine level in the PFC (Lewis et al., 2001; Moron and al., 2002). Specifically, it has been suggested that an optimal dopamine level for brain function would be more frequently reached by the Val/Met carriers Schacht (2016), while Val/Val and Met/Met COMT variations would lead to a non-optimal dopamine degradation. As previous research showed, dopamine levels affect the extent of the brain activity, especially in the case of prefrontal regions. In particular, the “inverted U-shaped” theory states that PFC requires an optimal, balanced level of dopamine and that higher or lower levels can produce prefrontal impairment or deregulated activity (Egan et al., 2001; Htunet al., 2014; Joober et al., 2002). Coherently with these evidences, our results showed that the neural responses of COMT heterozygous individuals (Val/Met) had greater amplitude compared to those elicited in COMT homozygous carriers (Val/Val and Met/Met). As previously suggested by Schacht et al. (2016), this phenomenon may relate to a

balanced dopamine degradation rate occurring in COMT heterozygotes, that would be reflected in a stronger neural response to deviant sounds when compared to homozygous participants. Our findings may be explained in the light of evidence from animal studies reporting a necessary role of prefrontal D1 receptor-mediated activity in cortical layer V for sharpening glutamatergic transmission, with specific regard to prefrontal cortical areas (Yang and Seamans, 1996; Seamans et al., 2001; Seamans and Yang, 2004). Since glutamatergic transmission through N-methyl-D-aspartate receptor (NMDAR) activation is critical for the activity of the pyramidal neurons recorded by the EEG signal (Buzsáki et al., 2014) and for the MMN generation in particular (Javitt et al., 1996; Kreitschmann-Andermahr et al., 2001; Ehrlichman et al., 2008), a balanced dopaminergic activity as the one found in Val/Met carriers may lead to a higher signal-to-noise ratio of the MMN signal, resulting in its increased MMN levels enhancement compared with homozygotes. On the same line, imbalanced levels of Dopamine as those found in Val/Val or Met/Met carriers may lead to a lower clarity of the NMDAR-mediated neural signals and therefore smaller amplitude of the electrophysiological responses recorded at the scalp.

Additionally, our results can find support in the EEG findings on clinical populations by Horikoshi et al. (2019) and by Baker et al. (2005), both reporting reduced MMN amplitude in case of exceeding or reduced COMT activity. In their study on patients with schizophrenia, Horikoshi et al. (2019) reported reduced MMN amplitude in Val/Val compared to Met carriers (Met/Met and Val/Met), suggesting that the excessive dopamine turnover rate occurring in Val homozygotes impairs cortical excitability. On the contrary, Baker et al. (2005) reported reduced MMN amplitudes in response to speech stimuli of Met carriers affected by 22q11DS, for whom one of the COMT alleles is deleted. Specifically, 22q11DS patients hemizygous for the Met (Met/-) allele presented a poorer MMN signal compared to Val carriers (Val/-) and to healthy controls. Interestingly, the MMN amplitude in Val carriers showed no significant differences compared to healthy controls. Instead, they presented an intermediate amplitude between healthy controls and 22q11DS Met carrier patients. As the Val allele promotes a faster degradation compared to the Met allele, the presence of a single allele encoding for the COMT enzyme may lead to the productions of a balanced quantity of COMT, comparable to the one found in Val/Met carriers. Thus, the catecholamine degradation might occur more efficiently in this Val/- subjects compared to the Met/- ones, leading to MMN amplitude values lying in normal ranges.

Altogether, these studies bring support to the “inverted-U” curve theory in relation to the electrical cortical activity, suggesting that a better dopaminergic tuning might be provided by a heterozygous genotype with intermediate endophenotype versus the homozygous one.

In this frame, our findings partially supported their results and largely extended their significance. Indeed, for the first time to our knowledge, in a large sample of 108 healthy participants we revealed a rather robust relationship between the suggested ideal dopamine level of the COMT heterozygous genotype Val/Met (Htun et al., 2014; Schacht, 2016) and MMN responses. Moreover, our results emerged from the combination of MEG and MRI and a complex musical-multifeature paradigm. Additionally, our beamforming analysis localized the sources of the difference between heterozygous and homozygous participants mainly within prefrontal areas such as inferior frontal cortex and secondary auditory regions as superior and middle temporal cortices. Notably, no differences were detected with regards to primary auditory cortex which is usually the main generator of the MMN. This evidence suggests that SNPs in COMT gene may specifically affect the activity of the most frontal generators of neural responses to deviants. Such pattern finds support in the strong modulation of prefrontal regions exerted by dopamine levels, which are largely regulated by COMT (Frank and Fossella, 2011; Meyer-Lindenberg et al., 2005; Seamans and Yang, 2004). Similarly, prior studies investigating the role of COMT Val158Met SNP in auditory event-related potentials reported allele-dependent differential activity in prefrontal but not auditory cortical areas (Majic et al., 2011; Marco-Pallarés et al., 2010), confirming the role played by dopamine in PFC. The frontal generators of MMN have been previously related to the involuntary attention-switching process towards critical unattended events suddenly occurring in the acoustic environment (Näätänen, Paavilainen, Rinne, and Alho, 2007). Interestingly, prefrontal dopamine has been linked to attentional shifting and prediction error processes (Frank et al., 2011; Nieoullon, 2002; Takahashi et al., 2017). Besides frontal regions, our results also highlighted significant differences between the brain signal of COMT heterozygotes vs homozygotes which originated from middle temporal cortices. Although previous literature about temporal modulation by COMT genotype is somewhat scarce, few studies reported differential medio-temporal activity depending on Val158Met polymorphism. Specifically, previous studies identified overall higher activity in the amygdala (Smolka et al., 2005) and hippocampus (Drabant et al., 2006) for Met homozygotes compared to Val carriers. These studies, together with our findings, suggest that the relationship between COMT genotypes and neural activity is mainly but not exclusively ascribable to prefrontal brain areas.

Taken together, our results provide evidence for a possible non-linear link between COMT Val158Met polymorphism, dopamine degradation and neural responses to deviants indexing automatic brain predictive processes.

Although the paradigm used in the present study was mainly designed to elicit MMNs, our findings focused not only on the MMN component but on the full neural response to deviant stimulation (i.e. taking into account a larger time-window that includes P3a as well). In this regard, our results can be interpreted as prediction error processing and extended to the superordinate framework represented by PCT, suggesting that to make adequate predictions and succesfully detect unexpected deviations the brain may require the optimal dopamine levels connected to the COMT heterozygote genotype (Val/Met). An alternative view explains the MMN as a consequence of sensory adaptation and disihinibtion of neuronal assemblies by infrequent sound stimuli (e.g May and Tiitinen 2010). However, as discussed in the recent work by Harms et al. (2020), sensory adaptation and predictive coding are two different but compatible hypotheses that could be used to explain MMN generation and that not necessarily exclude each other. Thus, we cannot exclude that sensory adaptation plays a role in the generation of a response to the deviant stimulus. Nonetheless, phenomena of sensory adaptation would be more likely to occur within the primary auditory cortex, whilst our findings reveal activity in prefrontal areas and secondary auditory cortex, mostly involved in higher cognitive functions. Further, we are here analyzing the role of the dopaminergic system in neural responses to deviant sounds. As previously demonstrated, dopaminergic neurons implicated in prediction error processing are localized in prefrontal areas, where we found the major differences in activity. Thus, in the light of our results, we consider PCT as one exhaustive explanation to our findings.

## 4. Limitations

The present study presents a correlation between different COMT genotypes and neural responses to errors. Being error processing a complex cognitive process, it is plausibly associated to a wider pool of genes of which COMT is only one, and to the interaction of individual genotypes with the environment. We therefore cannot infer a direct causality of our results, despite the support to our evidence. Further, given the different grouping strategy in respect to most of the former literature, our results cannot be directly compared to most of the prior evidence. However, prior literature offers contrasting evidence regarding the Val158Met variant, with findings reporting a higher cognitive performance either for the Met homozygotes or for the Val homozygotes. Indeed, the Val/Met carriers were sometimes included in the Met carriers’ group, and some other times in the Val carriers’ group. In all cases, they appeared to belong to the better performing group. Thus, based on

such controversial findings, in this study we decided to adopt a grouping strategy that could best describe the balanced dopamine levels suggested by the inverted-U shape theory, which we believed corresponds to that of the heterozygote carriers of the COMT gene Val158Met SNP. Remarkably, when comparing the neural responses to deviants between the three COMT genotype groups (Val/Val, Met/Met and Val, Met, **Figure S1**), we did not reveal any difference between Val/Val and Met/Met, suggesting that our grouping strategy (COMT homozygotes vs heterozygotes) may be the best one to detect different neural responses to deviant stimulations.

Finally, our study adopted the musical multifeature paradigm, a reliable and powerful tool to obtain MMN and P3a to deviant sound stimulations inserted in a complex acoustic context. Even if we believe that using such paradigm represents a strength of our work since it allows us to generalize our results across a variety of different deviants, we acknowledge that the stronger neural responses for the heterozygotes group occurred within slightly different time-windows for the six deviants of the paradigm. This result may be explained by the different latency and strength of the neural responses occurring for the six deviants and thus we believe that it does not represent a particular issue. However, it is worthy to highlight it as a potential limitation of our study that could be better investigated by future research.

## 5. Conclusions

In conclusion, our study showed the relationship between COMT Val158Met polymorphism and successful deviant detection in relation to automatic brain predictive processes, suggesting the relevance of investigating the complex interplay occurring between neurophysiology and genetics. Such interplay would be crucial to better understand fundamental brain principles.

Specifically, given the multiple roles played by dopamine on cognition, reaching a better understanding of the interplay between genetics, dopamine and cognition would be useful to, on the one hand, partly explain individual variations in cognition in the healthy population and, on the other hand, to predict differential responses to pharmacological treatments and the predisposition to develop some neurological disorders as well as its severity in patients.

In conclusion, future research is called for to further explore the relationship between different COMT genotypes and brain activity and, to complement our work, especially focus on conscious attentional processes and higher level-cognitive abilities as well as the implications in pathological conditions.

## 6. Materials and methods

### 6.1. Participants

This study was conducted within the large Tunteet protocol that involved the collection of neurophysiological, behavioral and genetical data of 140 participants. Previous results obtained from analysis of this dataset have been published in Bonetti et al. (2017), Bonetti et al. (2018), Haumann et al. (2021), Haumann, Hansen, Houtilainen, Vuust, & Brattico (2020), Kliuchko et al. (2019) Kliuchko et al. (2018); and Kliuchko, et al. (2016).

In this study, we considered the participants who took part in both the neurophysiological and genetical data gathering. The resulting sample consisted of 108 participants, 47 males (43.5%) and 61 females (56.5%), as reported in **Table ST1**. All participants were healthy, reporting no previous or current drug and alcohol abuse, were not under medication, did not report having had any neurological or psychiatric problems in their past, and declared to have normal hearing. Furthermore, their socio-economic and educational status was homogeneous, according to data collected at the Biomag laboratory right before the MEG session using paper-and-pencil questionnaires administered in a room adjacent to the MEG one. These pieces of information were collected by using questionnaires involving a few questions about participants' age, educational level, income, etc. Further details on experimental procedures can be found in Kliuchko et al. (2016). The experimental procedures for this study were approved by the Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (approval number: 315/13/03/00/11, obtained on March the 11th, 2012). Moreover, all procedures were conducted in agreement with the ethical principles of Declaration of Helsinki.

### 6.2. Stimuli and procedure

The stimuli adopted were piano tones from the Wizoo Acoustic Pianosample sounds from the software sampler Halion in Cubase (Steinberg Media Technologies GmbH). The peak amplitude was normalized using Audition, Adobe Systems Incorporated. Because of its efficacy for balancing sounds on the basis on their most salient portion, peak amplitude normalization was used, labelled as the sharp attack, returning sounds that were relatively natural and pleasant to listen. We employed the neurophysiological data elicited by the musical multi-feature paradigm (MuMUFE) because of its higher complexity with respect to other paradigms (e.g. oddball paradigm). Indeed, the deviants in the MuMUFE paradigm typically elicit clear MMN and P3a responses with varying latencies according to their feature type, and they seem effective for eliciting prefrontal MMN and for studying individual differences (Bonetti et al., 2018; Bonetti, Haumann, Vuust, Kliuchko, and Brattico, 2017; Vuust, Brattico, Seppänen, Näätänen, and Tervaniemi, 2012). The tones organization followed the common musical figure in Western music, known as "Alberti bass", in patterns of four and with the arrangement in an arpeggiated chord (first–fifth–third–fifth). All the piano tones were of 200 ms in duration with 5 ms of raise and fall time. Interstimulus interval (ISI) was 5 ms. Every six patterns, the musical key of the presentation changed in pseudorandom order. The used keys were 24 (12 major and 12 minor) and were kept in the middle register. In each pattern, the third tone was replaced with a deviant of one of six types: pitch, timbre, location, intensity, slide and rhythm, as shown in **Fig. 1A**. The deviant sounds were created by modifying one sound feature in Adobe Audition. The pitch deviant has been designed mistuning the third tone of the Alberti Bass by 24 cents, tuned downwards in the major mode and upwards in the minor one. To create timbre deviant, the "old-time radio" effect of Adobe Audition was applied to the sound. The location deviant was made by decreasing the intensity in one of the audio channels that resulted in perceptual shift of a sound source location from the center to a side. The intensity deviant was a reduction of a sound intensity by 6 dB. Slide deviant was made by gradual change of pitch from one note below up to the standard over the sound duration. The rhythm deviant was made by shortening a tone by 60 ms but keeping ISI of 5 ms, resulting in the consequent tone arriving earlier than expected. All the deviants were presented 144 times, half of which were played in a major and half in a minor mode, for an overall presentation of 12 min. Randomization was conducted in Matlab and the stimuli were presented to the participants through Presentation software (Neurobehavioural Systems, Berkeley, CA). Participants were instructed to passively listen to sound sequences using headphones, Sennheiser HD 210.

Before the preparation for MEG recording, participants filled background questionnaire and performed a hearing threshold test utilizing the same sounds as in the experiment. We set the sound pressure level to 50 dB above the individual threshold. Then, participants were requested to watch a silenced documentary movie while comfortably sitting on a chair in a shielded chamber.

### 6.3. MEG data acquisition

MEG data were collected at the Biomag Laboratory of the Helsinki University Central Hospital, in an electrically and magnetically shielded

room (ETS-Lindgren Euroshield, Eura, Finland) with Vectorview™ 306-channel MEG scanner (Elekta Neuromag®, Elekta Oy, Helsinki, Finland). The scanner presented 102 sensor elements comprehending 102 orthogonal pairs of two planar gradiometer SQUID sensors and 102 axial magnetometer SQUID sensors. We placed the ground electrode on the right cheek, while the reference one was on the nose tip. Blinks, as well as horizontal and vertical eye movements, were measured with four electrodes attached above and below the left eye and close to the external eye corners on both sides. The sample rate of the registration was 600 Hz.

### 6.4. MRI data acquisition

MRI data acquisition was conducted using a 3T MAGNETOM Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany) and a standard 32-channel head-neck coil. The measurements took place at the Advanced Magnetic Imaging (AMI) Centre (Aalto University, Espoo, Finland). We collected T1-weighted structural images to be able to perform individual co-registration with MEG data during our offline analysis. In this case, we used the following parameters: 176 slices; field of view = 256 × 256 mm; matrix = 256 × 256; slice thickness = 1 mm; interslice skip = 0 mm; pulse sequence = MPRAGE.

### 6.5. Preprocessing of MEG signals

First, aiming to minimize the affection of external and nearby noise sources and automatically individuate and correct bad MEG channels, the data was pre-processed by using Elekta Neuromag™ MaxFilter 2.2 (Elexta Oy, Helsinki, Finland) temporal Signal Space Separation (tSSS) (Taulu and Hari, 2009). We utilized the default inside expansion order of eight, outside expansion order of three, automatic optimization of both outside and inside bases, raw data buffer length of 10 s and subspace correlation limit of .98. The following data processing was performed by using FieldTrip, version r9093 (Donders Institute for Brain, Cognition and Behaviour/Max Planck Institute, Nijmegen, the Netherlands) (Oostenveld et al., 2011), and OSL (Woolrich et al., 2009), open source Matlab (MathWorks, Natick, Massachusetts) toolboxes widely used for MEG analysis. On average one channel (within the range 0 to 10 channels) per participant was marked 'bad' and replaced by interpolations of the activity measured in the neighbouring channels. The data was down-sampled from 600 to 300 Hz, and high- and low-pass filters were applied with cut-off frequencies at 1 and 25 Hz, respectively. Artefacts such as eye movements and cardiac activity were detected and removed by applying Independent Component Analysis (ICA) with the logistic infomax algorithm implemented in the *runica* function for Matlab (Haumann et al., 2016; Makeig et al., 1996). The number of removed artefactual ICA components per participant was on average .6 (range 1 to 3 components) for the MEG gradiometers and 2.6 (range 1 to 3 components) for the MEG magnetometers. Then, the data was segmented into epochs related to the six different deviant types and standard trials, choosing a pre-stimulus baseline correction from -100 to 0 ms in relation to the stimulus onset and a post-stimulus time-window of 300 ms. We rejected trials with artefacts with amplitudes exceeding 2000fT, or 400fT/cm. The average of rejected trials was 2% for the MEG gradiometer data, evenly distributed across the deviant types and standard trials. Conversely, we did not discard any data for the MEG magnetometers. The average standard response of each participant was then subtracted from the correspondent average deviant responses to isolate the neural waveforms associated to deviant detection. Moreover, to present a more complete overview of the relationship between COMT Val158Met polymorphism and neural response indexing deviant detection, we have provided a new figure (Figure S3) in the Supplementary Materials showing the relative contribution of neural responses to deviants and standards (meaning without subtracting standards from deviants) grouped according to COMT polymorphism.

### 6.6. Genotyping

Deoxyribonucleic acid (DNA) extraction was performed by THL Biobank, National Institute for Health and Welfare, Helsinki, Finland. DNA was extracted from K2-EDTA-blood tubes using chemagic 360 instrument with the CMG-704 kit (PerkinElmer), which uses patented magnetic bead technology. Next, DNA was eluted in 400µl 10mM Tris-EDTA elution buffer (PerkinElmer) and its concentration measured with Quant-iT™ PicoGreen™ dsDNA Assay Kit. DNA samples were aliquoted with Tecan Genesis/Tecan Freedom Evo and shipped on dry ice for genetic analyses. Genotyping was performed with Illumina Infinium PsychArray BeadChip and quality control (QC) was carried out with PLINK. Markers were removed for missingness (>5%), Hardy-Weinberg equilibrium (p-value $< 1 \times 10^{-6}$), and low minor allele frequency (< 0.01). Individuals were checked for missing genotypes (>5%), relatedness (identical by descent calculation, PI_HAT>0.2) and population stratification (multidimensional scaling).

### 6.7. COMT descriptive statistics

As illustrated in **Fig. 1B**, participants were divided into two different groups, according to their COMT genotype. These groups were formed on the basis of the hypothesis that different COMT genotypes altered the optimum flux of catecholamines in the brain, and especially pre-frontal cortex (PFC) (on the "Inverted U" shaped model). Thus, COMT homozygotes Val/Val and Met/Met (altered level of catecholamines, lower and higher respectively) were grouped together into the homozygous group (50 participants), while Val/Met (optimum level) were grouped in the heterozygote group (58 participants). Differences between groups among demographic data and handedness were calculated through independent sample Student t-tests for continuous variables, and Chi-squared ($X^2$) tests for categorical variables. Results are reported in **Table ST1**.

### 6.8. MEG sensor brain responses to deviants and COMT

We performed statistical analysis only for MEG gradiometers because of their better signal-to-noise ratio compared to MEG magnetometers (in Bonetti et al. 2017, 2018, and Haumann et al., 2016 are presented quantitative measures of signal-to-noise ratio for this same dataset). Thus, we have combined the planar gradiometers channels by root-sum-square, obtaining a neural signal that was less noisy and deprived from its original polarity. As illustrated in **Fig. 1C**, to test the hypothesized difference in terms of neural amplitude to deviants between the two COMT groups, a two-sample Student's t-test was performed for each time point and each of the 102 pairs of combined gradiometer MEG channels. The differences were considered significant with $p < .01$. The t-tests were conducted in a 300 ms time-window from the sounds onset with a sampling rate of 300 Hz, resulting in 92 time-points ( 3.33 ms each). To correct for multiple comparisons, a 1000-permutation MCS was computed to identify the significant clusters over time and space of neighbouring channels where the neural amplitude differed between the two COMT groups. First, we conducted this procedure on the neural responses averaged for the six deviants. Afterward, in order to deepen the analyses, we performed the same procedure independently for the neural response to each deviant. We considered significant the clusters that emerged from the MCS with a cluster-forming threshold of $p < .0014$ (corresponding to $\alpha = .01$ divided by the seven independent analyses that we performed. This was done to correct for multiple comparisons). Finally, we calculated analogous MCS also on the other direction of the contrast (COMT homozygotes vs heterozygotes).

### 6.9. Source reconstruction and COMT

As depicted in **Fig. 1B**, after computing the statistical analysis for MEG sensors, we conducted a further investigation in source space.

To this aim, using OSL, a freely available toolbox for MEG analysis (Woolrich et al., 2009), we reconstructed the sources of the MEG signal recorded above the scalp by using an overlapping-spheres forward model built by combining MRI T1 data with fiducial points recorded during the MEG session and a beamformer algorithm as inverse model Hillebrand and Barnes (2005). We used an 8 mm grid including both planar gradiometers and magnetometers. Specifically, the spheres model was an approximation of the MNI-co-registered anatomy, represented as a simplified geometric model that used a basic set of spherical harmonic volumes (Huang, Mosher, and Leahy, 1999). Conversely, the beamforming algorithm utilized a set of weights that were sequentially applied to the source locations to estimate the contribution of each brain source to the activity recorded by the MEG sensors. This was done for each time-point (Brookes et al., 2007; Hillebrand and Barnes, 2005). Then, we contrasted the brain activity reconstructed in source space in response to deviant vs standard sound stimulation. This was done by using a GLM at each dipole location and for each time-point (Hunt et al., 2012). Afterwards, we calculated the absolute value of the reconstructed time-series to prevent sign ambiguity of the neural signal and we computed first-level analysis, consisting of contrasts of parameter estimates for each time-point, dipole and participant. These results were then submitted to a second-level analysis, using paired-sample t-tests contrasting COMT heterozygous vs homozygous participants. Here, we employed a spatially smoothed variance computed with a Gaussian kernel (full-width at half-maximum: 50 mm). In conclusion, to correct for multiple comparisons, we utilized a cluster-based permutation test (Hunt et al., 2012) with 5000 permutations on the second-level analysis results. In this case, we investigated only the significant time-windows emerged from MEG sensor level analysis independently for each deviant and therefore we considered an $\alpha$ level = .05, corresponding to a cluster forming threshold $t$-value = 1.7.

Please note that the required statement for data and codes availability has been provided at the end of this document as well as in the dedicated document attached to this submission.

## 7. Data availability statement

The code and anonymized neuroimaging data from the experiment are available upon request. The codes can be made available without particular restrictions and parts of the analysis and figures may be reproduced by running such codes. The parts that cannot be reproduced regard large computations (mainly related to preprocessing steps) that required a cluster of computers as the one that we use in our facilities at Aarhus University. However, the codes should provide all the necessary information even when they cannot be run. Regarding the data, we will be able to share upon request data that is completely anonymized and that cannot lead in any way to the original participants identity, according to Danish regulations. Otherwise, a data sharing agreement must be made .

## Declaration of Competing Interest

The authors declare no competing interests.

## Credit authorship contribution statement

**L. Bonetti:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curtion, Writing – original draft, Writing – review & editing, Visualization. **S.E.P. Bruzzone:** Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **N.A. Sedghi:** Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing. **N.T. Haumann:** Methodology, Software, Formal analysis, Data curtion. **T. Paunio:** Conceptualization, Investigation, Resources, Writing – review & editing, Supervision. **K. Kantojärvi:** Investigation. **M. Kliuchko:** Investigation. **P. Vuust:** Validation, Resources, Writing – review & editing, Supervision, Funding acquisition. **E. Brattico:** Conceptualization, Validation, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2021.117954.

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