Genetic polymorphisms in COMT and BDNF influence synchronization dynamics of human neuronal oscillations

Jaana Simola *1,2,3¶, Felix Siebenhühner 1¶, Vladislav Myrov 1,4, Katri Kantojärvi 5,6,

Tiina Paunio 5,6, J. Matias Palva 1,4,7, Elvira Brattico 8,9& & Satu Palva *1,7&

1 Neuroscience Center, Helsinki Institute of Life Science, University of Helsinki, P.O. Box 21, (Haartmaninkatu 3), FI-00014 Helsinki, Finland
2 Helsinki Collegium for Advanced Studies (HCAS), University of Helsinki, Finland
3 BioMag Laboratory, HUS Medical Imaging Centre, FI-00029 HUS, Finland.
4 Department of Neuroscience and Bioengineering (NBE), Aalto University, 02150 Espoo, Finland
5 Genomics and Biomarkers Unit, Finnish Institute for Health and Welfare, Helsinki, FI-00271 Helsinki, Finland
6 Department of Psychiatry and SleepWell Research Program, Faculty of Medicine, University of Helsinki and Helsinki University Central Hospital, Helsinki, FI-00014 Helsinki, Finland
7 Centre for Cognitive Neuroimaging (CCNi), Institute of Neuroscience and Psychology, University of Glasgow, Glasgow G12 8QB, UK.
8 Center for Music in the Brain (MIB), Department of Clinical Medicine, Aarhus University & The Royal Academy of Music Aarhus/Aalborg, 8000 Aarhus C, Denmark
9 Department of Education, Psychology, Communication, University of Bari Aldo Moro, 70121 Bari, Italy

* Corresponding authors:
E-mail: jaana.simola@helsinki.fi (JS); satu.palva@helsinki.fi (SP)

¶These authors contributed equally to this work.
&These authors also contributed equally to this work.
**Abbreviations**

5-HT = 5-hydroxytryptamine

DA = dopamine

DAN = Dorsal attention network

DMN = Default Mode network

FPN = Frontoparietal network

Lim = Limbic system

NE = noradrenaline

SM= Somatomotor network

VAN = Ventral attention network

Vis = Visual network
Abstract

Neuronal oscillations, their inter-areal synchronization and scale-free dynamics constitute fundamental mechanisms for cognition by regulating communication in neuronal networks. These oscillatory dynamics have large inter-individual variability that is partly heritable. However, the genetic underpinnings of oscillatory dynamics have remained poorly understood. We recorded resting-state magnetoencephalography (MEG) from 82 participants and investigated whether oscillation dynamics were influenced by genetic polymorphisms in Catechol-O-methyltransferase (COMT) Val$^{158}$Met and brain-derived neurotrophic factor (BDNF) Val$^{66}$Met. Both COMT and BDNF polymorphisms influenced local oscillation amplitudes and their long-range temporal correlations (LRTCs), while only BDNF polymorphism affected the strength of large-scale synchronization. Brain criticality framework and computational modelling of near-critical synchronization dynamics suggested that COMT and BDNF polymorphisms influenced local oscillations via differences in net excitation-inhibition balance. Our findings demonstrate that COMT and BDNF genetic polymorphisms contribute to inter-individual variability in local and large-scale synchronization dynamics of neuronal oscillations.
Introduction

Spontaneous brain activity is characterized by neuronal oscillations from infra-slow (0.01–1 Hz) to high (200–600 Hz) frequency bands throughout the neuroanatomical scales from microcircuits to whole-brain networks. Sub-second time-scale oscillations (> 1 Hz) and their inter-areal synchronization play fundamental mechanistic roles in cognitive functions by regulating neuronal processing and communication across distributed brain areas [1-3]. In humans, dynamics of neuronal oscillations and their long-range phase synchronization, i.e., electrophysiological functional connectivity (FC), that can be observed non-invasively in magneto- (MEG) and electroencephalography (EEG) recordings, serve fundamental roles in a variety of sensory, motor, and cognitive functions [4-8]. During rest, brain activity in sub-second time-scales is dominated by alpha oscillations [6], but involves frequency-specific inter-areal correlation structures throughout the 1–100 Hz range [9-14]. Importantly, the intrinsic spatial organization of spontaneous resting-state FCs observed both with MEG and functional magnetic resonance imaging (fMRI) is predictive of individual variability in task performance [12, 14-16], suggesting that such resting-state FC networks reflect underlying individual brain structural organization [17, 18].

Whole-brain modeling of multimodal neuroimaging data shows that neuromodulatory systems dynamically modulate the structural connectome over time, allowing flexible and complex computations [19]. Neuromodulation is involved in, e.g., sustained attention, arousal, and vigilance, where it is associated with fluctuations in neuronal excitability [20, 21] in the time-scale of seconds to minutes. Catecholaminergic, dopamine (DA) and noradrenaline (NE) [22, 23], as well as the serotonergic (5-hydroxytryptamine; 5-HT) [20, 24, 25] neuromodulatory drive could constitute an important source for variability in neuronal dynamics by modulating oscillations either via changes of instantaneous activity state through common excitatory drive / gain or via dynamic state changes on slower timescales [20, 26-28].
In human MEG/EEG and intracranial electrophysiology, slow (0.1–1 Hz) and infra-slow
(0.01–0.1 Hz) fluctuations are visible in scalp potentials and amplitude envelopes of fast > 1 Hz
oscillations [9, 29, 30]. These fluctuations impact behavioral performance in sustained tasks [29].
Further, these fluctuations are scale-free, i.e. without a characteristic time-scale and exhibit power-
law autocorrelations in their strength known as long-range-temporal correlations (LRTCs) [29, 31-
35]. Similarly to instantaneous oscillations dynamics, inter-individual variability in neuronal
LRTCs predicts variability in task-related behavioral LRCTs [35, 36].
A large fraction of variability in these neuronal dynamics could be heritable and explained
by differences in genetic background. MEG spectral power shows similarities between siblings [37,
38]. Twin studies indicate that peak frequencies [39] as well as LRTCs of local cortical oscillations
[40] have a genetic basis, so that up to 60% of the variance in neuronal LRTCs [40] and up to 85%
of the variance in cognitive ability [41] can be attributed to genetic factors. However, what these
genetic factors are and how they contribute to the inter-individual variability of synchronization
dynamics, including oscillation amplitudes, large-scale synchronization, and LRTCs, have
remained central unresolved questions.
Genetic polymorphism in the genes regulating the catabolism and re-uptake of the
neurotransmitters could constitute an important source for this variability by modulating
fluctuations of oscillations via their influence in the neuromodulator levels. Brain DA and NE levels
are regulated by their catabolism via COMT enzyme [42, 43] of which activity is influenced by a
common single-nucleotide polymorphism (SNP) in the COMT gene substituting methionine (Met)
for valine (Val) at codon 158 at sequence 4680 (Val^{158}Met (rs4680)). COMT Val^{158} homozygotes
have higher COMT activity and therefore lower brain DA and NE levels than Met^{158} homozygotes,
with activity for heterozygotes falling in the middle [44]. A considerable fraction of the variance in
serotonin levels, on the other hand, is explained by Val^{66}Met (rs6265) polymorphism of the gene
coding for BDNF, which influences 5-HT receptor binding [45] and the activity-dependent secretion of BDNF [46]. Compelling evidence indicates that COMT Val158Met (rs4680) polymorphism is associated with modulation of neuronal activity in fMRI, especially in the prefrontal cortex (PFC) and with cognitive functions dependent on PFC [23, 47-49] while BDNF Val66Met polymorphism is implicated in many aspects of behavior and cognition [24, 25]. In addition to modulation 5-HT levels, activity-dependent release of BDNF also influences the maintenance and formation of neuronal networks [50, 51], thereby influencing cognition and behavior over lifetime.

We hypothesized here that COMT Val158Met and BDNF Val66Met polymorphisms could influence oscillation amplitudes, phase synchronization, and their LRTCs and contribute to the large inter-individual variability therein. We furthermore postulated that these effects could be achieved via modulations of brain criticality. More specifically, scale-free LRTCs are hallmarks of systems with critical or near-critical dynamics, suggesting that the brain operates near a critical phase transition between disorder and order, i.e., between inadequate and excessive synchronization, respectively. Importantly, brain criticality is primarily thought to be controlled by the excitation-inhibition (E/I) ratio so that critical dynamics emerge at balanced E/I while excess of inhibition or excitation leads to sub- or super-critical dynamics, respectively [33, 52, 53]. Here, the E/I balance, or “neuronal gain”, indicates the functional net effects of inhibitory and excitatory synaptic, cellular, biophysical, and microcircuit mechanisms at the systems-level [54]. Brains may normally operate in a slightly subcritical regime [55], where LRTCs in human brain activity [31, 32, 35, 36] exhibit large inter-individual variability. We hypothesized that modulations in oscillation dynamics would be obtained via inter-individual differences in the neuromodulation levels, which could result in differences in systems-level net E/I balance (or neural gain). In the brain criticality framework, the carriers of different variants of the COMT Val158Met and BDNF
Val\textsuperscript{66}Met polymorphisms, would therefore be located closer to or further away from the critical point (Fig 1A-B). This would lead to the different genotype cohorts (Fig 1B) showing consistent differences in local amplitudes, global synchronization, and LRTCs (Fig 1C-D, see Fig 1A).

Alternatively, \textit{COMT} and especially \textit{BDNF} could induce plastic changes in the structural connectivity networks (SC) \cite{50, 51} which in turn could lead to changes in FC \cite{17}. To test these hypotheses, we measured resting-state brain dynamics with MEG and estimated local oscillation amplitudes, large-scale phase synchronization, and LRTCs from individually source-reconstructed MEG data. We then investigated their correlation with the \textit{COMT} Val\textsuperscript{158}Met and \textit{BDNF} Val\textsuperscript{66}Met polymorphisms estimated from SNP analysis (Fig 1) and compared the results with predictions from computational modeling. In line with the predictions of the brain criticality framework and computational modeling, we found that the \textit{COMT} Val\textsuperscript{158}Met and \textit{BDNF} Val\textsuperscript{66}Met polymorphisms influenced local oscillation amplitudes and LRTCs, and that correlations between oscillation amplitudes and LRTCs were stronger in the polymorphism groups that were located closer to the critical point. The \textit{BDNF} polymorphism contributed also to the strength of large-scale synchronization, but the strongest effects on global synchronization were due to other mechanisms than the shift in the system’s E/I balance.

\textbf{Fig 1. A schematic of study outline and rationale.}

(A) Computational model of local and inter-areal synchronization dynamics in the realistic human connectome shows that both local (amplitude) and inter-areal synchronization increase monotonically with increasing coupling (control parameter K) and exhibit a phase-transition between low- (subcritical) and high-synchronization (supercritical) regimes. Conversely, the DFA scaling exponent, a measure of long-range temporal correlations (LRTCs), peaks at the critical point. The model predicts that two cohorts (A, B) with subjects operating in different parts of the
subcritical regime should exhibit group differences in amplitude, LRTCs, and inter-areal synchronization. (B) Genotyping of the participants \((N = 82)\) was used to identify the \textit{COMT} Val\textsuperscript{158}Met (rs4680) and \textit{BNDF} Val\textsuperscript{66}Met (rs6265) genetic polymorphisms. (C) MEG data were source-reconstructed using minimum-norm estimation with individual MRI-based head and cortical surface anatomy and filtered to narrowband signals of cortical parcels. Oscillation mean amplitudes and LRTCs were estimated for each parcel and inter-parcel phase synchronization for all parcel pairs. (D) In group analyses, we assessed the anatomical distribution of mean amplitudes, LRTCs, and synchronization within the polymorphism groups and identified statistically significant differences between these groups (Figs 2–4).

**Results**

\textit{COMT} Val/Met and \textit{BDNF} Val polymorphisms are associated with the strongest oscillation amplitudes

To characterize local synchronization, we first evaluated mean oscillation amplitudes for 26 wavelet frequencies between 3–60 Hz and averaged the mean amplitudes across 148 cortical parcels separately for participants grouped according to the \textit{COMT} Val\textsuperscript{158}Met (Val/Val, Val/Met, Met/Met) and the \textit{BDNF} Val\textsuperscript{66}Met (Val/Val and the combined Val/Met and Met/Met) polymorphisms. As observed commonly in resting state, oscillation amplitudes peaked in the alpha band \((\alpha, 8–14 \text{ Hz})\) (Fig 2A). We then clustered oscillations to frequency bands based on the similarity of the anatomical amplitude maps using Louvain clustering (S1 Fig) that revealed spatial similarity in theta \((\theta, 3–7 \text{ Hz})\), alpha, beta \((\beta, 14–30 \text{ Hz})\) and gamma \((\gamma, 30–60 \text{ Hz})\) frequency bands. Statistical analysis for these frequency bands using repeated measures ANOVA demonstrated a main effect of frequency \([F(1.86, 150.76) = 98.54, p = 6.47E-27, \eta^2_p = 0.549]\) \((N = 82)\) on oscillation amplitudes.
at the whole-brain level. Post-hoc tests indicated that the oscillation amplitudes were stronger in
the $\alpha$ band than in the $\theta$ ($t(81) = 14.14, p = 8.93E-23$), $\beta$ ($t(81) = 2.75, p = 0.043$) and $\gamma$ ($t(81) = 5.11, p = 1.3E-5$) bands (t-test, Bonferroni corrected). $\beta$-band amplitudes were also stronger than in $\theta$ ($t(81) = 15.71, p = 1.57E-25$) and $\gamma$ ($t(81) = 5.49, p = 3.0E-6$) bands, and $\gamma$ amplitudes were stronger than $\theta$ band amplitudes ($t(81) = 12.73, p = 2.75E-20$). We also showed in these frequency bands that $COMT$ Val$^{158}$Met and $BDNF$ Val$^{66}$Met polymorphisms had no impact on oscillation amplitudes at the whole-brain level (S2 Fig). We further confirmed that oscillation amplitudes were not dependent on the age or gender of the participants (S1 and S2 Tables).

**Fig 2. COMT and BDNF polymorphisms influence oscillation amplitudes.**

(A) Oscillation amplitudes averaged across parcels for the $COMT$ (Val/Val, purple, $n = 18$; Val/Met, turquoise; $n = 48$; and Met/Met, orange, $n = 16$) and $BDNF$ polymorphism groups (Val/Val, purple, $n = 66$; Met carriers, orange, $n = 16$). Shaded areas represent 95% bootstrapped confidence intervals of the group means. (B) The fraction $P$ of parcels with a significant positive and negative pairwise difference (shown separately) between the $COMT$ and $BDNF$ polymorphisms groups in oscillation amplitudes (Mann–Whitney-U test, $p < 0.05$). The light grey area indicates the 5% alpha level for findings expected by chance under the null hypothesis and the dark grey area indicates the range (3% total) in fractions of significant parcels observable by chance at $p_q < 0.05$ in any single frequency band across the spectrum (26 frequencies). (C) Cortical parcels where the amplitudes differed significantly between polymorphism groups (indicated above the brain surfaces) in the $\theta$ (3–7 Hz), $\beta$–$\gamma$ (20–60 Hz), and $\alpha$ to low-$\beta$ (7–18 Hz) frequency ranges in at least one of the individual frequencies. The color scale indicates the max-normalized amplitude differences for $COMT$ (red) and $BDNF$ (blue) polymorphisms independently, so that parcels where the effects are co-localized have purple hues. Abbreviations are formed from a combination of i)
Areas: a = anterior, ca = calcarine, d = dorsal, i = inferior, la = lateral, m = middle, mrg = marginal, opc = opercular, p = posterior, s = superior, tr = triangular and ii) Lobes: C = central / cingulate, F = frontal, P = parietal, O = occipital, T = temporal, and iii) Gyrus = G, Sulcus = S. Additional abbreviations subC = subcentral gyrus/sulcus, preCN = precuneus.

To identify possible anatomically limited polymorphism effects, we tested significant pairwise differences between polymorphism groups at the anatomical resolution of individual parcels and for each frequency. For COMT, the amplitudes were stronger (Mann-Whitney-U test, $p < 0.05$) for Val/Met heterozygotes than for Met or Val homozygotes in the $\theta$ band as well as in the $\alpha$ to low-$\beta$ bands (7–18 Hz) (in up to 24% and 17% of cortical parcels, respectively) (Fig 2B), whereas opposite effects were observed in the high-$\beta$ to $\gamma$ (20–60 Hz) bands (16% for Met, 9% for Val), along with stronger amplitudes in Met compared to Val homozygotes (9%). For BDNF, oscillation amplitudes were stronger for the Val homozygotes than for the Met carriers in the $\theta$ and in the $\alpha$ to low-$\beta$ bands (up to 23% of the parcels), whereas a small opposite effect was observed in high-$\beta$ to $\gamma$ bands. We next plotted the amplitudes in each cortical parcel separately for each polymorphism group (S3-S4 Figs) and their significant differences (Fig 2C) in the cortical anatomy. Stronger oscillation amplitudes for the COMT Val/Met heterozygotes were localized to the central sulcus (CS), anterior, mid- and posterior cingulate cortex (aCC, mCC, pCC), inferior frontal gyrys (iFG), right-hemispheric middle frontal gyrus (mFG) and inferior parietal gyrus (iPG), inferior part of the insula (iINS) and precuneus (preCN) (Fig 2C). The parcels were co-localized with fMRI-based functional parcellation (S5 Fig), which revealed that these parcels mostly belonged to the frontoparietal network (FPN) and default mode network (DMN). Of these regions, iPG and left iINS and left CS showed also larger amplitudes for BDNF Val homozygotes than for Met carriers. However, the larger amplitudes for COMT Met homozygotes compared to Val/Met heterozygotes
in the $\beta$-$\gamma$ bands were localized to superior precentral sulcus (spreCS), corresponding to frontal eye fields (FEF). For $BDNF$ Val homozygotes, oscillation amplitudes were larger than in Met carriers in iFS, parieto-occipital sulcus (POS) and postcentral sulcus (poCS) in $\theta$ to low-$\beta$ bands. $COMT$ and $BDNF$ jointly affected the $\theta$ and the $\alpha$ to low-$\beta$ band oscillation amplitudes in the CS and iPG.

In the high-$\beta$ to $\gamma$ bands, oscillation amplitudes were stronger for the $COMT$ Val or Met homozygotes as compared to Val/Met heterozygotes in preCS, aCC, pCC and the middle frontal gyrus (mFG) and for the $BDNF$ Met carries as compared to $BDNF$ Val homozygotes in the superior frontal gyrus (sFG) of the left hemisphere and middle temporal gyrus (mTG) of both hemispheres (Fig 2C). However, when amplitudes were averaged within the fMRI-based functional systems, no evident patterns emerged (S5-S6 Figs).

$COMT$ Val$^{158}$Met and $BDNF$ Val$^{66}$Met polymorphisms influence DFA scaling exponents

We quantified long-range temporal correlations (LRTCs) in oscillation amplitude fluctuations by using detrended fluctuation analysis (DFA) [56] and estimated the mean DFA scaling exponents in all wavelet frequencies (3–60 Hz). To obtain a whole brain view on LRTCs, DFA exponents were first averaged across parcels separately for each $COMT$ Val$^{158}$Met and $BDNF$ Val$^{66}$Met polymorphism group for each frequency (Fig 3A). Statistical analysis for the canonical frequency bands with repeated measures ANOVA showed a main effect of frequency [$F(2.16, 174.70) = 123.65, p = 9.85E-36, \eta^2_p = 0.604]$ ($N = 82$). Post-hoc test indicated that DFA exponents in $\alpha$ band were stronger than in $\theta$ ($t(81) = 13.00, p = 1.00E-22$), $\beta$ ($t(81) = 10.00, p = 1.14E-11$) and $\gamma$ ($t(81) = 12.80, p = 3.58E-21$) bands (t-test, Bonferroni corrected). Similarly, also the $\beta$ band DFA exponents were stronger than in $\theta$ ($t(81) = 10.33, p = 5.09E-14$) and $\gamma$ ($t(81) = 10.75, p = 6.04E-17$)
bands, and the DFA exponents in $\theta$ band were stronger than in $\gamma$ band ($t(81) = 3.00, p = 0.008$).

$COMT$ polymorphism had an effect on whole-brain DFA exponents in the $\gamma$ frequency band averaged across the brain and within the canonical frequency band (univariate ANOVA, $[F(2, 75) = 3.80, p = .027, \eta^2_p = 0.092]$), when age was controlled for ($n = 79$) (S2 Fig). Group mean exponents were higher at the $\gamma$-band for the $COMT$ Val/Met individuals than for the Val/Val ($t(64) = 2.08, p = 0.043$, uncorrected) and Met/Met ($t(62) = 3.50, p = 0.001$) individuals when equal variances were not assumed. The $BDNF$ polymorphism affected the whole-brain DFA exponents in the $\alpha$ band $[F(1, 76) = 4.19, p = .044, \eta^2_p = .052]$ whereby the Val homozygotes exhibited larger LRTC exponents than the Met carriers (Fig 3A and S2).

Fig 3. Influence of $COMT$ and $BDNF$ polymorphisms on LRTCs. (A) Detrended fluctuation analysis (DFA) exponents averaged across parcels for the $COMT$ and $BDNF$ polymorphism groups. Shaded areas represent 95% bootstrapped confidence intervals of group means. Black bar with asterisk denotes the range of frequencies with significant differences between the $BDNF$ polymorphism groups (Kruskal-Wallis, $p < 0.05$, uncorrected). (B) Fractions ($P$) of parcels with a significant positive and negative difference between $COMT$ and $BDNF$ polymorphism groups in the DFA exponents (Mann–Whitney-U test, $p < 0.05$), as in Fig 2B. (C) Cortical areas where significant differences between polymorphism groups in the DFA exponents were found in the $\theta$, $\beta$–$\gamma$ and $\alpha$–$\beta$-bands (Mann–Whitney U test, $p < 0.05$, corrected). Colors and abbreviations as in Fig 2C.

Similar to oscillation amplitudes, $COMT$ Val$^{158}$Met and $BDNF$ Val$^{66}$Met polymorphisms had a more robust effect on the DFA exponents at the resolution of cortical parcels indicating large anatomical heterogeneity. DFA exponents were greater for the $COMT$ Val/Met heterozygotes than
for the COMT Met homozygotes (Mann-Whitney-U test, \( p < 0.05 \)) in the \( \theta \) band (up to 35% of parcels) and in the \( \beta-\gamma \) band (up to 60%) (Fig 3B). Further, \( \theta \) band DFA exponents were greater for Val/Val than for Met/Met (18%) and \( \beta-\gamma \) DFA exponents were greater in Val/Met than for Val/Val (49%) (Fig 3B). For BDNF, a robust effect of polymorphism was found for DFA exponents. These were greater for Val homozygotes than Met carriers in the \( \theta \) band (57%) and in \( \alpha \)- low-\( \beta \) bands (83%) (Fig 3B). The effect of COMT Val\(^{158}\)Met and BDNF Val\(^{66}\)Met on DFA exponents was thus more extensive compared to that found for oscillation amplitudes. The localization of DFA exponents for each polymorphism group (S7-S8 Figs), and their significant differences (Fig 3C) revealed wide-spread group differences. In the \( \theta \) band, large differences between COMT Val/Met heterozygotes and Met homozygotes and between BDNF Val homozygotes and Met carriers were co-localized to preCS, mCC, and mFG (Fig 3C). DFA exponents in \( \theta \) band were also greater for COMT Val/Met group in INS, pCC, and in \( \beta-\gamma \) band particularly in parcels of the somatomotor (SM) network, and DMN. BDNF Val homozygotes had greater \( \alpha \)-low-\( \beta \) band LRTC exponents than Met carriers nearly in all parcels of the cortex (Fig 3C). Co-localization with fMRI-based functional parcellations reproduced these findings, but again revealed no evident patterns in the localization (S9 Fig).

Finally, to gain insight for the common effects of COMT Val\(^{158}\)Met and BDNF Val\(^{66}\)Met polymorphisms on oscillation amplitudes and DFA exponents, we co-localized their effects. This revealed co-localization in the parcels of PFC and PPC, CS and anterior cingulate structures (S10 Fig). The effects of COMT and BDNF polymorphisms on LRTCts were widespread, in line with prior work and with the idea that LRTCts reflect global fluctuations in neuronal activity across the brain’s modular structure [13, 29, 35].
**BDNF** polymorphism correlates with the strength of large-scale phase-synchronization

To obtain a global view on the influence of **COMT** Val^{158}Met and **BDNF** Val^{66}Met polymorphisms on neuronal dynamics, we estimated their impact on inter-areal phase coupling of neuronal oscillations a.k.a. synchronization that constitutes a key characteristic of individual cortical dynamics and has fundamental influence on behavior [1, 3, 4, 7, 11, 16]. We estimated phase-synchrony among all cortical parcels with the weighted phase-lag index (wPLI) that is less sensitive to linear source mixing [57] and computed the mean synchronization for each of the **COMT** Val^{158}Met and **BDNF** Val^{66}Met polymorphism group (Fig 4A). At the whole brain level, the mean phase-synchrony varied between the canonical frequency bands as indexed by a main effect of frequency in a repeated measures ANOVA \[F(1.69, 136.53) = 18.29, \ p = 5.45E-7, \ \eta_p^2 = .184\] \(N = 82, \) S2 Fig. Synchronization was stronger in the \(\alpha\) band compared to \(\theta\) \((t(81) = 3.00, \ p = 2.12E-4)\) and \(\beta\) bands \((t(81) = 13.04, \ p = 3.14E-20)\), while mean synchrony did not differ between \(\alpha\) and \(\gamma\), and \(\theta\) and \(\gamma\) bands \((t-test, \) Bonferroni corrected). Synchronization was overall weakest in the \(\beta\) band as compared with \(\theta\) \((t(81) = 7.54, \ p = 7.09E-11)\), \(\alpha\) and \(\gamma\) \((t(81) = 3.00, \ p = 0.004)\) bands.

**Fig 4.** **BDNF** polymorphisms influence large-scale phase-synchronization. (A) Phase-synchronization averaged across the whole brain for the **COMT** Val^{158}Met and **BDNF** Val^{66}Met polymorphism groups with 95\% bootstrapped confidence intervals. Black bars with asterisks denote the frequencies where a significant group difference was found \((Kruskal-Wallis, \ p < 0.05, \) uncorrected). (B) The differences in the phase synchrony \((\Delta\text{-wPLI})\) within and between functional systems for the **BDNF** Val homozygotes and Met carries, averaged across hemispheres and wavelet
frequencies in these frequency bands. Color indicates $\Delta$-wPLI, red indicating stronger synchronization for $BDNF$ Val$^{66}$ homozygotes and blue for Met carriers. Stars denote the brain system pairs where the group difference was significant (Kruskal-Wallis, *: $p < 0.05$, uncorrected, **: $p < 0.05$, Benjamini-Hochberg corrected). Abbreviations: DAN = Dorsal attention network, DMN = Default Mode network, FPN = Frontoparietal network, Lim = Limbic system, SM = Somatomotor network, Vis = Visual network, VAN = Ventral attention network.

We did not find significant differences (Kruskal-Wallis test, $p < 0.05$) among the $COMT$ Val$^{158}$Met polymorphism groups, but the mean synchronization for $BDNF$ Val homozygotes was stronger than for $BDNF$ Met carriers in the $\theta$ and $\alpha$ frequencies (Fig 4A). To acquire neuroanatomical insight into the patterns of inter-areal synchronization in functional brain systems, we collapsed the parcel-wise synchronization estimates within brain systems defined by fMRI functional connectivity [58] and for the same frequency bands that were used for estimating oscillation amplitudes and LRTCs (S1 Fig). Corroborating the mean-synchronization result, synchronization between or within the subsystems did not differ significantly among the $COMT$ Val$^{158}$Met polymorphisms (absolute values in S11 Fig). However, $BDNF$ Val homozygotes exhibited stronger synchronization than Met carriers in the $\alpha$ band between and within nearly all subsystems (Fig 4B and S11 Fig, Kruskal-Wallis test, $p < 0.05$, corrected with Benjamini-Hochberg). We also computed synchronization separately for each hemisphere and between the hemispheres. Interestingly, synchronization in the $\alpha$ and $\beta$ bands was more robust for the left- and inter-hemispheric connections than for the right-hemispheric connections (S12 Fig). Additionally, $\beta$-band synchronization was stronger for $BDNF$ Val homozygotes than Met carriers in the left-hemispheric attentional networks including FPN, dorsal attention network (DAN), ventral attention (VAN) and Limbic networks (Lim) and DMN.
Computational model-based approach to neuromodulation effects on critical synchronization dynamics.

We hypothesized that at the level of macroscopic brain dynamics, the effects of COMT Val\textsuperscript{158}Met and BDNF Val\textsuperscript{66}Met polymorphisms, could be addressed in the context of brain criticality if these polymorphisms bias the underlying “control parameter” that tunes the distance of neuronal systems to criticality. To assess the relationships of the observable brain dynamics measures with the control parameter, we used a computational model of synchronization dynamics exhibiting a transition from sub- to super-critical dynamics. We implemented a nested Kuramoto model with separable local network (cortical parcel) and large-scale (whole-brain network) levels [12]. Synchronization here was regulated by local and global coupling parameters that simulate the E/I balance (or neural gain) that is the likely primary control parameter for brain criticality [52, 59]. In the model, increasing coupling led to parallel strengthening of local amplitudes, large-scale synchronization, and LRTCs throughout the subcritical regime up to the critical point (Fig 1A). We used modelling to predict the synchronization dynamics of neuronal oscillations for two hypothetical cohorts (A and B) operating in a subcritical regime. The model predicted that the cohort (B), operating at greater excitability / gain, exhibited greater oscillation amplitudes, LRTCs, and large-scale synchronization (Fig 1A, Fig 5A), and as a novel model-predicted measure, their mutual correlations (Fig 5B). To investigate whether COMT and BDNF polymorphism could influence synchronization dynamics via these mechanisms, we computed these dynamics separately for different polymorphism groups. In line with the model predictions, the BDNF Val/Val (Fig 5C) and COMT Val/Met (Fig 5D) groups were associated with significantly elevated amplitudes and LRTCs compared to the other polymorphisms. The BDNF Val/Val group also showed stronger global synchronization (Fig 5C). Further, local correlations between amplitude and criticality in the
θ band were stronger among the BDNF Val/Val and COMT Val/Met groups (Fig 5 E-F) and in the γ bands for BDNF (S13 Fig). While there were no group differences in the correlation between global inter-areal synchronization and criticality in the α band (Fig 5E) where the BDNF polymorphism effects were the strongest, the group differences were in line with the model predictions in the θ band, in which the influence of BDNF polymorphism on global synchronization was weaker. These findings thus provide converging evidence that locally, COMT Val<sup>158</sup>Met and BDNF Val<sup>66</sup>Met polymorphisms impact oscillation dynamics as predicted by the framework of brain criticality under the hypothesis that these polymorphisms influence the control parameter of cortical critical dynamics. In contrast, the most robust effects of BDNF on large-scale synchronization were not in line of the model predictions, suggesting that these were mediated by other factors than the control parameter of brain criticality.

**Fig 5. Model and experimental evidence for modulation of brain criticality.** (A) Local amplitude (A), inter-areal phase synchronization (PLV), and DFA exponents in modeled data for two cohorts A (orange) and B (purple). All metrics are greater for the cohort B that is designed to operate closer to the critical point (see Fig 1) than cohort A. The box ends indicate the lower quartile (Q1, 25th percentile) and upper quartile (Q3, 75th percentile) across cortical regions/parcels, notches indicate the median, and whiskers indicate the range of Q1 – 1.5 * IQR and Q3 + 1.5 * IQR, where IQR is the inter-quartile range (Q3-Q1). (B) Correlations between amplitude and DFA exponents, and between PLV and DFA, in modeled data are also larger for cohort B than the more subcritical cohort A. (C) A and DFA exponents in θ band, and global phase synchronization (wPLI) in α band for the BDNF Val homozygotes (purple) and Met carriers (orange) in MEG data. (D) A and DFA exponents for COMT Val<sup>158</sup>Met polymorphism groups in the θ band. (E) Correlation between A and DFA exponents differs between BDNF Val<sup>66</sup>Met polymorphism groups in the θ-
band, as does the correlation between wPLI and DFA exponents in $\theta$ but not in $\alpha$ band. (F)

Correlation between $A$ and DFA exponents in $\theta$ band differs between $COMT$ Val$^{158}$Met polymorphism groups.

Discussion

Inter-individual variability in spontaneous brain dynamics shapes human behavioral performance and cognitive ability [4, 12, 16, 60, 61]. While the causes of this variability are diverse, genetics influences numerous factors that are important for brain oscillation dynamics on multiple scales observed in human MEG and EEG data [37, 39, 40]. Cellular level influence of macroscopic oscillations can be achieved through regulation of neural circuits and dynamic circuit motifs [2, 37, 39] as well as coupling of metabolic activity and connectivity [15]. However, it is not well understood how the genetic biases of molecular, cellular, and micro-circuit mechanisms translate into alterations of macroscopic brain dynamics that are observable in electrophysiological neuroimaging. We tested here the hypothesis that the $COMT$ Val$^{158}$Met and $BDNF$ Val$^{66}$Met genetic polymorphisms contribute to the variability in emergent local (oscillation amplitudes and LRTCs) and global (inter-areal phase synchronization) dynamics of neuronal oscillations via their regulation of the neuromodulators dopamine (DA), norepinephrine (NE), and serotonin (5-HT). We showed that, indeed, both $COMT$ and $BDNF$ polymorphisms influenced oscillation amplitudes and LRTCs, while the $BDNF$ polymorphism also impacted the strength of global synchronization.
Local oscillation strength and dynamics are modulated by genetic polymorphism in COMT and BDNF

The amplitude of $\theta$ oscillations was greater for COMT Val/Met heterozygotes than for COMT Val or Met homozygotes, and the amplitudes of $\theta$ and $\alpha$ oscillations were greater for BDNF Val homozygotes than for Met carriers. These data thus add to scarce prior observations about COMT polymorphism effects on electrophysiological activity [62-64], which have shown using EEG sensor level analysis that COMT Val homozygotes had lower individual $\alpha$ power in both waking state and sleep than Met homozygotes [63] and that the COMT polymorphism influences phase-resetting of $\gamma$ oscillatory activity in attention [64]. Our results provide strong evidence for COMT polymorphism influencing local amplitude dynamics in widespread brain areas. We furthermore found the BDNF Val homozygotes to exhibit stronger $\alpha$ band amplitudes bilaterally in frontoparietal regions and parcels of the visual system in line with previous research [65] and that 5-HT plays a critical role in modulating cortical activity and neuronal oscillations [66, 67].

To our knowledge, this study is the first to report the influence of genetic polymorphism on LRTCs in oscillation amplitude fluctuations. LRTCs were stronger for the COMT Val/Met heterozygotes than for Val or Met homozygotes and stronger for BDNF Val homozygotes than for Met carriers, demonstrating that near-critical dynamics of brain oscillations is influenced by COMT and BDNF polymorphisms. The temporally widespread effects of COMT and BDNF polymorphisms on both instantaneous amplitudes and their LRTCs could putatively stem from COMT influencing both phasic and tonic firing modes of DA neuronal spiking [68] and/or from multi-scale cortical ensemble codes by NE [69].

The finding of the strongest amplitudes and LRTCs in the COMT Val/Met polymorphism group, is consistent with previous findings showing that the impact of neuromodulation on
cognition follows an “inverted-U-shaped” function, where both too little and too much neuromodulation impairs performance [20, 47, 70-72]. The association between COMT Val¹⁵⁸Met polymorphism and neuronal activity has been frequently observed in fMRI to be predominantly localized to PFC, which has low DA reuptake and higher COMT levels. In our data, the influence of COMT Val¹⁵⁸Met polymorphism on instantaneous amplitudes was not localized specifically to PFC, but to multiple specific cortical regions in the FPN and cingulo-opercular (CO) networks. These networks underlie the dual control of executive functions [73] and have been shown to be functionally coupled also in the resting state [74] which is in agreement with the role of DA in cognitive control [70, 75]. Further, our results are in line with brain-wide distribution of catecholamine-induced changes in DA and NE in intrinsic fMRI correlations [21] and with findings that DA innervation covers the entire cortex [76] and Locus Coeruleus’ NE projections reach a variety of targets [69]. Overall, these results support the idea that via DA and NE COMT influences local oscillation dynamics in a variety of cortical regions important for cognition.

**Polymorphism in BDNF but not in COMT influences inter-areal synchronization dynamics**

The influence of BDNF and COMT polymorphisms on large-scale synchronization networks have this far remained uncharted. We found that BDNF Val⁶⁶Met polymorphism influenced large-scale global inter-areal phase synchronization. This effect was robust in the α band, in which stronger synchronization was observed for BDNF Val homozygotes in all functional subsystems except within the visual system. BDNF Val homozygotes also had stronger β band synchronization between the frontoparietal attention networks and DMN, and stronger θ synchronization between DAN and SM networks, but only in the left hemisphere. This robust
modulation of synchronization dynamics by BDNF polymorphism could contribute to significant differences across individuals in behavior and cognition, which have been shown to be strongly influenced by spatial and spectral characteristics of oscillatory synchronization [12, 14, 17].

However, large-scale synchronization was not influenced by COMT Val<sup>158</sup>Met polymorphism. This suggests that catecholaminergic neuromodulatory drive does not play a significant role in instantaneous resting-state network synchronization even though it modulates local oscillatory dynamics in both sub-second and seconds-to-minutes timescales. This finding differs from prior results which have found catecholamines to be related to fMRI-based changes in functional connectivity by using catecholamine blocker atomoxetine [21]. These differences might be explained by different effects of catecholaminergic levels on BOLD signal and electrophysiological connectivity or by COMT polymorphism having more subtle effects on neuronal dynamics compared to neuropharmacological interventions.

**Computational modelling predicts local influences to depend on net excitability**

Near-critical synchronization dynamics has been proposed as a fundamental operating principle of brain functioning, enabling transient and flexible computations that are beneficial for the individual by maximizing information storage and transmission [60, 77-81]. This notion has been supported experimentally by behavioral data [82] and in vitro studies [52]. Here we show that genetic polymorphism in COMT and BDNF influenced the individual near-critical synchronization dynamics and proximity to the critical point.

The systems-level E/I ratio (or gain) is thought to be the primary control parameter for the regulation of critical brain dynamics [52, 59], and to influence brain dynamics using whole-brain modeling [83]. We postulated that the observed differences in neuronal synchronization dynamics
are due to neuromodulation-related shifts in the system’s net E/I ratio and/or gain. Comparison of
the experimental and computational-model data showed that the COMT Val$^{158}$Met and BDNF
Val$^{66}$Met polymorphisms influenced local oscillatory dynamics and their correlations in line with
the brain criticality framework. More specifically, COMT Val$^{158}$Met heterozygotes and BDNF
Val$^{66}$ homozygotes had greater values of and correlations between LRTCs and oscillation
amplitudes than the other polymorphism groups, indicating that they are associated with a higher
value of the underlying control parameter, i.e., with greater net excitatory drive or neuronal gain
[28] compared to COMT$^{158}$ homozygotes and BDNF$^{66}$ Met carriers. This is in accordance with the
framework in which neuromodulatory drive influence brain-state energy landscape facilitating with
transitions in the whole-brain neural states [84, 85].

In contrast, large-scale synchronization that was influenced by BDNF Val$^{66}$Met
polymorphism, was modulated only partially in line with the model predictions. Global α-band
synchronization that was robustly modulated by the BDNF Val$^{66}$Met polymorphism, was correlated
with LRTCs according to the model predictions, but there were no differences between
polymorphism groups. This finding implies that the strongest effects of BDNF polymorphisms on
global synchronization are not due to a shift in the system’s excitation, but to other mechanisms
such as the influence of BDNF on maintenance, maturation, and formation of neuronal networks
[50, 51] putatively via receptor TrkB (neurotrophic receptor tyrosine kinase 2) signaling [86, 87].
These could impact large-scale network synchronization via changes in structural connectivity [17].
Yet, the weaker effect of BDNF polymorphism on θ and β band synchronization was congruent
with changes in the model’s control parameter, suggesting that these global synchronization
patterns might be strengthened also by increased excitatory drive for the BDNF Val$^{66}$ homozygotes.
This finding is in agreement with computational modeling results showing that the dynamic
connectome is explained by dynamical mutual coupling between 5-HT neurotransmitter systems
Thus, $BDNF$ seems to influence critical synchronization dynamics both via modulations in the brain serotonin levels leading to changes in the neuronal gain as well as via other mechanisms influencing the formation and survival of neuronal networks.

Conclusions

Our data showed that the $COMT$ Val$^{158}$Met and $BDNF$ Val$^{66}$Met polymorphisms contribute to the variability of oscillation dynamics. In addition to $COMT$ and $BDNF$, many other genetic factors are likely to contribute to these oscillation dynamics, as observed for the cortical structure [88]. $COMT$ Val$^{158}$Met and $BDNF$ Val$^{66}$Met polymorphisms influenced local oscillatory dynamics putatively via modulations in the neuromodulator levels leading to changes in net excitatory drive or gain in the neuronal networks. At the synaptic level, DA, NE, and 5HT could influence E/I ratio and gain control via various cellular, biophysical, and network mechanisms, including their temporal aspects. Taken that this study did not use neuropharmacological interventions, the specific mechanisms by which $COMT$ and $BDNF$ genetic polymorphisms influence critical oscillation dynamics are beyond the scope of this study.

Because oscillation amplitude fluctuations, LRTCs, and global synchronization dynamics are predictive of behavioral variability over both long [35, 36] and sub-second time scales [4], $COMT$ Val$^{158}$Met and $BDNF$ Val$^{66}$Met polymorphisms may underlie individual differences in trait-like behavior and cognitive performance via their effect on critical oscillatory dynamics and synchronization. Differences in these dynamics caused by genetic polymorphism are likely to influence individuals’ cognitive and mental development and may predispose them to specific brain diseases. In line with the latter idea, alterations in the brain E/I ratio have been suggested to predispose individuals to dementia and Alzheimer’s disease [89]. Our results thus point in new
directions for the investigation of how genetic factors could translate to behavioral variability via modulations of the systems-level neuronal dynamics.

**Materials and methods**

**Experimental Design**

Resting-state brain activity was recorded from healthy volunteers ($N = 82$, 18–55 years of age; mean age: 29 years; 6 left-handed; 44 female) with 306-channel MEG (Vectorview, Elekta-Neuromag, LtD) at a sampling rate of 600 Hz. The subjects fixated on a central fixation cross throughout the ~8 min resting-state MEG-recording (duration 7.8 ± 2.9 min, mean ± standard deviation, S1 and S2 Tables). Blood samples for the collection of DNA were obtained before each MEG session. T1-weighted anatomical magnetic resonance imaging (MRI) MP-RAGE scans were obtained for each participant at a resolution of $1 \times 1 \times 1$ mm using a 1.5 T MRI scanner (Siemens, Germany) on a separate day. The dataset collected for this study is part of a broader project “Tunteet” that includes also other datasets and paradigms. The study was performed in accordance with the Declaration of Helsinki and with permission of the Ethical Committee of the Helsinki University Central Hospital. All participants gave a written informed consent prior to the recordings.

**Genotyping**

DNA was extracted from blood samples according to standard procedures at the National Institute for Health and Welfare. DNA samples were genotyped at Estonian Genome Center using Infinium PsychArray-24 v1.1 (Illumina). Quality control (QC) was performed with PLINK 1.9 ([www.cog-genomics.org/plink/1.9/](http://www.cog-genomics.org/plink/1.9/)) [90]. Markers were removed for missingness (> 5%) and
Hardy-Weinberg equilibrium ($p < 1 \times 10^{-6}$). Individuals were checked for missing genotypes (> 5%), relatedness (identical by descent calculation, PI_HAT > 0.2) and population stratification (multidimensional scaling). Our sample for the COMT gene consisted of 18 Val/Val, 48 Val/Met, and 16 Met/Met individuals (S1 Table). A one-way ANOVA confirmed that the COMT polymorphism groups did not differ in terms of age [$F(2, 46) = 0.05, p = .984$] and the duration of the resting state recording [$F(2, 46) = 0.32, p = .726$]. A chi-square test further confirmed that the percentages of female and male participants did not differ between the COMT polymorphism groups [$X^2(2) = 2.11, p = .349$]. The BDNF sample consisted of 66 Val/Val, 14 Val/Met, and 2 Met/Met individuals (S2 Table). As the Met/Met polymorphism had a low frequency, we combined Met carriers (i.e., Val/Met and Met/Met polymorphisms) into one group [see also 91]. An independent samples t-test (2-tailed) confirmed that the BDNF polymorphisms did not differ in terms of age [$t(32) = 0.20, p = .847$] or the length of the resting state recording [$t(32) = 0.76, p = .444$]. A chi-square test showed no differences in the percentages of female and male participants between the BDNF polymorphisms [$X^2(1) = 0.00, p = .995$].

**Preprocessing and filtering of MEG data**

Signal space separation method (tSSS) [92] with the Maxfilter software (Elekta Neuromag, Helsinki, Finland) was used first to suppress extracranial noise, interpolate bad channels and to coregister the recordings in signal space individually for each participant. Next, independent component analysis (ICA, Matlab toolbox Fieldtrip [93] was used to extract and exclude signal components that were correlated with eye movement, blink and cardiac artifacts. The preprocessed MEG data were filtered into 26 logarithmically spaced frequency bands, $f_{min} = 3$ Hz; $f_{max} = 60$ Hz using complex Morlet Wavelets.
where $\sigma_t = m/2\pi f_0$, $i$ is the imaginary unit, $m (=5)$ defines the compromise between time and frequency resolution, and $f_0$ is the center frequency. After filtering, the time-series data were decimated to a frequency-dependent sampling rate of between 2 and 5 times the center frequency.

**Source Analysis and Surface Parcellations**

Volumetric segmentation of the MRI data, surface reconstruction, flattening, cortical parcellations and neuroanatomical labeling with the Freesurfer/Destrieux atlas [94] were performed using FreeSurfer software (http://surfer.nmr.mgh.harvard.edu/). Single-layer boundary element conductivity models and cortically constrained source models for the MEG-MRI co-localization and the preparation of the forward and inverse operators [95] were carried out using minimum norm estimate with MNE software (https://mne.tools/stable/index.html) [96]. Noise covariance matrices (NCMs) were computed using preprocessed broad-band filtered (125–195 Hz, with 150 Hz notch) MEG time series around synthetic resting state events that were spaced in every 1 seconds and then used to compute minimum-norm estimate (MNE) inverse operators for all wavelet frequencies. These inverse operators were used to project the sensor-space data into source-space. The source models had dipole orientations fixed to the pial surface normal and a 5 mm inter-dipole separation through the cortex, which yielded models containing 5000–8000 source vertices per hemisphere. As in previous studies [12, 97], source-vertex time-series were then collapsed into parcel time series with an individually source-reconstruction-accuracy- (fidelity-) optimized collapse operators. We used a 400-parcel parcellation that was obtained by iteratively splitting the largest parcels of the Destrieux atlas (148 parcels) [94] along their most elongated axis using the same parcel-wise splits for all participants. Parcels were also assigned to functional systems based on Yeo’s 7-parcel
scheme derived from fMRI-connectivity [58]. To control for source-reconstruction accuracy, we estimated parcel fidelity as a measure of source-reconstruction accuracy [97].

**Estimation of oscillation amplitudes and long-range temporal correlations**

The parcel-wise narrow-band filtered time-series were used for cortex-wide mapping of induced oscillation amplitudes (A), LRTCs in oscillation amplitude envelopes, as well as for mapping cortex-wide phase-synchronization networks. Data were averaged for each cortical parcel and frequency separately for subjects in each COMT and BDNF polymorphisms group. The LRTC exponents of the amplitude envelopes were quantified with detrended fluctuation analysis (DFA) [56].

DFA was applied in two stages. First, time series $X(k)$ were normalized to zero mean and the cumulative sum of the signal was computed:

$$y(k) = \sum_{i=1}^{k} [X(i) - \langle X \rangle]$$

The integrated signal $y(k)$ was then segmented into multiple time windows $\Delta t$ from 1 to 100 s with minimum window length of 20 cycles and maximum of 100 (length multiplier 1.2) [31]. Second, each segment of integrated data was locally fitted to a linear function $y_{\Delta t}(k)$ and the mean-squared residual $F(\Delta t)$ was computed:

$$\sqrt{\frac{1}{N} \sum_{k=1}^{N} [y(k) - y_{\Delta t}(k)]^2}$$

where $N$ is the total number of data points.
The power law scaling exponent $\beta$ was defined as the slope of linear regression of the function $F(\Delta t)$ plotted in log–log coordinates, estimated using a least-squares algorithm. The scaling exponent $\beta$ can be considered a measure of temporal clustering so that $0.5 < \beta < 1.0$ indicates power-law scaling behavior and the presence of temporal correlations, whereas values around 0.5 indicate uncorrelated noise.

### Analysis of inter-areal synchronization

To estimate cortex-wide synchronization connectomes, we computed for each subject and for each frequency, phase synchronization between all 400 parcels (or parcels within the left or right hemisphere) using the weighted phase-lag index (wPLI) [98] which is defined as

$$wPLI_{a,b} = \frac{E\{|im(X_{ab})|\}}{E\{|im(X_{ab})|\}} = \frac{|E\{|im(X_{ab})|\text{sign}(im(X_{ab}))\}|}{E\{|im(X_{ab})|\}}$$

where $im(X_{ab})$ is the imaginary part of the cross-spectrum of the complex narrowband time series $Z_a$ and $Z_b$, and $E\{\}$ is the expectancy value operator. The cross-spectrum $X_{ab}$ can be substituted with $Z_aZ_b^*$, where $*$ denotes the complex conjugate, and the mean over samples can be taken as the expectancy value [12]. The wPLI is insensitive to artificial connections arising as direct effects of zero-phase lagged linear signal mixing that is a major issue in connectivity analysis using MEG/EEG data [4]. Spurious interactions, however, remain as 2nd order effects even when using zero-phase lag insensitive connectivity metrics. Since spurious connections are more likely to be reported for regions with low source-reconstruction accuracy, we removed from the analysis parcels with $fidelity < 0.2$, which led to the exclusion of 9.27%, of possible parcel pairs [12, 97].

Graph theory [99] was used to characterize the network structures in group-level adjacency matrices. Each thresholded adjacency matrix defined a graph made up of nodes and edges, where nodes are cortical parcels and edges are the significant interactions between nodes. The mean
connection strengths were obtained by averaging the strength of all valid edges in the connectome for each subject and then over subjects in each COMT and BDNF polymorphism group. For functional subsystem analysis, all pairwise interactions were averaged across the frequency bands defined by clustering analyses (S1 Fig) and then collapsed into the 7 functional systems of the Yeo parcellation [58].

**Computational modelling**

We used a nested Kuramoto model [12] to investigate the covariance and mutual correlations of local synchronization (node/parcel amplitude), inter-areal synchronization, and local LRTCs in a heuristic model of synchronization dynamics. The model was adapted from a conventional Kuramoto model so that it comprised 100 nodes (corresponding to 100 cortical parcels) and each node was modelled by a Kuramoto model of 500 oscillators. The model was defined so that for each node $k$, the temporal evolution of the phase $\theta$ of each oscillator $i$ was described by:

$$\frac{d\theta_k}{dt} = \omega_i + \frac{K}{N_{osc.}} \sum_{j=1}^{N_{osc.}} \sin(\theta_j - \theta_i) + \sum_{l=1}^{N_{nodes}} W_{k,l} \sin(\varphi_l - \theta_i) + N(0, \sigma)$$

where $\omega_i$ is the oscillation frequency of an oscillator, $K$ is the local coupling (control) parameter, $\varphi_l$ is the average phase of the node $l$, $W_{k,l}$ is the connection strength between the node $k$ and other nodes $j$, and $N(0, \sigma)$ is Gaussian noise. For the connection strengths $W$, we used the log-scaled structural connectome of fiber counts based on the Schaefer parcellation with 100 parcels [100] multiplied by a global coupling (control) parameter $L$ at $L = 0.5$.

Node time series mimicking the parcel time series in MEG data were obtained by averaging the complex time series of the oscillators in the node. Local synchronization was measured by the absolute value of the complex node time series (Kuramoto order) that is comparable to the 28
amplitude of MEG parcel time series. Phase Locking Value (PLV) was used to measure the pairwise
synchrony between nodes and, as in MEG data, the LRTCs we quantified with DFA. We estimated
the correlation between amplitudes and DFA exponents, and between synchronization and DFA
exponents, across all nodes, by using Spearman’s correlation coefficient.

**Statistical analysis**

Before statistical testing, time-series were collapsed into the 148 parcels of the original
Destrieux atlas [94] to limit the number of comparisons and to improve statistical stability by
averaging out anatomical variability, which is large across individuals. Group-level upper and lower
confidence limits (2.5% and 97.5%) were computed for each polymorphism group with a
bootstrapping approach, using $N = 1000$ resamplings with replacement of the subjects in the group.
We first used a nonparametric Kruskal-Wallis test ($p < 0.05$) to examine whether amplitudes and
DFA averaged across all parcels within each Morlet frequency were significantly different between
any of the polymorphism groups (Fig 2A, 3A). We then tested pair-wise differences between the
polymorphism groups separately for each parcel and wavelet frequency using the Mann–Whitney
U-test ($p < 0.05$) with multiple comparisons initially accounted for with false discovery reduction
(FDR) by discarding as many least-significant observations as were predicted to be false by the
alpha-level (5% at $\alpha = 0.05$) for each time-frequency bin. We further estimated a threshold (see
dark grey area in Figs. 2B and 3B) for the residual fraction of significants so that the probability,
$p_q$, for finding a fraction of significant value above this threshold by chance in any single frequency
out of all wavelet frequencies is $p_q < 0.05$.

To test the *COMT* and *BDNF* polymorphism effects on A and DFA on canonical frequency
bands, we first estimated spatial similarity across frequency-bands separately for oscillation
amplitudes and DFA exponents using machine learning by Louvain community detection [101]
with gamma value of 1.09. This analysis identified canonical frequency bands of theta (\(\theta\), 3–7 Hz),
alpha (\(\alpha\), 8–14 Hz), beta (\(\beta\), 14–30 Hz), and gamma (\(\gamma\), 30–60 Hz) (S1 Fig). We used repeated-measures analysis of variance (ANOVA) (IBM SPSS Statistics) and univariate ANOVA for testing differences in the induced oscillation amplitudes (A), LRTC exponents (\(\beta\)) and inter-areal synchronization (weighted phase-lag index, wPLI) averaged across all parcels between the frequency-bands and between the polymorphism groups respectively. Post-hoc comparisons between group means were made using a \(t\) test (two-tailed). Multiple comparisons were corrected with Bonferroni correction. The \(p\) values were also corrected according to the Greenhouse-Geisser procedure when the sphericity assumption was violated. Partial eta squared (\(\eta^2_p\)) is reported as a measure of effect size.

For inter-areal synchronization, confidence intervals were computed with a bootstrapping approach (\(N = 1000\)). We tested, for each frequency, whether there was a significant difference between polymorphism groups with a nonparametric Kruskal-Wallis test (\(p < 0.05\)) and then used the Benjamini-Hochberg method to correct for multiple comparisons. Connection density (\(K\)) of the mean connection strengths was used to index the proportion of significant edges from all possible interactions. Differences within and between subsystem connectivity’s between the polymorphism groups were then tested for statistical significance with the Kruskal-Wallis test (\(p < 0.05\)) and corrected for multiple comparisons with Benjamini-Hochberg (Fig 4A-C).

Finally, we estimated the correlation coefficient between amplitudes and LTRC exponents and between synchronization and LRTC exponents, for each parcel and wavelet frequency across subjects, within the polymorphism groups using Spearman’s rank correlation test. Values were then averaged across all parcels and within frequency bands. Confidence limits from 2.5% to 97.5% were obtained from bootstrapping (\(N = 1000\)) as above. Significance testing for difference between polymorphism groups was done with permutation statistics (\(N = 1000\)) where the subjects were
randomly assigned, without replacement, to original-sized polymorphism groups. A difference between groups was considered significant if it exceeded that of 95% of the permutations.

**Competing interests**

Authors declare that they have no competing interests.

**Data availability**

Ethical restrictions apply to data and original data cannot be shared on a public server. Data underlying figures, statistics, and main conclusions will be uploaded to Dryad server (https://doi.org/10.5061/dryad.3n5tb2rjp) upon acceptance. All original code has been deposited at https://github.com/palvalab/RS-Gen and is publicly available as of the date of publication.

**References**


Supporting information

**S1 Fig. Frequency-band clustering.** Spatial similarity across frequency-bands obtained by Louvain community detection [101] for (A) oscillation amplitudes and (B) DFA exponents averaged across participants ($N = 82$). The clustering on spatial similarity yielded the frequency–frequency-band clusters of theta ($\theta$, 3–7 Hz), alpha ($\alpha$, 8–14 Hz), beta ($\beta$, 14–30 Hz), and gamma ($\gamma$, 30–60 Hz) bands. The color scales indicate the correlation coefficients.

**S2 Fig. Whole brain averaged oscillation amplitudes, DFA and phase synchronization.** Box plots of A, DFA and wPLI averaged over theta ($\theta$, 3–7 Hz), alpha ($\alpha$, 8–14 Hz), beta ($\beta$, 14–30 Hz), and gamma ($\gamma$, 30–60 Hz) frequency bands separately for each COMT (Val/Val in purple $n = 18$, Val/Met in turquoise $n = 48$, and Met/Met in orange $n = 16$) and BDNF polymorphism (Val/Val in purple $n = 66$ and combined Val/Met & Met/Met in orange $n = 16$) groups. The box ends indicate the lower quartile (Q1, 25th percentile) and upper quartile (Q3, 75th percentile). The central notches denote the median, and the whiskers correspond to the range of $Q1 - 1.5 \times IQR$ and $Q3 + 1.5 \times IQR$ (where IQR is the inter-quartile range) and give roughly a 95% CI for comparing the medians. Asterisks denote significant group differences (*: $p < 0.05$, *: $p < 0.01$, t-test with unequal variances).

**S3 Fig. Mean oscillation amplitudes for COMT polymorphism groups.** Mean amplitudes separately for each COMT (Val/Val, Val/Met, and Met/Met) polymorphism group averaged over theta ($\theta$, 3–7 Hz), alpha ($\alpha$, 8–14 Hz), beta ($\beta$, 14–30 Hz), and gamma ($\gamma$, 30–60 Hz) frequency bands plotted on inflated cortical surface. The color indicates the strength of the oscillations. Note that the scales vary across the frequency bands.
**S4 Fig. Mean oscillation amplitudes for BDNF polymorphisms.** Mean amplitudes separately for each BDNF polymorphism (Val/Val and Met-carriers) group averaged over theta (θ, 3–7 Hz), alpha (α, 8–14 Hz), beta (β, 14–30 Hz), and gamma (γ, 30–60 Hz) frequency bands plotted on inflated cortical surface. The color indicates the strength of the oscillations. Note that the scales vary across the frequency bands.

**S5 Fig. The functional subsystems.** Cortical parcels of the Destrieux atlas [94] plotted on inflated cortical surface. Color indicates the functional subsystems defined by fMRI functional connectivity [58].

**S6 Fig. Mean oscillation amplitudes across the functional subsystems.** Box plots of A averaged over the functional subsystems across the frequency bands: theta (θ, 3–7 Hz), alpha (α, 8–14 Hz), beta (β, 14–30 Hz), and gamma (γ, 30–60 Hz) and separately for each COMT (Val/Val, Val/Met, and Met/Met, upper panels) and each BDNF (Val/Val and Met-carriers, lower panels) polymorphism group. Abbreviations of the functional subsystems as in S5 Fig and box plot details as in S2 Fig.

**S7 Fig. Mean LRTCs for COMT polymorphisms.** Mean DFA exponents are plotted separately for each COMT (Val/Val, Val/Met, and Met/Met) group, averaged over theta (θ, 3–7 Hz), alpha (α, 8–14 Hz), beta (β, 14–30 Hz), and gamma (γ, 30–60 Hz) frequency bands plotted on inflated cortical surface. The color indicates the strength of the DFA exponents. Note that the scales vary across the frequency bands.
S8 Fig. Mean LRTCs for BDNF polymorphisms. Mean DFA exponents are plotted separately for each BDNF polymorphism (Val/Val and Met-carriers) groups averaged over theta (θ, 3–7 Hz), alpha (α, 8–14 Hz), beta (β, 14–30 Hz), and gamma (γ, 30–60 Hz) frequency bands plotted on inflated cortical surface. The color indicates the strength of the DFA exponents. Note that the scales vary across frequency bands.

S9 Fig. Mean DFA exponents across the functional subsystems. Box plots of DFA exponents averaged over the functional subsystems defined by fMRI functional connectivity across the frequency bands: theta (θ, 3–7 Hz), alpha (α, 8–14 Hz), beta (β, 14–30 Hz), and gamma (γ, 30–60 Hz) and separately for each COMT (Val/Val, Val/Met, and Met/Met, upper panels) and each BDNF (Val/Val and Met-carriers, lower panels) polymorphism groups. Abbreviations of the functional subsystems as in S5 Fig and box plot details as in S2 Fig.

S10 Fig. Co-localization of oscillation amplitudes and LRTCs. Cortical parcels in which amplitudes and DFA exponents were significantly larger for COMT Val/Met than Met/Met polymorphism groups in θ (3–7 Hz, upper left panel) and in β-γ (20–60 Hz, lower left panel) band, and for BDNF Val homozygotes than Met-carriers in θ (upper right panel), as well as for COMT Val/Met than Val/Val polymorphism groups in β-γ (lower right panel). The color indicates the difference in oscillation amplitudes (red) and DFA exponents (blue), as well as their joint effects (purple).

S11 Fig. Phase synchronization associated with COMT and BDNF polymorphisms. The mean phase-synchronization within and among functional Yeo subsystems across the whole brain in the canonical frequency bands for the COMT Val/Val, Val/Met and Met/Met polymorphism groups.
and the BDNF Val/Val alleles and Met carriers. Inter-areal phase phase-synchrony was estimated between and within functional subsystems using the weighted phase-lag index (wPLI), of which the strength is indicated by the color scales. No differences in inter-areal phase coupling were found between COMT polymorphisms. BDNF Val/Val alleles showed stronger synchronization than Met carriers particularly in the $\alpha$, $\beta$ and $\gamma$ bands, these differences are shown in Fig 4C. Note that the scales vary across the frequency bands. Abbreviations of the functional subsystems as in S5 Fig.

**S12 Fig. Hemispheric phase synchronization for the BDNF polymorphism groups.** The differences in the mean phase synchronization, as estimated with wPLI, within and between functional subsystems separately for left-, right- and cross-hemispheric connections. BDNF Val/Val homozygotes had stronger phase synchronization compared to Met-carriers averaged over frequency bands. Color indicates the Val > Met difference in mean phase-synchronization. Stars denote network pairs where the group difference was significant (Kruskal-Wallis, *: $p < 0.05$, uncorrected, **: $p < 0.01$, corrected with Benjamini-Hochberg). Abbreviations of the functional subsystems as in S5 Fig.

**S13 Fig. Correlations of local and global synchronization with LRTCs.** Box plots of correlations of between A and wPLI with DFA exponents averaged over theta ($\theta$, 3–7 Hz), alpha ($\alpha$, 7–14 Hz), beta ($\beta$, 14–30 Hz), and gamma ($\gamma$, 30–60 Hz) frequency bands. Correlations are shown separately for each COMT (Val/Val, Val/Met, and Met/Met, upper panels) and each BDNF (Val/Val and Met-carriers, lower panels) polymorphism group. Box plot details as in S2 Fig.

**S1 Table. Mean sample characteristics (SD in parentheses) by the COMT polymorphisms.**

**S2 Table. Mean sample characteristics (SD in parenthesis) by the BDNF polymorphisms.**
Fig 1
Fig 2
Fig 3
Fig 4
Fig 5