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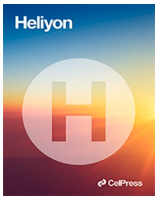

Moderate associations between *BDNF* Val66Met gene polymorphism, musical expertise, and mismatch negativity

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A R T I C L E I N F O

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A B S T R A C T

Auditory predictive processing relies on a complex interaction between environmental, neurophysiological, and genetic factors. In this view, the mismatch negativity (MMN) and intensive training on a musical instrument for several years have been used for studying environment-driven neural adaptations in audition. In addition, brain-derived neurotrophic factor (*BDNF*) has been shown crucial for both the neurogenesis and the later adaptation of the auditory system. The functional single-nucleotide polymorphism (SNP) Val66Met (rs6265) in the *BDNF* gene can affect BDNF protein levels, which are involved in neurobiological and neurophysiological processes such as neurogenesis and neuronal plasticity. In this study, we hypothesised that genetic variation within the *BDNF* gene would be associated with different levels of neuroplasticity of the auditory cortex in 74 musically trained participants. To achieve this goal, musicians and non-musicians were recruited and divided in Val/Val and Met- (Val/Met and Met/Met) carriers and their brain activity was measured with magnetoencephalography (MEG) while they listened to a regular auditory sequence eliciting different types of prediction errors. MMN responses indexing those prediction errors were overall enhanced in Val/Val carriers who underwent intensive musical training, compared to Met-carriers and non-musicians with either genotype. Although this study calls for replications with larger samples, our results provide a first glimpse of the possible role of gene-regulated neurotrophic factors in the neural adaptations of automatic predictive processing in the auditory domain after long-term training.

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1. Introduction

According to the predictive coding theory (PCT), humans anticipate the regularities of environmental stimuli based on internal models or priors, that are automatically updated according to domain-specific experience [1–3]. The ability to predict outcomes based on previously learned information is fundamental to adapt to the continuously evolving environmental demands and is the result of complex cognitive processes arising from the interaction of genetic and physiological factors [4–7].

In the auditory cortex, predictions are often reflected in increased neuronal activity in supratemporal and fronto-parietal areas, as indexed by the well-known event related potential/field (ERP/ERF) named mismatch negativity (MMN). Occurring within 100–250 ms from the deviant stimulus [8,9], MMN has been linked to the bottom-up process of automatic error detection [3,10]. The plasticity of such learning processes is well exemplified by professional musicians, whose auditory predictive abilities are enhanced as a result of their years of musical training [11–20].

Training-dependent neurophysiological changes have been proposed to depend on a combination of environmental and genetic factors [21–24]. However, genetic basis of musical competence are under exploration [25–28]. Some researchers have proposed that individual genetic factors may play a role in music-induced neuroplasticity, although this relationship has yet to be confirmed empirically [24,29]. In this framework, Val66Met (or rs6265), a common single-nucleotide polymorphism (SNP) occurring in the gene coding for the brain-derived neurotrophic factor (gene: *BDNF*; protein: BDNF), offers a good opportunity to clarify the genetic implications of training-dependent plasticity. BDNF is a widespread neurotrophin that plays a key role in neural development and brain plasticity, mediating neuronal differentiation, synaptogenesis, long-term potentiation (LTP) and depression (LTD) [30–33]. Moreover, it is implicated in cognitive processes such as learning and memory. Notably, BDNF also promotes the development and the later adaptations of the auditory cortex, where it mediates the refining of the auditory cortical receptive fields in response to environmental demands [34–38]. Research on animal models suggests a link between low BDNF levels and abnormal hippocampal neuron morphology [39] as well as impairments in NMDA-mediated transmission and LTP processes [40–42]. Conversely, increased BDNF levels in hippocampus have been linked to enhanced neurogenesis and plasticity upon exposure to auditory enriched stimulation in the form of music [43–45]. In addition to hippocampus, tropomyosin receptor kinase B (TrkB) and related BDNF levels also impact cortical activity and plasticity via parvalbumin (PV) interneurons in the cortex [46,47].

Similarly, in humans, greater BDNF plasma levels have been found after listening to music [48] and in musicians compared to non-musicians [49,50], reflecting environment-dependent physiological changes. Moreover, genetically determined high levels of BDNF have been associated with increased plasticity and better cognitive performances [51–56]. Some studies have suggested that the availability of circulating BDNF in healthy adults can be affected by Val66Met, an SNP originating from a missense substitution of valine (Val) with a methionine (Met) in position 66 of the pro-domain region of the *BDNF* precursor pro-BDNF, which is indispensable for the trafficking and secretion of the mature peptide. The mutation leads to reduced BDNF release and has been generally associated with lower baseline levels in Met-carriers, compared to those with Val/Val genotype [51,53,57,58]. Nonetheless, conflicting findings have been reported when measuring plasma BDNF levels as a function of Val66Met [57,59,60]. This might be due to various factors which affect plasma BDNF levels, such as linkage disequilibrium with Val66Met [61], developmental or environmental factors.

Imaging genetics studies have shown a link between the Met allele and altered episodic memory, brain structure, and function in both healthy [51,55] and clinical populations [52–54,56,62–65], though results are not always consistent . Magnetic resonance imaging (MRI) studies have reported reduced volume in the hippocampus [56,62,65–67], prefrontal cortex [56], and temporal and occipital lobes [54] in Met-carriers (Val/Met and Met/Met-carriers) compared to Val/Val homozygotes. Further, several studies described anomalous hippocampal activity during memory tasks associated to the Met allele [51,53,67].

Overall, most of the previous studies indicates that high levels of BDNF are generally associated with better cognitive performance and enhanced neuroplasticity, and that Val/Val individuals reported better performances and higher levels of BDNF. However, there are a few studies which provided an alternative view, suggesting that the relationship between *BDNF*, cognitive abilities and neuroplasticity may be less straightforward. For instance, Lang, Hellweg, Sander and Gallinat [57] observed decreased BDNF serum concentrations in healthy Val/Val participants when compared to Met-carriers (Val/Met) individuals. Another study [59] investigated the association between the Val66Met polymorphism, BDNF serum levels, and gender. They found a significant interaction between sex and genotype on BDNF serum levels. In particular, male Met-carriers reported higher BDNF levels than Val/Val homozygotes. Conversely, no effect was observed in females. In addition, Luykx and colleagues [60] reported no significant differences in plasma BDNF concentration between Val/Val and Met-carriers (Met/Met) groups, suggesting that the allelic variation at rs6265 does not necessarily affect the levels of plasma BDNF. In summary, these studies provided alternative perspectives on the relationship between BDNF, cognitive performance, and neuroplasticity and suggested that it may be more complex than previously proposed.

Although the role of *BNDF* Val66Met SNP in cognition has captured the attention of a discrete number of studies, evidence on the contribution of the polymorphism to the neurophysiology of auditory predictive processes is still largely missing. In a recent work by Bonetti and colleagues [68], another polymorphism, the Val158Met SNP in the catechol-O-methyl-transferase (COMT) gene, has been shown to affect auditory predictive processes, suggesting a genetic influence on the generation of MMN. Hence, in the present study we aim to provide a first glimpse of the genetic contribution to experience-dependent neural plasticity, particularly that induced by long-term musical training, on auditory predictive processing, as indexed by MMN.

Answering this question is important to contribute bridging the knowledge gap between cognitive neuroscience, psychology, and genetics. In fact, the interplay between neurophysiology and psychological and genetic factors has often been underestimated, partially due to the complexity of connecting these different fields. For these reasons, here we aim to take a first step towards understanding the possible role of gene-regulated neurotrophic factors in the neural adaptations of automatic predictive processing in the

auditory domain after long-term training. We hypothesize that the neuroplastic changes induced by intensive musical training would be modulated by different variants of the *BDNF* Val66Met polymorphism, with Val/Val musicians showing enhanced auditory predictive processes compared Met carriers.

2. Results

2.1. Genetic and demographic data

The distribution of *BDNF* Val66Met was: Val/Val = 57 (77.03%); Met-carriers: Val/Met = 16 (21.62%) and Met/Met = 1 (1.35%) and it was in Hardy–Weinberg equilibrium ($\chi^2 = 0.01$; $df = 1$; p-value = .917).

Detailed demographic information is reported in Table 1. In addition, we tested whether the musical training was significantly different across the four experimental groups. This was done using a two-way analysis of variance (ANOVA). As expected, the amount of musical training was strongly different for musicians versus non-musicians: F (1, 73) = 227.71, $p < .001$. Conversely, the musical training was not significantly different between genetic groups ($p > .05$). The interaction between musicianship and genetics was also not significant ($p > .05$).

2.2. BDNF and neural responses to deviants

Before assessing the relationship between genetics, musical training and MMN (Fig. 1), we computed the neural responses to deviants to visually inspect the quality of the data and to control the clarity of the isolated MMN peaks. Coherently with previous literature that used the same paradigm as the one used in this study [16,68–71] , we assessed that such peaks were stronger for musicians compared to non-musicians. In agreement with what reported in those studies, we observed that the clearest MMN peaks occurred for localization, slide and timbre deviants, while rhythm, intensity and pitch showed a reduced response. Waveforms, topoplots and neural sources are depicted, respectively, in Fig. 2A, **2B** and **2C**, and reported in details in Table ST1.

Waveforms (A), topoplots (B) and brain sources (C) of the neural signal responses to deviants, shown for all participants and separately for musicians and non-musicians. Specifically, waveform images refer to the MEG gradiometer channel (1332 + 1333) where we recorded the peak amplitude in response to deviants. Dotted lines represent standard errors. The topoplots (fT/cm) and neural sources indicate the location of the brain activity at the peak amplitude depicted in the waveforms. In the brain templates, we depicted the t-values emerging from the contrast between neural responses to deviants and baseline.

We used six two-way ANOVAs to compare the MMN to each deviant among our four experimental groups ($M_{Val/Val}$, $M_{Met\text{-}carriers}$, $NM_{Val/Val}$, $NM_{Met\text{-}carriers}$). In these analyses, musicianship and genetic information were used as independent variables and MMN amplitude as dependent variable. The results highlighted significant and nearly significant relationships indicating that the interaction between musical training and genetic information affected the MMN amplitude. In particular, our findings showed that musicians who carried the BDNF Val/Val had overall stronger neural responses to deviants than those who carried Val/Met and Met/Met alleles. This was particularly evident for pitch, slide and rhythm deviants. Detailed statistical results are reported in Tables 2 and 3 and depicted in Fig. 3.

3. Discussion

In this study, we investigated the interplay between environmental (long-lasting musical training) and genetic (*BDNF* Val66Met SNP) factors on neural automatic predictive processes, as indexed by MMN. We found that individuals with Val/Val genotype who underwent years-long musical training had overall enhanced neurophysiological prediction error signals compared to both their non-musician and genetic counterparts. Using a relatively complex auditory stimulation, MMN were elicited for six different types of deviants. Overall, the strongest MMN error signals were in response to changes in localization, followed by those in slide and timbre. The weakest MMN signal was found for intensity, consistent with previous studies using the same auditory paradigm and a subset of these participants [19,68–72]. As expected, source reconstruction analysis of the activity recorded at MEG sensors level showed stronger neural activation within temporal areas associated with MMN generation, proportionally to the intensity of the signal generated by the individual deviants. Moreover, consistent with previous findings about experience-dependent plasticity in musicians,

Table 1
Demographic data of the participants described according to their *BDNF* genetic variation ($M_{Val/Val}$ = musicians Val/Val; $NM_{Val/Val}$ = non-musicians Val/Val; $M_{Met\text{-}carriers}$ = musicians Val/Met and Met/Met; $NM_{Met\text{-}carriers}$ = non-musicians Val/Met and Met/Met). The table shows means for *age* (± indicates standard deviation) and frequencies for *number of participants*, *sex* (M = males; F = females) and self-reported *handedness* (L = left-handed; R = right-handed; A = ambidextrous).

Information	Whole sample	$M_{Val/Val}$	$M_{Met\text{-}carriers}$	$NM_{Val/Val}$	$NM_{Met\text{-}carriers}$
Number of participants	74	19	8	38	9
Age	28.70 ± 8.34	29.58 ± 7.21	28.38 ± 9.41	28.16 ± 9.11	29.44 ± 7.21
Sex	M = 32; F = 42	M = 8; F = 11	M = 5; F = 3	M = 17; F = 21	M = 2; F = 7
Handedness	L = 5; R = 67; A = 1 *(1 missing)*	L = 2; R = 16 *(1 missing)*	L = 0; R = 7; A = 1	L = 2; R = 36	L = 1; R = 8
Years of formal music training	6.56 ± 9.03	16.00 ± 4.74	19.62 ± 10.24	0.59 ± 1.05	0.22 ± 0.66

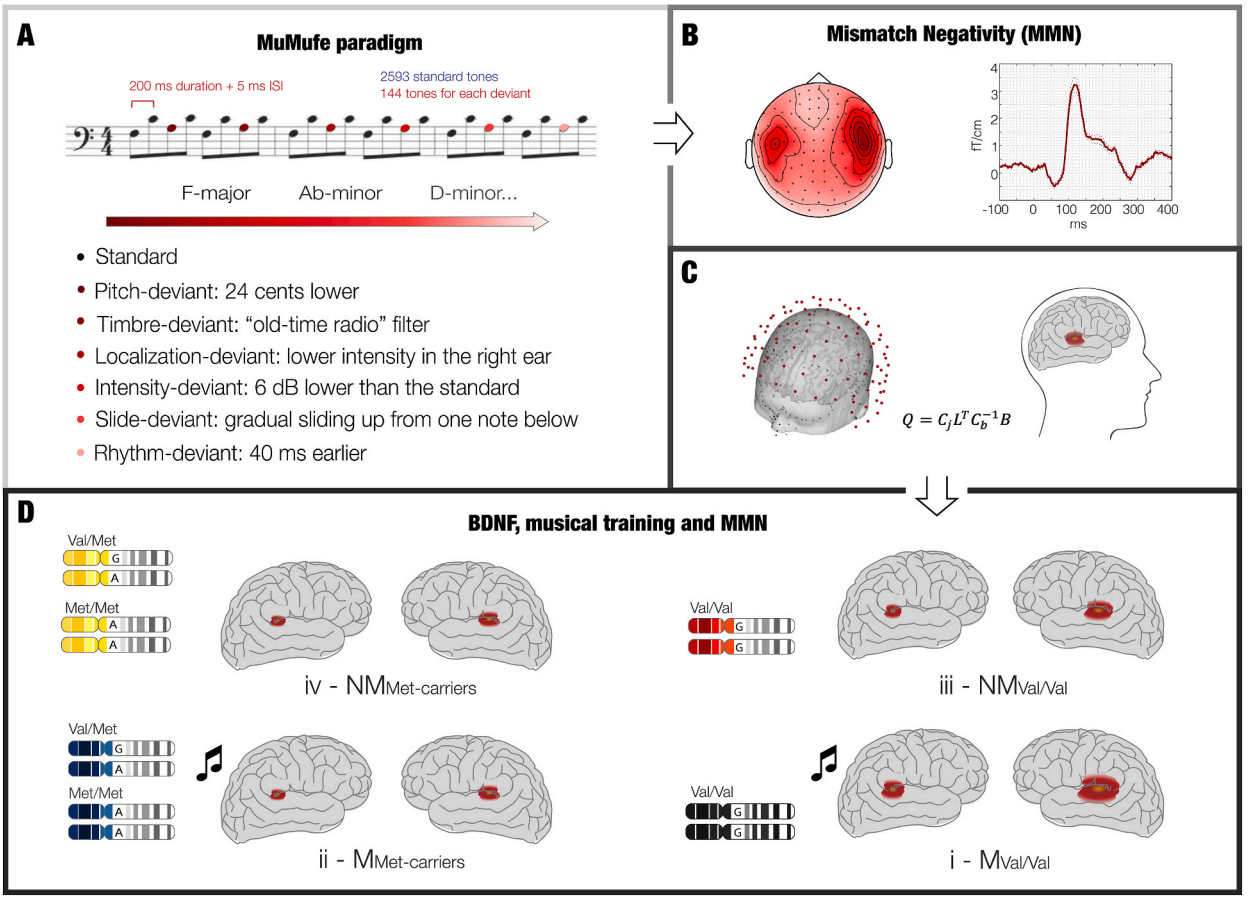

Fig. 1. Overview of the analysis pipeline. **A** – Participants were presented with the musical multifeatures paradigm (MuMufe) during MEG recording. With this paradigm, we obtained neural responses to deviant acoustic stimulations. **B** - MEG data has been collected and pre-processed and typical event-related components elicited by deviant stimulation such as mismatch negativity (MMN) have been identified. **C** – Source reconstruction has been estimated by using an MEG overlapping sphere forward model and a beamforming approach as inverse model. **D** – Participants have been divided into different groups according to their BDNF genetic variation and their musical expertise and their different brain response to deviants tested through analysis of variance (ANOVA). Specifically, we split the participants into four groups: $M_{Val/Val}$ = musicians Val/Val; $NM_{Val/Val}$ = non-musicians Val/Val; $M_{Met\text{-}carriers}$ = musicians Val/Met and Met/Met; $NM_{Met\text{-}carriers}$ = non-musicians Val/Met and Met/Met.

we observed overall enhanced auditory ERPs in musicians compared to non-musicians, with greater magnitude of MMN components [11,16,17,19,23,72–78].

In accordance with our hypothesis, we found a moderate yet consistent relationship between Val66Met polymorphism, MMN amplitude and long-term musical training. Specifically, stronger MMN amplitudes were obtained for $M_{Val/Val}$ compared to the other three experimental groups ($M_{Met\text{-}carriers}$, $NM_{Met\text{-}carriers}$, $NM_{Val/Val}$). This difference was particularly pronounced for slide, pitch and rhythm deviants. Similar results were observed for location and timbre, while intensity did not show any difference between the experimental groups. This is consistent with the findings of previous studies that have used the same paradigm as ours, such as those conducted by Bonetti and colleagues [70] and Kliuchko and colleagues [16], who have reported small MMN amplitudes for intensity deviants. For this reason, not detecting any difference between $M_{Val/Val}$ and the other groups may be related to the lower signal-to-noise ratio of the MMN for intensity.

Coherently with our results which reported differential amplitudes for MMN that originated in the auditory cortex and medial temporal lobe, previous literature showed differential morphology of temporal and insular areas that in relation to the Val66Met. An MRI study conducted on a large cohort of healthy volunteers [65] reported increased surface expansion of the anterior insular cortex, accompanied by a greater connectivity with the dorsolateral prefrontal cortex (DLPFC) for Val/Val individuals as compared to Met-carriers. Similarly, Hoet al. [54] reported reduced grey matter in the left temporal and superior frontal gyrus of healthy Met-carriers. Finally, multiple studies reported associations between the Met allele, reduced hippocampal volume and altered hippocampal functioning [51,53,56,62,65–67]. Although in our study we focused on neural activity and not on volumetric differences, the brain areas responsible for the MMN generation largely overlapped with the areas that showed changes associated with Val66Met.

Our findings are also in line with a recent study that investigated the relationship between *BDNF* Val66Met polymorphism and neural oscillations during eyes-open resting-state. The study by Roy and colleagues [79] found that the Met/Met group had increased

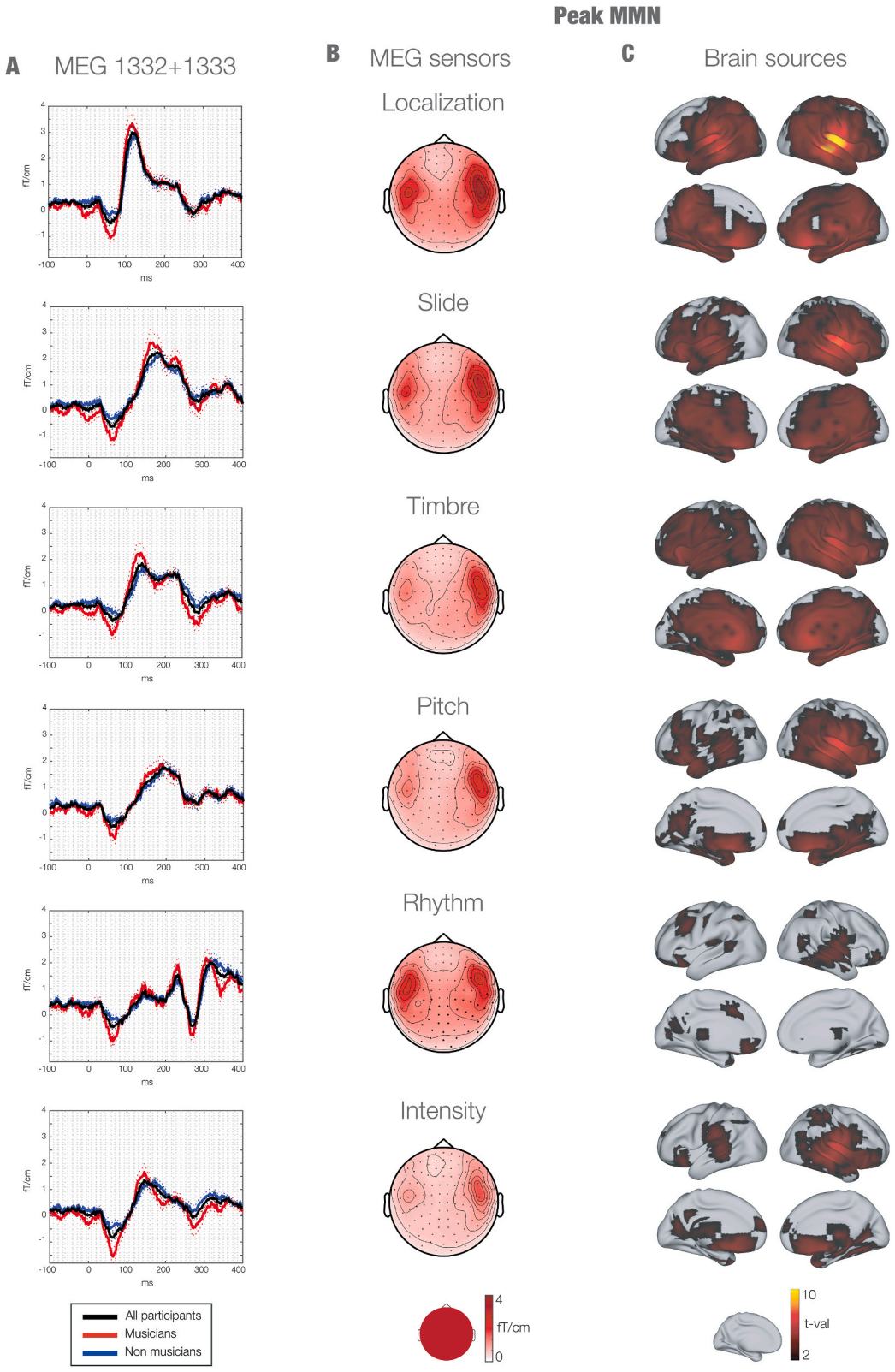

Fig. 2. Neural responses to deviants.

Table 2
Results of the two-way ANOVAs, computed independently for each deviant. *F* and *p* values refer to the main effect of musicianship and *BDNF*, as well as their interaction. *df* refers to the degrees of freedom.

Deviant	F_{mus}	F_{BDNF}	$F_{interact}$	*df*	p_{mus}	p_{BDNF}	$p_{interact}$
Pitch	**5.59**	2.44	1.65	1,73	**.02**	.12	.20
Slide	1.77	1.75	**4.15**	1,73	.18	.19	**.04**
Intensity	.38	.01	.24	1,73	.54	.93	.63
Localization	.01	**3.39**	.01	1,73	.95	**.06**	.94
Timbre	2.56	.76	.29	1,73	.11	.38	.59
Rhythm	1.43	1.85	**3.16**	1,73	.24	.18	**.07**

Table 3
Average values of the MMN over participants for each deviant and experimental group. These results highlighted the overall higher neural responses recorded for musicians *BDNF* Val/Val vs musicians *BDNF* Met-carriers. To be noted, although our results often showed only a nearly significant trend due to the low statistical power of the small sample of this study, the differences in amplitude between $M_{Val/Val}$ and $M_{Met\text{-}carriers}$ were clearly discernible.

Deviant	$M_{Val/Val}$ (fT)	$M_{Met\text{-}carriers}$ (fT)	$NM_{Val/Val}$ (fT)	$NM_{Met\text{-}carriers}$ (fT)
Pitch	57.60 ± 32.82	39.81 ± 16.17	34.79 ± 18.00	33.07 ± 13.73
Slide	77.00 ± 55.61	42.30 ± 22.23	42.20 ± 28.70	49.59 ± 25.69
Intensity	39.29 ± 21.31	35.89 ± 15.28	32.79 ± 23.15	35.11 ± 12.93
Localization	59.99 ± 27.00	45.70 ± 14.65	60.11 ± 32.47	44.63 ± 23.64
Timbre	48.14 ± 28.16	40.68 ± 16.29	36.85 ± 14.82	35.09 ± 8.12
Rhythm	67.90 ± 38.49	43.22 ± 20.30	44.50 ± 25.03	47.79 ± 16.55

delta and decreased alpha activity in the right fronto-parietal region compared to Val/Val and Val/Met participants. Additionally, they observed stronger beta activity in the frontal region for Val/Met individuals compared to Val/Val. These results suggested that the BDNF Val66Met polymorphism may affect neural oscillations differently than event-related potential components such as the MMN, as found in our research.

The results of our study, together with the previous findings on *BDNF* Val66Met, suggest that this SNP may orchestrate a subtle yet consistent modulation in the structure and function of temporal areas. Interestingly, our results indicate that the effect of *BDNF* Val66Met polymorphism on such neural plasticity might appear only upon year-long activities that directly involve BDNF signalling, such as extensive practice of a musical instrument. This is in line with the findings showing that BDNF levels influence experience-dependent induced plasticity [47]. Moreover, the stronger MMN amplitude in $M_{Val/Val}$ group suggests that higher BDNF concentrations of the Val/Val genotype may favor the development of a better functional optimization of the auditory cortex after a long-term training. Indeed, expressed and released by cortical pyramidal neurons [80], BDNF/TrkB signaling promotes the functional organization of the auditory cortex via parvalbumin inhibitory interneurons. In the auditory cortex, inhibitory neurons regulate experience-dependent adaptations, by sharpening the receptive fields of the auditory neurons and promoting their maturation [34,36,37,81]. Thus, BDNF promotes functional and perceptual long-lasting changes to auditory stimuli [38], being one of the key factors underlying the plastic changes that favor the augmented ability to discriminate sound features which is proper of musicians. This claim is also supported by the higher BDNF plasma levels found in musicians compared to non-musicians [49], which might reflect the enhanced plastic properties reported by previous neuroimaging and neurophysiology studies [17,19–23,76]. Furthermore, the enhanced MMN responses found in the $M_{Val/Val}$ group might be explained in consideration of the role of BDNF in regulating glutamatergic transmission and NMDA-dependent LTP [4,39,41,42]. Thus, because the generation of MMN requires NMDA transmission, higher BDNF levels might indeed facilitate the communication and plasticity of cortical pyramidal neurons, resulting in greater amplitude of the signal recorded at the scalp for $M_{Val/Val}$ vs $M_{Met\text{-}carriers}$.

In summary, the majority of previous studies reported associations between high levels of BDNF, better cognitive performance and enhanced neuroplasticity. Moreover, they have repeatedly suggested that Val/Val participants were characterized by better performances and higher levels of BDNF than Met-carriers (Val/Met and Met/Met). Accordingly, our findings also showed stronger neural responses indicating neuroplasticity in Val/Val individuals. However, it is important to highlight that before drawing definite conclusions, additional research is required. This is in consideration of the previous research which provided alternative views on the *BDNF* Val66Met SNP. For example, previous studies reported decreased levels of BDNF serum in healthy Val/Val versus Met-carriers [57,59,82].

In conclusion, our results revealed a significant relationship between the *BDNF* Val66Met polymorphism and experience-dependent plasticity, showing an enhanced neuroplasticity of auditory predictive processes in Val/Val individuals upon long-lasting musical training, as indexed by the stronger MMN elicited in Val/Val musicians compared to Met-carrier musicians. This may suggest that the *BDNF* Val66Met polymorphism may be one of the genetic contributors to inter-individual variation in experience-dependent plasticity.

3.1. Limitations and future perspectives

A central limitation of this study is represented by the low statistical power due to the small size of our experimental populations. In

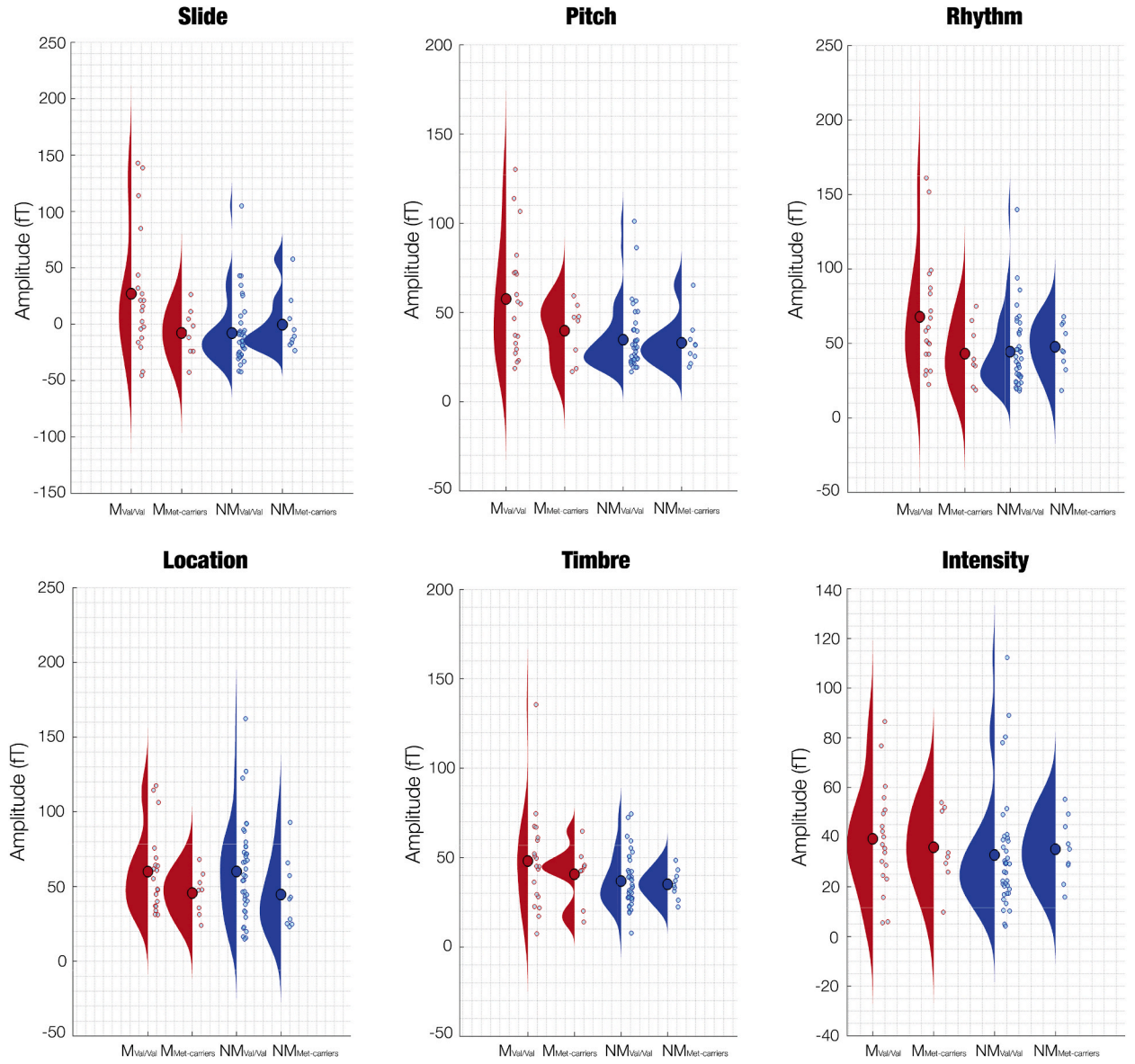

Fig. 3. Scatter plots and violin plots of the average values across participants of the MMN amplitude. The six plots represent the results for each experimental group (: $M_{Val/Val}$ = musicians Val/Val; $NM_{Val/Val}$ = non-musicians Val/Val; $M_{Met\text{-}carriers}$ = musicians Val/Met and Met/Met; $NM_{Met\text{-}carriers}$ = non-musicians Val/Met and Met/Met) independently for each of the six deviants (Slide, Pitch, Rhythm, Location, Timbre, Intensity). These results highlighted the overall higher neural responses recorded for musicians BDNF Val/Val vs musicians BDNF Met-carriers and vs non-musicians. The large colored circles represent the mean of the MMN amplitude over participants.

particular, the Met-carriers were only 17 whereas the Val/Val carriers were 57, with a consistent difference between the two non-musician groups ($M_{Val/Val}$: N = 19, $M_{Met\text{-}carriers}$: N = 38). In turn, the musician groups were of comparable size ($M_{Val/Val}$: N = 9, $M_{Met\text{-}carriers}$: N = 8), but their absolute numerosity was scarce. Moreover, only one participant was homozygous for the Met allele, which did not allow us to investigate the differences according to the three possible *BDNF* variants. Nonetheless, this is in line with the distribution of the Met/Met genotype across the population as well as with the previous studies about Val66Met [52–54,56,61,65,83]. Thus, on the one hand, the small sample size has limited the statistical power of the analysis reported in this research. However, on the other hand, some of our results achieved statistical significance even with a small sample size because of the large magnitude of the effect that we observed. Moreover, even the results that were not statistically significant approached the significance threshold and showed the same trend. Thus, our results provide novel insights on the relationship between *BDNF* Val66Met polymorphism, MMN and musical training, but future studies recruiting a sample 30–40% larger than the one used in this research are needed to replicate and expand on our findings.

In addition, it is important to underline the correlational nature of the results presented in this study. Given the complexity of the

cognitive processes involved in prediction error and learning, it is plausible to assume that the genetic contribution to these functions depends not only on a single SNP but on the combination of a larger pool of genes, together with their diverse interaction with the environment. Although our study provided a first glimpse of the relationship linking genetics and experience-dependent neurophysiological changes in humans, more genetic and environmental variables should be taken into account to support our hypothesis. On the genetic level, studies on larger populations would allow to get a stronger statistical power and to carry out genome-wide association studies (GWAS) that might help clarify and possibly confirm the genetic contribution of *BDNF* Val66Met to experience-dependent plasticity. On the environmental level, since many studies showed a relationship between musical expertise, cognitive abilities, music perception and neurophysiological responses [11–13,19,29,76,78,84–92], a better control on the total hours of musical practice, on the musical training starting age and on the cognitive abilities of the participants would provide greater insights on the role of *BDNF* gene in learning.

4. Methods

4.1. Participants

Participants were a sub-sample of the full sample collected for the broader project "Tunteet" ("Emotions" in Finnish), a research protocol involving the collection of neurophysiological, genetic, behavioural and psychological measures regarding cognitive and musical skills, audition and affective behaviour. The complete dataset consisted of 140 volunteers, recruited in the area of Helsinki, Finland. The protocol was 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). The procedures were conducted complying with the ethical principles stated by the Declaration of Helsinki. Further information about this research protocol and related findings are reported in separate studies [16,68–71,89,93–96].

All participants were in good health, had normal hearing and were not under any medication. Further, no history of neurological nor psychiatric disease was reported. An informed consent was signed before the beginning of the experiment and a compensation for the participation in the study was given through vouchers that they could use for culture and sports (e.g., concerts, museums or swimming pools.

Participants were divided into musicians (M) and non-musicians (NM) according to the criteria previously used by Criscuolo and colleagues [89]. The information on their musical expertise was obtained by using an online survey named Helsinki Inventory for Music and Affect Behavior (HIMAB) [97]. On the basis of such information, participants were classified as 'musicians' when they met all the following criteria: (i) having more than five years of music practice; (ii) considering themselves as musicians; (iii) having obtained a final degree at a music academy, being involved in musical education or monetarily compensation for their music performance or teaching activities. Conversely, participants with less than three years of musical training were considered 'non-musicians'.

Then, the two groups were further classified according to their genotype, based on the allelic distribution of Val66Met in the European population [61]: group 1 included individuals with the Val/Val genotype, whereas group 2 included Met-carriers (individuals with both Met/Met and Met/Val genotypes). Consistently with previous literature, Val/Met and Met/Met genotypes were merged into one single group for all analyses. Sixty-six participants were excluded for missing genetic information or because they did not encounter the criteria needed for the subdivision between musicians and non-musicians. Detailed information about demographic data and musical expertise for the final pool of participants is reported in Table 1.

We determined whether the allelic frequencies were in Hardy–Weinberg equilibrium (computed as $p^2 + 2pq + q^2 = 1$; where p = frequency of homozygous dominant genotype; pq = frequency of heterozygous genotype; q = frequency of homozygous recessive genotype) and used a *Chi*-squared test with significance set at $\alpha = .05$ to determine any deviation from the equilibrium. Specifically, a significant outcome of the *Chi*-squared test would indicate that the allelic frequencies were not in Hardy–Weinberg equilibrium, while a non-significant outcome means that the allelic frequencies were in Hardy–Weinberg equilibrium.

In addition, we tested whether the musical training was significantly different across the four experimental groups. This was done using a two-way analysis of variance (ANOVA), inserting musicianship and genetic information as independent variables and musical training as dependent variable.

4.2. Experimental design and stimuli

Mismatch negativity (MMN) responses were evoked with a fast musical-multifeature MMN paradigm (MuMuFe), involving four-tone patterns arranged in an "Alberti bass" configuration [16,68–72]. Sound stimuli were synthesized with the software sampler "Halion" in Cubase (Steinberg Media Technologies GmbH) and consisted of the sample sounds of Wizoo acoustic piano. The musical patterns were played on the piano (standard tones) with the exception of the third tone, that was replaced with one of the following six types of deviants: pitch, timbre, localization, intensity, slide or rhythm. Deviants were generated in Adobe Audition (Adobe Systems Incorporated©) by modifying the sound features of interest as follows (Fig. 1A):

- **Pitch**: the tone was mistuned by 24 cents (downwards tuning for the major mode and upwards tuning for the minor mode).
- **Timbre**: the timbre of the tone was altered with the "old-time radio" effect of Adobe Audition with a 4-channel parametric equalizer.

- **Location**: the amplitude of the right channel was decreased of 10 dB, which resulted in a sound perceived as coming from a localization centred to the left (~70°) compared to the midline.
- **Intensity**: the original intensity was reduced by 6 dB.
- **Slide**: gradual change of the pitch from two semitones below up to the standard over the sound presentation.
- **Rhythm**: 40 ms shorter than the standard tone, maintaining the same interstimulus interval (ISI). This resulted in the consequent tone arriving earlier than expected.

The musical patterns were played in each of the 24 possible keys (12 major and 12 minor), with the key changing once every six patterns in a pseudo-random order. Each tone (except for the rhythm deviant, which was 160 ms long) had a duration of 200 ms and 5 ms of raise and fall time, with an ISI of 5 ms. Each deviant was presented 144 times in pseudo-random order, 50% of which was played in major mode and the other 50% in minor mode. The total duration of the paradigm was 12 min. The stimuli were randomized in Matlab and delivered with Presentation software (Neurobehavioral Systems, Berkley, CA). The auditory stimulation was presented through a pair of pneumatic headphones (Sennheiser HD 210). Before starting the experiment, participants' auditory threshold was assessed. Then, volume of the sounds was set to 50 dB above the individual hearing threshold. Participants were seated in a chair with their heads placed in the helmet-like space of the MEG device. Recordings were taken while the auditory paradigm was presented. Participants passively listened to the sounds while watching a silenced movie of their choice (e.g. Charlie Chaplin) with subtitles. Participants were instructed to focus on the movie and not to pay attention to the sounds that were played at the same time. This is a standard procedure in MMN studies [16,19,20,68–72].

5. Data acquisition

5.1. Genotyping

DNA analyses were carried out at THL Biobank, National Institute for Health and Welfare, Helsinki, Finland. Deoxyribonucleic acid (DNA) was isolated from blood samples complying with standard extraction protocols. The DNA extraction from K2-EDTA-blood tubes was performed with chemagic 360 instrument and the CMG-704 kit (PerkinElmer), which uses magnetic bead technology. The DNA concentration was measured with Quant-iT™ PicoGreen™ dsDNA Assay Kit after it was eluted in 400 μl 10 mM Tris-EDTA elution buffer (PerkinElmer). Aliquots of DNA samples were produced with Tecan Genesis/Tecan Freedom Evo and then shipped on dry ice for genetic analyses. *BDNF* Val66Met was genotyped with Illumina Infinium PsychArray BeadChip and quality control (QC) was assessed with PLINK. Some markers were removed due to pattern missingness (>5%). Individual participants were checked for missing genotypes (>5%), relatedness (identical by descent calculation, PI_HAT >0.2) and population stratification (multidimensional scaling).

5.2. MEG data acquisition

The data were collected with a 306-channel Vectorview whole-head MEG scanner (Elekta Neuromag, Elekta Oy, Helsinki, Finland) at the Biomag Laboratory of the Helsinki University Central Hospital. The recordings were carried out in an electrically and magnetically shielded room (ETS-Lindgren Euroshield, Eura, Finland). The MEG device comprised 102 axial magnetometers and 102 pairs of planar gradiometers, for a total of 306 SQUID sensors. MEG data were recorded with a sampling rate of 600 Hz.

5.3. MRI data acquisition

We acquired MRI data employing a 3T MAGNETOM Skyra whole-body scanner (Siemens Healthcare, Erlangen, Germany) and a standard 32-channel head-neck coil. The recordings were carried out at the Advanced Magnetic Imaging (AMI) Center (Aalto University, Espoo, Finland) on a separate date either before or after the MEG session.

T1-weighted structural images were collected for individual co-registration with MEG data and proper estimation of neural sources with the following acquisition parameters: 176 slices; slice thickness = 1 mm; field of view = 256 × 256 mm; interslice skip = 0 mm; matrix = 256 × 256; pulse sequence = MPRAGE.

5.4. Neural data preprocessing

MEG sensor data of both planar gradiometers (n = 204) and magnetometers (n = 102) were pre-processed with MaxFilter 2.2 (Taulu & Simola, 2006). Interference originated from external and nearby sources was attenuated by applying signal space separation and the signal was adjusted for head movement. The sampling rate was 600 Hz and no down-sampling was performed. The pre-processed data were converted into SPM objects [98] and further analyzed in Matlab (Math-Works, Natick, Massachusetts, United States of America), with OSL, a free source toolbox using a combination of Fieltrip [99], SPM [98] and FSL [100] functions, together with in-house-built codes. The data were then low-pass filtered at 30 Hz. Minimum parts of the signal contained bad trials that were removed manually following visual inspection. Heartbeat and eye blink related artefacts were detected by means of independent component analysis (ICA) and removed manually. The signal was epoched into 500-ms segments (from −100 ms to 400 ms with regards to the target deviants) to visually inspect the quality of the data over a long time window. The baseline correction was computed by subtracting the averaged brain activity of the baseline (from 100 ms before the target stimulus to the onset of the target stimulus) from the entire epoch.

5.5. MMN detection

To obtain the MMNs (Fig. 1B), we computed the difference waveforms by subtracting the average standard waveform from each of the deviant waveforms, as it is commonly done in MEEG studies [9,16,69–71].

In addition, we detected the neural sources which generated the MMN signal recorded by the MEG sensors (Fig. 1C). This was done by using an overlapping-spheres (forward model) approach and a beamformer approach (inverse model) [101]. Signal from both magnetometers and gradiometers and an 8-mm grid were used. The forward model depicted the MNI-co-registered anatomy (obtained through MRI structural T1 recording for each participant) as a simplified geometric volume by using a set of spheres [102]. The inverse model sequentially applied a set of weights to the source locations to isolate the contribution of each source to the general MEG activity recorded by the sensors at each time-point [101,103–109]. This procedure allowed us to reconstruct the sources of the MMN that were mainly located in the auditory cortex and medial temporal lobe, confirming the quality of our data.

5.6. BDNF and neural responses to deviants

To analyze the relationship between MMN, musicianship, and genetics, we first identified the peak amplitude of the MMN to each deviant. As done by Bonetti, Haumann, Vuust, Kliuchko and Brattico [70], we focused on the eight MEG channels which recorded the strongest MMN peak (four in the right hemisphere: 1311, 1321, 1331, 2611; and four in the left hemisphere: 211, 221, 241, 1511). This has been done to use only the channels that strongly peaked the MMN up and minimize the noise. Then, we isolated the latency of the grand-averaged (over participants) MMN peak for each deviant. For each participant, MEG channel and deviant, we obtained the MMN amplitude by averaging the neural signal over the MMN peaks ($\pm$25 ms around the peaks). This returned one value for each participant, deviant, and MEG channel. Afterwards, we averaged these values over the eight MEG channels to isolate the MMN amplitude, having one value for each participant and each deviant. Finally, as shown in Fig. 1D, we used six two-way ANOVAs to compare the MMN to each deviant among our four experimental groups ($M_{Val/Val}$, $M_{Met\text{-}carriers}$, $NM_{Val/Val}$, $NM_{Met\text{-}carriers}$). In these analyses, musicianship and genetic information were used as independent variables and MMN amplitude as dependent variable. Detailed statistical results are reported in Table 2 and depicted in Fig. 3.

Production notes

Author contribution statement

Leonardo Bonetti: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Silvia Elisabetta Portis Bruzzone: Analyzed and interpreted the data; Wrote the paper.

Tina Paunio, Katri Kantojärvi: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data.

Marina Kliuchko: Conceived and designed the experiments; Performed the experiments.

Peter Vuust: Conceived and designed the experiments.

Satu Palva: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Elvira Brattico: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare the following conflict of interests: We hereby disclose that Leonardo Bonetti and the co-author Elvira Brattico are associate editors and advisory board member of Heliyon, respectfully. We trust that will not bias the decision of the other excellent editors of Heliyon, but we wish to disclose it for ethical reasons.

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Appendix A. Supplementary data

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