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# Genome-wide association study of musical beat synchronization demonstrates high polygenicity

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## 37 Abstract

38 **Moving in synchrony to the beat is a fundamental component of musicality. Here, we conducted a**  
39 **genome-wide association study (GWAS) to identify common genetic variants associated with beat**  
40 **synchronization in 606,825 individuals. Beat synchronization exhibited a highly polygenic architecture,**  
41 **with sixty-nine loci reaching genome-wide significance ( $p < 5 \times 10^{-8}$ ) and SNP-based heritability (on the**  
42 **liability scale) of 13%-16%. Heritability was enriched for genes expressed in brain tissues, and for fetal**  
43 **and adult brain-specific gene regulatory elements, underscoring the role of central nervous system-**  
44 **expressed genes linked to the genetic basis of the trait. We performed validations of the self-report**  
45 **phenotype (through internet-based experiments) and of the GWAS (polygenic scores for beat**  
46 **synchronization were associated with patients algorithmically classified as musicians in medical**  
47 **records of a separate biobank). Genetic correlations with breathing function, motor function,**  
48 **processing speed, and chronotype suggest shared genetic architecture with beat synchronization and**  
49 **provide avenues for new phenotypic and genetic explorations.**  
50

## 51 Introduction

52 Our tendency to perceive, create, and appreciate rhythms in a variety of contexts (e.g., speech, music,  
53 movement) is a key feature of the human experience<sup>1-3</sup>. Rhythmic patterns provide predictable and  
54 robust sensorimotor structure to every-day interactions<sup>4,5</sup>, helping guide our attention to  
55 communicatively important moments in time<sup>6,7</sup>. Even young children are sensitive to the social and  
56 linguistic signals carried by rhythm<sup>8-10</sup> and parents use rhythmic vocalizations and synchronous  
57 movement (e.g., lullabies and rocking) to interact with their infants from birth<sup>11,12</sup>. Rhythmic musical  
58 interactions are structured around the percept of a stable periodic pulse (termed the “beat” in Western  
59 music and present in music of most cultures<sup>1,13</sup>, though its precise instantiation in musical structure  
60 varies cross-culturally<sup>14,15</sup>). While music in general and rhythmic structures in particular vary globally<sup>15-17</sup>,  
61 there is evidence that hierarchical beat structure of most music is robust to cultural transmission<sup>2</sup> and  
62 indeed common in many types of music<sup>1</sup>.

63  
64 *Beat perception and synchronization* (i.e. perceiving, predicting, and moving predictively in synchrony to  
65 a musical beat<sup>18</sup>) is an important feature of musical experiences across many human cultures and  
66 musical genres<sup>1,19</sup>. The predictive temporal mechanisms afforded by beat structure enhance general  
67 perceptual and learning processes in music, including melody perception and production, singing, and  
68 joint music-making<sup>3,6</sup>. While some features of rhythm perception and production vary across listeners  
69 from different cultures<sup>13,19-21</sup>, the same studies showed considerable consistencies across cultures for  
70 other features (e.g., preference for beat-based isochrony). Musicality (broadly encompassing musical  
71 behavior, music engagement and musical skill<sup>22</sup>) impacts society by supporting pro-social behavior<sup>11,23</sup>  
72 and well-being<sup>24</sup>. Many have proposed that beat perception and synchronization evolved in humans to  
73 support communication and group cohesion<sup>18,22,25,26</sup>. In modern humans, beat perception and  
74 synchronization are predictive of language and literacy skills<sup>27,28</sup> and are related to cognition, motor  
75 function, and social coordination<sup>29</sup>. Thus, the biology of beat synchronization has general importance for  
76 understanding human ability to perceive and predict natural rhythms, may have relevance for  
77 characterizing phenotypes such as developmental speech-language disorders which demonstrate  
78 associations with atypical rhythm<sup>30</sup>, and may further elucidate mechanisms of rhythm-based  
79 rehabilitation (e.g., for stroke and Parkinson’s<sup>31</sup>).

80

81 Neuroimaging findings highlight auditory-motor networks in the brain underlying beat perception and  
82 production<sup>32</sup>, during which there is precise entrainment of neural oscillatory activity to musical signals,  
83 primarily involving motor planning areas and auditory regions of the brain, even during passive listening  
84 to music<sup>33,34</sup>. Neural mechanisms of entrainment, prediction, and reward work in concert to coordinate  
85 the timing of beat-related expectancies to musical signals during listening, playing, singing, and  
86 dance<sup>26,34</sup>. The significant inter-individual variation of beat synchronization<sup>35</sup> are thought to be  
87 influenced, in part, by common genetic variation; thus genetic approaches can be used to gain a  
88 foothold on the biological basis of musicality and human rhythm traits.

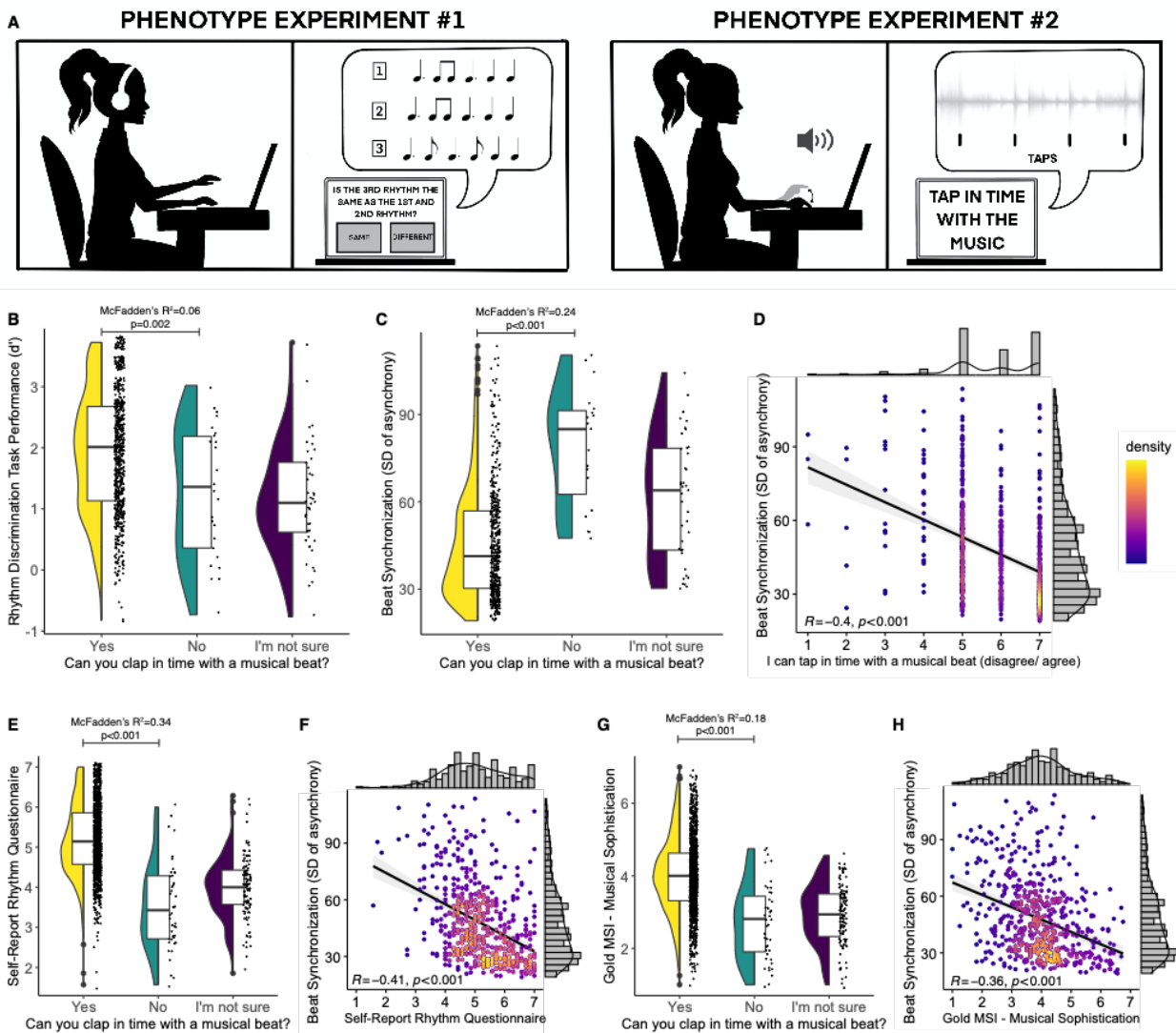
89  
90 Indeed, twin-modelling and other family-based studies point to moderate heritability of rhythm-related  
91 traits such as duration discrimination<sup>36,37</sup>, rhythm discrimination<sup>38</sup>, isochronous sensori-motor  
92 production<sup>39</sup>, and off-beat detection<sup>40</sup>. Much less is known at the molecular level about human genome  
93 variation underlying rhythm, and more generally musicality<sup>41</sup> which to date has been investigated in  
94 relatively small samples<sup>37</sup>, due to the challenge of assessing such phenotypes in samples large enough to  
95 provide sufficient power to detect common variants with small effects (as expected for complex traits<sup>42</sup>).  
96 Large-scale genome-wide association studies (GWASs) of rhythm-based traits (e.g. beat synchronization)  
97 are thus needed to advance this field. Our understanding of the biological underpinnings of beat  
98 synchronization, from its genetic architecture to its neural instantiation, behavioral manifestation, and  
99 relationship to health, requires mechanistic multi-methodological approaches. Post-GWAS approaches  
100 (i.e., enrichment of gene expression in central nervous system tissues and genetic correlations) can be  
101 deployed to illuminate the relationship between the genetic and neural architecture of music-related  
102 traits, and shared underlying biology with other health traits.

103  
104 Here, we report a large-scale genome-wide interrogation of beat synchronization. Our approach was as  
105 follows (Supplementary Figure 1): 1) We validated a subjective self-reported beat synchronization item  
106 (“Can you clap in time with a musical beat?”, referred to in this paper as the “target question”), in  
107 relation to measured beat synchronization and rhythm perception task performance. 2) We performed a  
108 GWAS in N=606,825 to identify genomic loci associated with beat synchronization. 3) We further  
109 investigated the genetic architecture of beat synchronization by estimating SNP-based heritability,  
110 partitioned heritability, and conducting gene property and gene set enrichment analyses. Lastly, we  
111 evaluated the contribution of genomic regions that have experienced significant human-specific  
112 evolutionary shifts. 4) We then validated GWAS results by testing whether a cumulative sum of the  
113 genetic effects for beat synchronization detected in our GWAS (i.e., polygenic score or PGS) was  
114 significantly associated with algorithmically identified musical engagement in a separate sample. 5) We  
115 explored shared genetic effects (pleiotropy) on beat synchronization and other traits through genetic  
116 correlation and genomic structural equation analyses.

## 117 **Results**

### 118 **Overview. Validating the self-reported beat synchronization phenotype**

119 In light of prior work suggesting that musicality and rhythm skills are complex traits that can be  
120 quantified with both objective (experiment-derived) assessment and subjective self-reported data<sup>43,44</sup>,  
121 we performed a series of validations of the GWAS target question (i.e., the self-report “Can you clap in  
122 time with a musical beat?”), in relation to rhythm perception and beat production tasks. Both studies  
123 were administered in English for consistency. We also explored the relationship between task-based  
124 beat synchronization ability, a self-reported rhythm scale, and musicality. Study overviews and key  
125 results are summarized in Figure 1.



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128 **Figure 1. Phenotype validation studies overview and results.** A) Schema of internet-based phenotype validation studies. In phenotype  
129 experiment #1, participants performed a musical rhythm perception test and provided self-report of the same target question in the GWAS  
130 study ("Can you clap in time with a musical beat?"). In phenotype experiment #2, participants performed beat synchronization tasks (which  
131 involved tapping to the beat of musical excerpts) as well as responding to the same target question, in addition to a series of other  
132 questionnaires about their musical engagement/ability and health traits. B) Phenotype Experiment 1 results in  $N=724$  show rhythm perception  
133 task performance is correlated with Yes vs. No responses to GWAS target question, Odds Ratio (OR)=1.92, McFadden's  $R^2 = 0.06$ ,  $p=0.002$ . C-H):  
134 Phenotype Experiment 2 results. C) Beat synchronization task performance ( $n=542$ ) is highly correlated with Yes vs. No responses to the target  
135 question in  $OR=0.28$ , McFadden's  $R^2=0.24$ ,  $p<0.001$ ; note that lower values of SD of the asynchrony correspond to more accurate tapping in  
136 time to the musical beat. D) Beat synchronization task performance is correlated with responses to a similar self-report question asked on a  
137 Likert scale, in  $n=542$ ,  $r=-0.40$ ,  $p<0.001$ . E) Self-reported rhythm questionnaire (seven-item scale in  $N=1,412$ ) is correlated with responses to the  
138 target question, McFadden's  $R^2=0.34$ ,  $p<0.001$ . F) Beat synchronization task performance is correlated with Self-reported rhythm questionnaire  
139 in  $n=542$ ,  $r=0.41$ ,  $p<0.001$ . G) Gold-MSI (self-reported musical sophistication questionnaire) is correlated with responses to the target question  
140 in  $N=1,412$ ,  $OR=4.16$ , McFadden's  $R^2 = 0.18$ ,  $p<0.001$ . H) Beat synchronization task performance is correlated with Gold-MSI in  $n=542$ ,  $r=-0.36$ ,  
141  $p<0.001$ . Within each plot for panels B,C,E and G, distributions are displayed using violin plots (mirrored density plot showing probability  
142 density on the left), jittered individual data plots (right), and box plots in the center (horizontal line at median, lower and upper hinges  
143 correspond to the first and third quartiles. The upper and lower whisker extends from the hinges to the value no further than  $1.5 * \text{interquartile}$   
144 range from the hinge). Data beyond the end of the whiskers are called "outlying" points and are plotted individually. Panels D, F, and H  
145 scatterplots are shown with dots colored by density to illustrate distribution. Taken together, these results show that self-reported beat  
146 synchronization is a reasonable proxy of the trait.

147 *Phenotype Experiment 1: Rhythm perception task performance.*

148 In this experiment N=724 (see Table 1 for demographics) were asked the target question and performed  
149 a musical rhythm perception test (Supplementary Figure 2). In each of the 32 trials of the task,  
150 participants judged whether two rhythms were the same or different (see Figure 1A), following a  
151 standard procedure for assessing musical perception ability<sup>45</sup> and utilizing rhythm sequences with  
152 simple (highly metrical) and complex (syncopated) rhythms<sup>46</sup>. The rhythm perception task yielded  
153 quantitative scores ( $d'$ ). Individuals with better performance in the rhythm perception test (higher total  
154  $d'$ ) were more likely to answer Yes (vs. No) to the target question (OR=1.92,  $p=0.002$ , McFadden's  
155  $R^2=0.06$ , 95% CI=1.27,2.95; Figure 1B). All tests in both phenotype experiments were two-tailed.

156

157 *Phenotype Experiment 2: Beat synchronization task performance*

158 We then validated self-reported beat synchronization phenotype (N=1,412) as a proxy for directly-  
159 measured beat synchronization ability. Participants (Table 1) completed a questionnaire on musicality,  
160 health, and personality, and were asked to tap in real time to the beat of 4 different musical excerpts  
161 (Supplementary Figure 3). Beat synchronization tapping accuracy was assessed similarly to lab-based  
162 studies<sup>35</sup>, but with a recently developed online-based technology that precisely measures asynchrony of  
163 participants' taps along to music clips - i.e., REPP (Rhythm ExPeriment Platform<sup>47</sup>) for additional details  
164 and pre-registered hypotheses (H1-H6), see Methods and Supplementary Notes. Key results of this study  
165 are summarized in Figure 1 and Supplementary Table 1. Note that more accurate tapping is reflected in  
166 lower tapping asynchrony scores, i.e., more accurate timing of taps in relation to the beat.

167

168 As predicted (OSF pre-registered H1), individuals who responded Yes to the target question ("Can you  
169 clap in time with a musical beat") had lower tapping asynchrony, OR=0.28,  $p<.001$ , McFadden's  $R^2=.24$ ,  
170 95% CI=0.18,0.42 (Figure 1C). Tapping asynchrony was also negatively correlated with responses to a  
171 highly similar item ("I can tap in time to a musical beat") when asked on a seven-point Likert agreement  
172 scale (1= disagree; 7 = agree),  $r= -.40$ ,  $p<.001$ , 95% CI=-0.47,-0.33] (H1a; Figure 1D). Similarly, individuals  
173 with higher self-reported rhythmic ability (from another multi-item questionnaire) were much more  
174 likely to respond "Yes" to the target question, OR=7.34,  $p<.001$ , McFadden's  $R^2=.34$ , 95% CI=4.90,11.52],  
175 (Figure 1E), and demonstrate lower tapping asynchrony,  $r= -.41$ ,  $p<.001$ , 95% CI=-0.47,-0.33] (Figure 1F)  
176 (H2). Controlling for confidence judgments or confidence as a personality trait did not diminish the  
177 associations between self-report and tapping asynchrony (H3; Supplementary Notes). Musical  
178 Sophistication<sup>43</sup> was positively associated with the target question, OR=4.16,  $p<.001$ , McFadden's  
179  $R^2=.18$ , 95% CI=2.90,6.12 (Figure 1G) and negatively correlated with tapping asynchrony  $r= -.36$ ,  $p<.001$ ,  
180 95% CI =-0.43,-0.28 (Figure 1H; H5). There was no credible evidence that Musical Sophistication or  
181 prior/current musician status interacted with the tapping asynchrony to predict responses to the target  
182 question (H6). All associations reported here were maintained when controlling for age, sex, and  
183 education (Supplementary Table 1). Key analyses were repeated using vector length (variability of  
184 relative phase of participants' tapping) as an outcome, and showed the same pattern of results as SD of  
185 the asynchrony (Methods and Supplementary Notes). Taken together, results show that the self-  
186 reported target question is a valid phenotype, and that other similar self-reported rhythm measures are  
187 also valid proxies of beat synchronization.

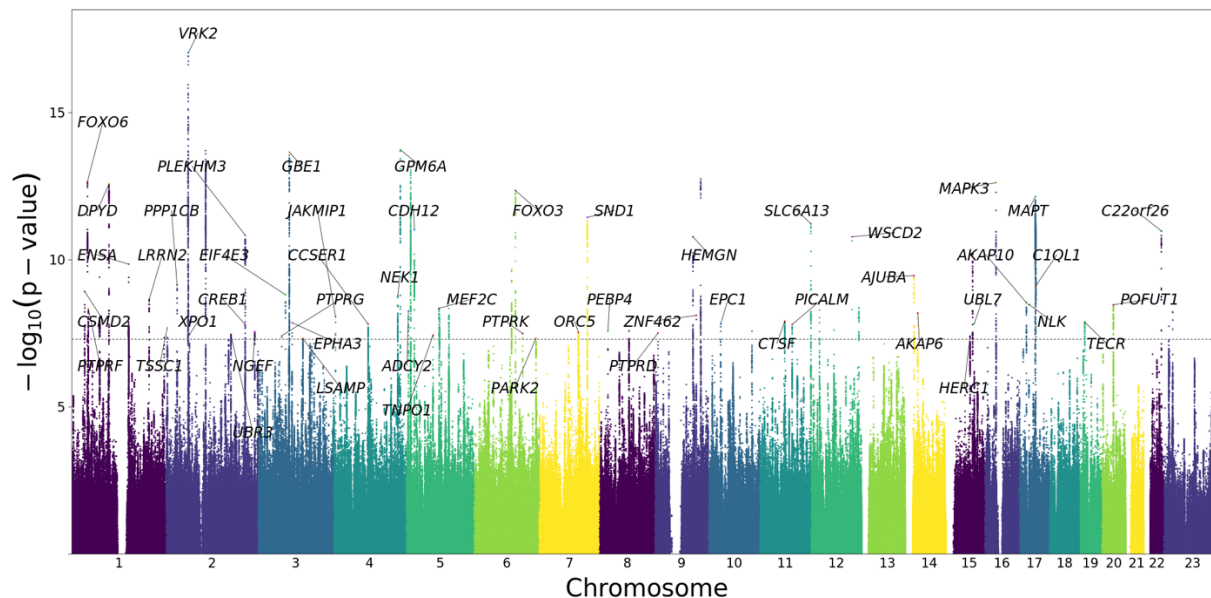
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189 **Beat Synchronization GWAS.**

190 *Genomic study population.* The discovery GWAS sample consisted of N=606,825 unrelated participants  
191 of European ancestry (see Table 1 for demographics), who consented to participate in research with  
192 23andMe, Inc. and answered Yes (91.57%) or No (8.43%) to the target question "Can you clap in time  
193 with a musical beat?"

194

195 **GWAS results and SNP-based heritability estimation.** GWAS was conducted using logistic regression  
 196 under an additive genetic model, while adjusting for age, sex, the first five principal components from  
 197 genetic data, and genotype platforms (Methods). Seventy “sentinel” SNPs (after two rounds of LD  
 198 pruning, first at  $r^2=0.6$  and then at  $r^2=0.1$ , kb = 250) at 69 genomic loci reached genome-wide  
 199 significance ( $p < 5 \times 10^{-8}$ ; two-tailed; Figure 2, Table 2, and Supplementary Table 2), with a total of 6,160  
 200 SNPs passing the genome-wide significance threshold. Sixty-seven loci were autosomal and two were on  
 201 the X chromosome; locus 28 contains two independent sentinel SNPs. QQ-plot is provided in  
 202 Supplementary Figure 4, and local association plots at each locus are in the Regional Plots Supplemental  
 203 document. The LD score regression intercept was 1.02 (se=0.01) the ratio was 0.03, indicating that the  
 204 majority of inflation in test statistics was due to true polygenicity instead of population stratification.  
 205



206  
 207 **Figure 2. Manhattan plot of GWAS results of beat synchronization.** Results of GWAS in N=606,825 with 23andMe. The GWAS phenotype is  
 208 participants’ responses of Yes (N=555,660) vs. No (N=51,165) to the question “Can you clap in time with a musical beat?”. The GWAS controlled  
 209 for age, sex, top 5 PC’s for ancestry, and genotype platform. The x-axis shows chromosomal position and the y-axis shows  $-\log_{10}$  p-values).  
 210 Sixty-nine loci (70 sentinel SNPs, with one locus containing two independent sentinel SNPs) surpassed the threshold for genome-wide  
 211 significance of  $p < 5 \times 10^{-8}$  (dotted horizontal line). For illustration purposes, only 500,000 SNPs with  $p < 0.1$  are shown; gene symbols for sentinel  
 212 SNPs are notated when FUMA provided a gene mapped to nearest sentinel SNP.

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 215 The top-associated locus (rs848293) was mapped at chromosome 2 close to *VRK2* (Vaccinia  
 216 Serine/Threonine Kinase 2 which codes for a protein kinase with multiple spliced isoforms expressed in  
 217 the brain) and *FANCL*, within a region previously linked to multiple neurological phenotypes<sup>48,49</sup>. Another  
 218 strongly associated locus at chromosome 17 (rs4792891) included the Microtubule Associated Protein  
 219 Tau (*MAPT*) gene, a Parkinson’s disease<sup>50</sup> associated locus. The Mitogen-Activated Protein Kinase 3  
 220 (*MAPK3*) gene at 16p11.2, a region known to harbor rare variants which influence neurodevelopmental  
 221 disorders<sup>51</sup> and language-related phenotypes<sup>52</sup>, was also strongly implicated. We also identified a locus  
 222 at Glycoprotein M6A (*GPM6A*), whose gene promoter contains a transcription factor binding site for  
 223 *GATA2*, a gene previously related to music phenotypes<sup>37</sup>.

224  
 225 SNP-based heritability estimates on the liability scale<sup>53</sup> ranged from 13% to 16% when adjusted for a  
 226 range of estimated population prevalence for atypical beat synchronization (3.0% to 6.5%;

227 Supplementary Table 3; see Supplementary Notes for explanation of prevalence estimates). The  
228 observed (unadjusted) genetic variance explained 5% (se=0.002) of the phenotypic variance.

229  
230 *Gene based GWAS.* Gene-based genome-wide association analyses performed with MAGMA yielded 129  
231 genes surpassing the threshold of  $p < 2.56 \times 10^{-6}$  (two-tailed; Supplementary Table 4), with top two hits at:  
232 *CCSER1*, in the 4q22 region in proximity to genes previously associated with multiple musicality  
233 phenotypes<sup>54</sup>, and *VRK2* (converging with the top locus in our SNP-based GWAS). Within these  
234 associations, we examined potential replication of 29 genetic associations with musicality in humans  
235 from prior reports<sup>37,54,55</sup>; none reached significance after genome-wide correction (Supplementary Table  
236 5, Supplementary Notes), neither independently, nor as a gene-set ( $p=0.297$ ).

237  
238 **In silico functional analyses.**

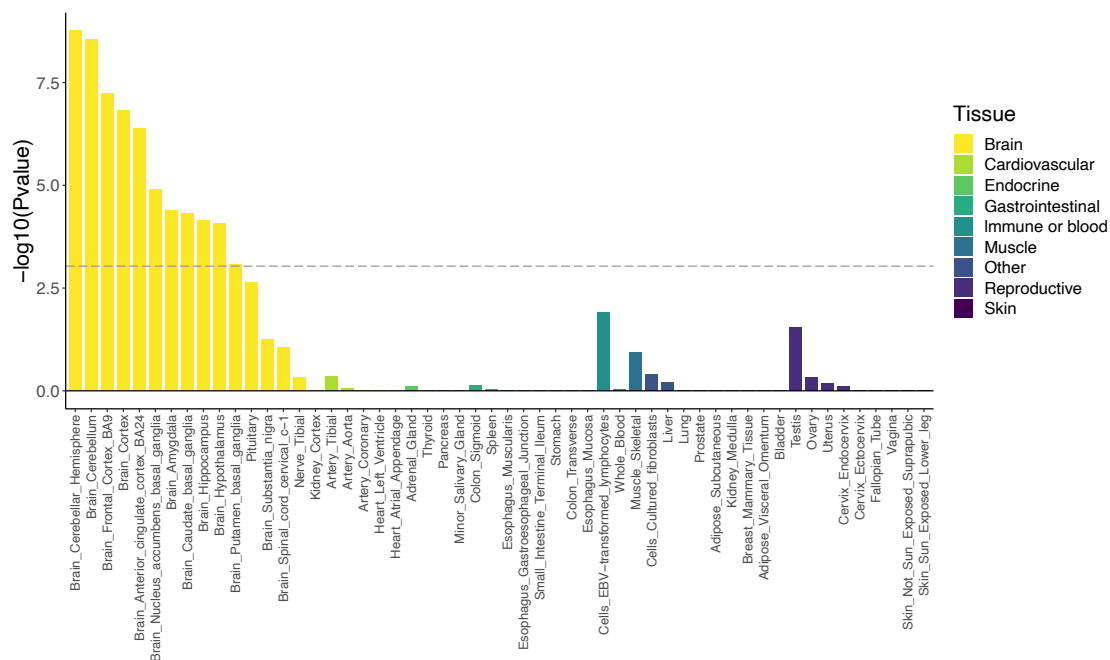
239 *Gene property and gene set enrichment analyses.* To understand the biological functions and gene  
240 expression associations of beat synchronization, we performed gene set analysis (GSA) and gene  
241 property enrichment analyses<sup>56</sup> on the gene-based p-values, using MAGMA<sup>57</sup> implemented in FUMA<sup>58</sup>.  
242 Results of conditional gene property analysis (based on GTEx data tissue types<sup>59</sup> and controlling for  
243 average expression) demonstrated that the genetic architecture of beat synchronization was  
244 significantly enriched in genes expressed in brain tissues (Figure 3A), including cortex, cerebellum, and  
245 basal ganglia (putamen, caudate and nucleus accumbens), converging with subcortical and cortical  
246 regions supporting beat perception and synchronization<sup>34</sup>.

247  
248 To further examine potential biological functions associated with beat synchronization, we performed  
249 exploratory GSA<sup>57</sup> (Supplementary Table 6). The genetic architecture of beat synchronization was  
250 enriched for two gene sets associated with nervous system function: gene sets for synaptic membrane  
251 adhesion ( $p=1.01 \times 10^{-7}$ ) and synaptic adhesion-like molecules ( $p=8.35 \times 10^{-7}$ ).

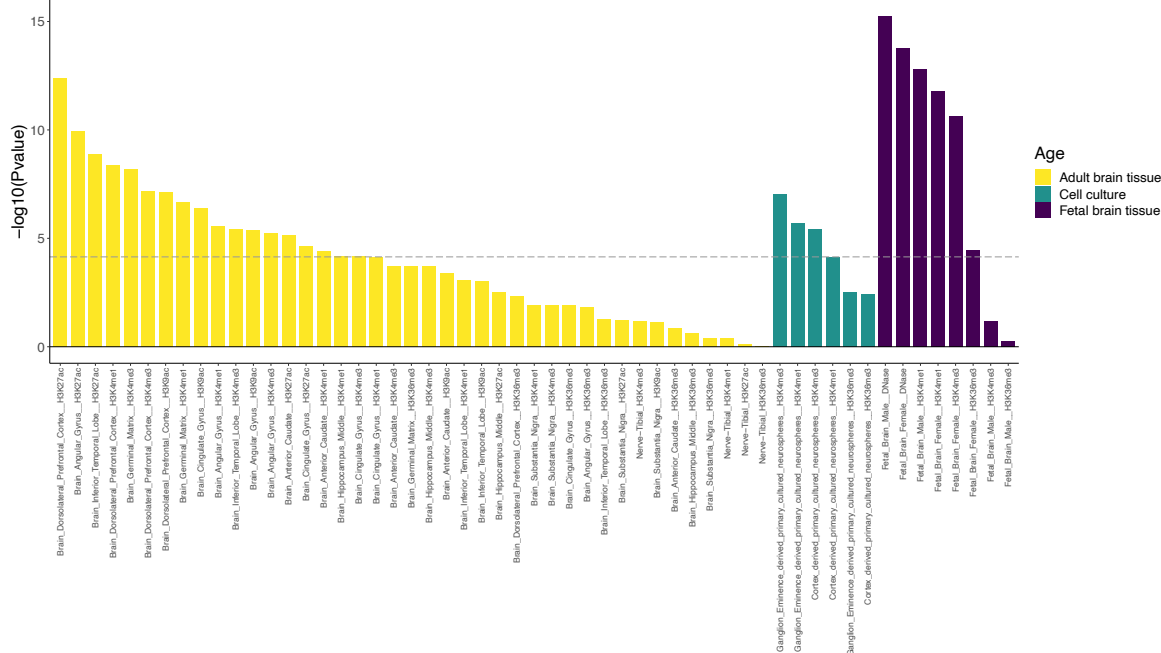
252  
253 *Partitioned Heritability.* Complementing these gene-based enrichment analyses, we also performed  
254 stratified LDSC<sup>60</sup> on the GWAS results to partition heritability according to genomic properties, using  
255 specific functional categories to gain insight into the types of variation that contribute most to beat  
256 synchronization. Among broad SNP annotation categories<sup>61</sup> (Supplementary Table 7), we found  
257 enrichment (all  $p < 9.6 \times 10^{-4}$ ) of: regions conserved in mammals (considered under purifying selection<sup>62</sup>),  
258 regulatory regions marked by acetylation of histone H3 at lysine 9 (H3K9ac; a marker for active  
259 chromatin, and monomethylation of histone H3 at lysine 4 (H3K4me1; a marker for enhancers),  
260 supporting the hypothesis that identified associations may affect gene regulation. We next used LDSC-  
261 Specifically Enriched Genes (LDSC-SEG<sup>63</sup>) to determine whether genes expressed in specific cell- or  
262 tissue-types (conditional to the other annotations) are enriched for beat synchronization-associated  
263 variants. For tissue-specific annotations of active chromatin and enhancers (marked by H3K9ac,  
264 H3K27ac, DNase hypersensitivity sites and H3K4me1), heritability was enriched in central-nervous-  
265 system- and skeletal muscle-specific regulatory regions (Supplementary Table 8). Cell-type specific,  
266 multi-tissue chromatin, and multi-tissue gene expression results are shown in Supplementary Figures 5,  
267 6 and 7 respectively. Enrichment in brain-specific regulatory elements, in multiple fetal and adult tissue-  
268 specific elements as well as CNS-specific cell cultures, are shown in Figure 3B.

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271

A



B



272  
273 **Figure 3. Genetic architecture of beat synchronization is enriched for brain-related expression.** **A. Genes associated with beat synchronization**  
274 **are enriched for expression in brain tissue.** Results of MAGMA gene-property analysis are based on gene expression levels from GTEx v8, in 54  
275 tissues, conditioned on average expression across tissues. Associations with beat synchronization were significantly enriched in brain-expressed  
276 genes (-log<sub>10</sub> p-values are on the y-axis, with tissue type on the x-axis). Dotted line shows p-value threshold for significant enrichment after  
277 Bonferroni correction. **B. Partitioned heritability shows enrichment in brain-specific regulatory regions of the genome.** Partitioned heritability  
278 analysis was performed with LDSC-SEG. Tissue-specific regulatory elements are marked by histone 3 acetylation or DNase hypersensitivity (for  
279 open chromatin) and H3K4me1 (for enhancers). Regulatory regions in adult brain tissues are shown in yellow, with regulatory elements in in



280 cell cultures in teal, and in fetal brain tissue shown in dark purple. The graph shows  $-\log_{10}$  p-values are on y-axis, with tissue and marker type  
281 on x-axis. The dotted line shows p-value threshold for significant enrichment after Bonferroni correction for number of gene sets tested.

282

283

## 284 **Evolutionary Analyses**

285 Given evolutionary hypotheses about the origins of rhythm<sup>4,18,64</sup>, we evaluated the contribution of  
286 regions of the human genome that have experienced significant human-specific shifts in evolutionary  
287 pressure, using stratified LDSC<sup>53,60</sup>. In particular, we analyzed the contribution to beat synchronization  
288 heritability from variants in genomic loci that are conserved across non-human species, but have  
289 elevated substitution rate on the human lineage<sup>65</sup>. Many of these human accelerated regions (HARs)  
290 play roles in human-enriched traits<sup>66</sup>, including cognition<sup>67</sup>. Two variants significantly ( $p < 5 \times 10^{-8}$ )  
291 associated with beat synchronization (rs14316 at locus 66, rs1464791 at locus 20) fall within HARs. This  
292 is 11.2 times more overlap than expected by chance ( $\mu=0.178$  overlaps;  $p=0.017$ , based on 10,000  
293 permutations). The rs1464791 variant is near *GBE1*, a gene associated with neuromuscular disease<sup>68</sup>,  
294 reaction time<sup>69</sup> and cognitive impairments<sup>70</sup>. Applying LDSC to consider the full set of association  
295 statistics, we find that genetic variants in HARs contribute 2.26 times more to the observed heritability  
296 of beat synchronization than would be expected if heritability were distributed uniformly across variants  
297 ( $p = 0.14$ ). Given the small number of common variants within HARs, this stratified heritability analysis is  
298 substantially underpowered (0.17% of variants considered are in HARs). The general agreement of these  
299 two approaches supports the enrichment of functional variation relevant to beat synchronization in  
300 HARs. We also evaluated the contribution of genetic variants detected in the Neanderthal genome to  
301 the heritability of beat synchronization (Supplementary Notes and Supplementary Table 9).

302

## 303 **Polygenic scores (PGS) for beat synchronization are related to musicality reported in a health care 304 context**

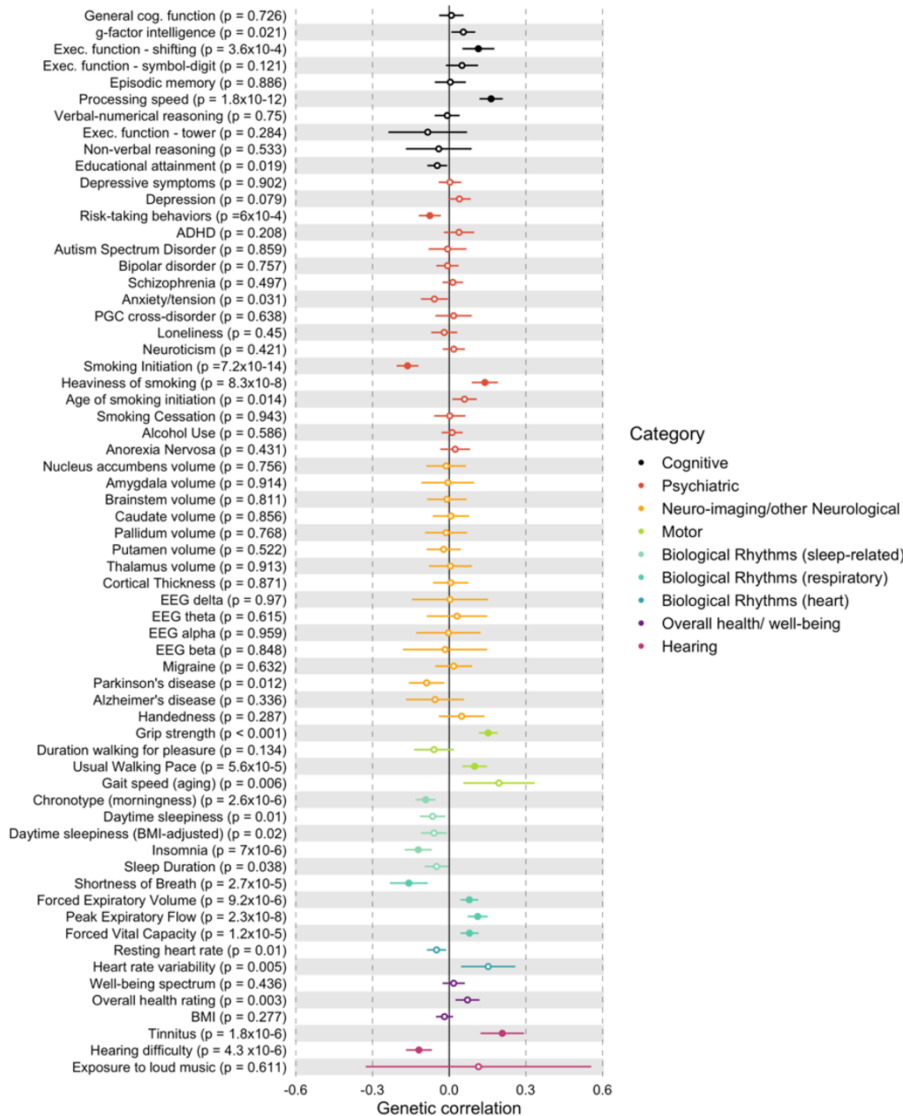
305 We investigated whether the polygenic model of beat synchronization from the GWAS would  
306 differentiate self-identified musicians from non-musicians in a separate sample. Musicians ( $n=1,259$ ) and  
307 matched controls ( $n=4,893$ ) were drawn from a study<sup>71</sup> that algorithmically identified musically active  
308 patients (Methods and Supplementary Notes). PGS for beat synchronization were significantly  
309 associated with musical engagement (OR=1.33 per SD increase in PGS,  $p < 2 \times 10^{-16}$ , Nagelkerke's  $R^2=2\%$ ,  
310 95% CI=1.25,1.42) consistent with beat synchronization capturing a dimension of musicality.

311

## 312 **Cross-trait analyses.**

313 *Genetic correlations.* To determine if beat synchronization shares genetic architecture with other traits,  
314 we tested genetic correlations<sup>72</sup> between beat synchronization GWAS and available GWAS of 64 traits  
315 classified into seven domains (Supplementary Table 10 and Supplementary Notes for details). There  
316 were 15 statistically significant genetic correlations ( $p < 7.8 \times 10^{-4}$ ) (Figure 4, Supplementary Table 11).  
317 Results included positive correlations with motor function (grip strength and usual walking pace) and  
318 heaviness of smoking, and negative correlations with risk-taking and smoking initiation. There were two  
319 correlations with hearing traits (positive correlation with tinnitus and negative correlation with hearing  
320 difficulty). From the cognitive traits, processing speed (faster perceptual motor speed) was genetically  
321 correlated with beat synchronization, in addition to executive function - shifting (from a GWAS of trail-  
322 making, a task that involves complex processing speed). There were multiple associations with other  
323 biological rhythms: breathing function traits (positive associations with peak expiratory flow, forced  
324 expiratory volume, forced vital capacity, and a negative correlation with shortness of breath) and  
325 negative associations with sleep-related traits (insomnia and morning chronotype).

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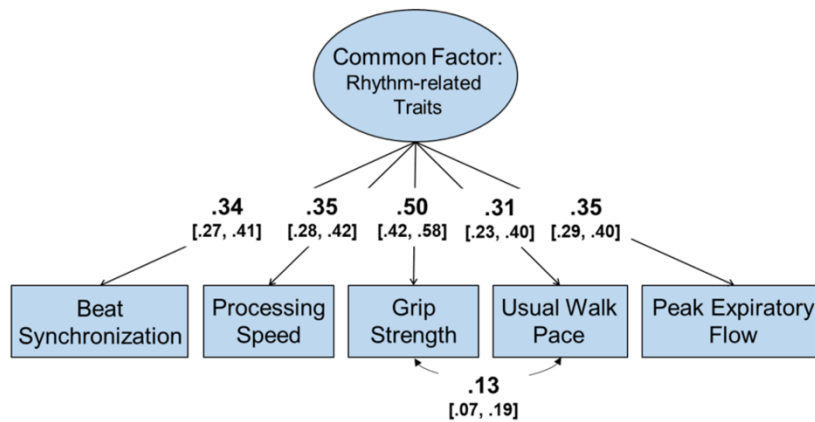


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**Figure 4. Cross-trait genetic correlations with beat synchronization.** Results of exploratory genetic correlation analyses between beat synchronization and 64 traits from eight domains, conducted with LDSC. The x-axis is magnitude of genetic correlation ( $r_g$ ) with standard error visualized, and the (uncorrected) p-values for each trait's correlation with beat synchronization are shown next to each trait label. Significant genetic correlations (after adjusting for multiple comparisons with a threshold of  $p < 7.8 \times 10^{-4}$ ) are shown with filled-in circles; empty circles are results that did not pass this threshold. See Supplementary Notes for detail on source studies. There are significant positive associations between beat synchronization and two of the cognitive domain GWASs; associations with smoking and risk-taking; two associations with hearing traits; two positive associations with motor function; and multiple associations with other biological rhythms (morning/evening chronotype, insomnia, and four breathing-related traits).

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**Genomic Structural Equation Modeling (SEM).** We conducted Genomic SEM<sup>73</sup> to examine whether specific associations between beat synchronization and a subset of associated traits (e.g., musculoskeletal strength, walking pace, breathing function, and processing speed<sup>74-76</sup>) that are known to be related among each other in prior research<sup>74-76</sup> represent distinct genetic relationships or share a common set of genetic influences with beat synchronization. The best fitting model, displayed in Figure 5, included a common genetic factor that accounted for genetic correlations among beat synchronization, grip strength, processing speed, usual walking pace, and expiratory flow. This common factor explained 11.6% of total variance in the beat synchronization GWAS and 9.6-25.0% of the variance in the other GWASs (see Supplementary Notes).



347  
348 **Figure 5. Genomic SEM model of beat synchronization and rhythm-related traits.** The best-fitting genomic structural equation model of beat  
349 synchronization with GWASs of processing speed, grip strength, usual walking pace, and peak expiratory flow. 95% confidence intervals of  
350 factor loadings and correlations are displayed in brackets. Results suggest that beat synchronization was associated with the other traits  
351 through a set of common genetic influences. Model fit:  $\chi^2(4) = 10.85$ ,  $p = .028$ , CFI = .983, SRMR = .017.

352  
353 *Common Factor GWAS: Rhythm-Related Traits.* Using genomic SEM, we conducted a multivariate GWAS  
354 (Supplementary Notes) on the latent genetic factor from the model presented above and portrayed in  
355 Figure 5. The heritability of this latent genetic factor was 7.27% (s.e.=0.25%) and there were 130  
356 genome-wide significant loci (Supplementary Table 12; Supplementary Figure 8). Heritability was  
357 enriched for genes expressed in cerebellum (Supplementary Figure 9).

358 *Cross-trait phenotypic extension of genetic correlations.* Data from Phenotype Experiment 2 was  
359 analyzed to examine whether a subset of genetic correlations would be reflected in true phenotypic  
360 associations (pre-registered H4). Less accurate beat synchronization was weakly associated with a  
361 morningness preference ( $r=-.10$ ,  $p=.015$ ), more shortness of breath ( $r=-.16$ ,  $p<.001$ ), and smoking 20 or  
362 more (lifetime) cigarettes ( $r=-.11$ ,  $p<.001$ ) (Supplementary Table 13). In other words, accuracy in beat  
363 synchronization was correlated with eveningness chronotype, reduced shortness of breath when  
364 walking on level ground, and smoking abstinence (these associations go in the same direction as the  
365 genetic correlations; moreover, these associations remained significant after controlling for age, sex and  
366 education, and/or removing professional musicians from the sample).

367  
368 *Additional sensitivity analyses.* Our results are robust to several potential biases (Supplementary Notes):  
369 the GWAS beat synchronization results are not driven by 1) shared genetic effects with general cognitive  
370 ability or educational attainment or 2) subtle residual population substructure, and 3) the *MAPT*  
371 association is not confounded with Parkinson's Disease.

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## 375 Discussion

376 Our GWAS revealed highly polygenic architecture of the human capacity to synchronize to a musical  
377 beat, representing a significant advancement of our understanding of the genomic basis of a musicality  
378 phenotype. Heritability of beat synchronization is enriched for functions of the central nervous system  
379 on a number of dimensions: SNPs involved in neural development and brain-specific regulatory regions  
380 of the genome; genes involved in synaptic function; and gene expression in cortical and subcortical brain  
381 tissues aligned with auditory-motor regions previously linked beat perception and synchronization<sup>34</sup>.  
382 Polygenic scores for beat synchronization were associated with self-identified musicians in a separate  
383 cohort, showing that the GWAS taps into the larger construct of musicality. Genetic correlations pointed  
384 to pleiotropy between beat synchronization and biological rhythms (including breathing function,  
385 walking pace, and chronotype), paving the way to a better understanding of the biological  
386 underpinnings of musicality and its health relevance.

387  
388 In a series of phenotypic experiments, we also demonstrate that self-reported beat  
389 synchronization/rhythm measures can be used in large-scale population-based studies as suitable  
390 proxies for measuring individual differences in beat synchronization. Our findings indicate that the  
391 GWAS phenotype beat synchronization question was highly related to beat synchronization task  
392 performance (i.e., accuracy in tapping along to musical excerpts). Clearly the self-report is an imperfect  
393 correlate of beat synchronization; nevertheless, we demonstrate that it is a suitable proxy for very large-  
394 scale studies in which task administration is impractical. Furthermore, the GWAS phenotype is also  
395 significantly associated with: rhythm perception task performance<sup>46</sup>, a multi-item Rhythm questionnaire,  
396 and a well-established assessment of musical sophistication<sup>43</sup>. These results also converge with earlier  
397 work showing shared variance among task performance of beat synchronization, rhythm perception,  
398 and musical engagement/training<sup>44,77-80</sup>. The phenotypic associations were robust to demographic  
399 factors and self-confidence, and were not driven by the presence of professional musicians in the  
400 sample. These phenotype validation studies represent critical groundwork (see<sup>81</sup>) enabling brief rhythm  
401 self-report questionnaires to be deployed online in large-scale population genetic cohorts.

402  
403 With sixty-nine loci surpassing the threshold for genome-wide significance, the polygenic architecture of  
404 the beat synchronization GWAS aligns with expectations for complex traits<sup>82,83</sup>. The top-associated locus  
405 mapped to *VRK2*, a gene previously associated with behavioral and psychiatric phenotypes (i.e.  
406 depression<sup>84</sup>, schizophrenia<sup>85</sup> and developmental delay<sup>86</sup>), suggesting a biological connection between  
407 beat synchronization and neurodevelopment. The SNP-based heritability of beat synchronization on the  
408 liability scale was moderate, ranging from 13 to 16%, similar to heritability estimates of other complex  
409 traits (e.g., chronotype GWAS<sup>87</sup>) and consistent with moderate heritability estimates of musical rhythm  
410 abilities reported in twin studies<sup>38-40</sup>. Still, the limitation of the heritability adjustment on the liability  
411 scale is that the exact population prevalence of atypical beat synchronization is unknown and had to be  
412 estimated based on other indices of rhythm (see Supplementary Notes); this limitation should be  
413 addressed in future work.

414  
415 We examined potential mechanisms linking genetic variation to neural architecture of the beat  
416 synchronization trait using multiple in-silico enrichment methods. Results showed enrichment of the  
417 heritability of beat synchronization in many brain tissues including cerebellum, dorso-lateral prefrontal  
418 cortex, inferior temporal lobe, and basal ganglia nuclei (i.e., putamen, caudate, and nucleus accumbens).  
419 This pattern of results likely reflects a genetic contribution to subcortical-cortical networks underlying  
420 musical rhythm perception and production<sup>32,34</sup>; furthermore, enrichment of brain-tissue-specific  
421 enhancers and active-regulatory regions in tandem with gene expression enrichments in brain tissue

422 suggest that regions of the genome involved in regulation of gene expression within the beat perception  
423 and synchronization network contribute to phenotypic variance. Moreover, the partitioning heritability  
424 chromatin results showed an enrichment in both fetal and adult brain tissues, suggesting that beat  
425 synchronization may be the result of neurodevelopmental or basic brain processes. Gene set  
426 enrichments were also observed for synaptic function in the nervous system. Taken together, these  
427 results are a building block towards understanding how genes influence neural processes during beat  
428 perception and production, complementing results obtained with neuroimaging methods<sup>88–93</sup>.

429  
430 Insights about the evolution of rhythm traits are suggested by the occurrence of two of the beat-  
431 synchronization-associated loci in human-accelerated regions (HARS) of the genome. In particular,  
432 rs1464791 is an expression quantitative trait locus (eQTL) that regulates expression of *GBE1* in multiple  
433 tissues, including muscle<sup>59</sup>; *GBE1* is also linked to neuromuscular disease<sup>68</sup> and reaction time<sup>69</sup>. HARS are  
434 involved in many functions, so it is difficult to explicitly link their accelerated evolution to beat  
435 synchronization. It is too early to tell whether the overlap between beat synchronization-associated loci  
436 and those two HARS supports evolutionary theories about music (e.g., joint synchronous music-making  
437 has been posited to exert selective pressures in early humans by enhancing group social cohesion and  
438 family bonding<sup>26,94</sup>). The contribution of the genetic architecture of motor function to beat  
439 synchronization is further suggested by enriched heritability of SNPs that are enhancers located in  
440 musculoskeletal-tissue-specific regulatory regions of the genome, as well as our findings of genetic  
441 correlations between walking pace, musculoskeletal strength, and beat synchronization.

442  
443 Moreover, our findings are promising for future large-scale genomic interrogations using comprehensive  
444 music phenotyping yielding continuous musicality variables (whether questionnaire-based<sup>43,95</sup> or  
445 measured aptitude-based variables<sup>38</sup>), providing a path to examine potential genetic correlations  
446 between beat synchronization and other musical traits, such as music training or pitch discrimination, in  
447 line with family-based findings<sup>36,37,41,96</sup>. While the current data show a clear connection between the  
448 beat synchronization and broader musicality at the phenotypic and genetic levels, further genomic  
449 investigation in well-powered samples is needed to disentangle the *specificity* of genetic influences on  
450 beat synchronization from other genetic influences on musical traits, or motor or auditory function.  
451 Finally, although our GWAS was based on self-report, the magnitude of the sample size bolstered  
452 statistical power. This is important because previous GWAS of other health traits based on self-report  
453 have effectively replicated associations from other GWAS of deeper phenotypes<sup>83</sup>, and it is generally  
454 acknowledged that powerful sample size can overcome some of the limitations arising from modest  
455 measurement error<sup>97</sup>.

456  
457 Moving in synchrony to a musical beat encompasses beat perception and extraction, motor periodicity,  
458 meter perception, and auditory-motor entrainment (see <sup>4,32,98</sup> and Glossary in Supplementary Notes).  
459 Despite this complexity, beat is a highly frequent feature of many musical systems<sup>1,3,26</sup>. Indeed, we  
460 found that the heritability of beat synchronization is enriched in auditory-motor regions known to be  
461 active during rhythm tasks.<sup>34</sup> It should be noted that beat perception and production does not depend  
462 on musical training or music genre, and atypical beat synchronization is not linked to lack of music  
463 exposure<sup>99</sup>. A limitation of the current work is the restriction of the genetic sample to a European  
464 ancestry (due to GWAS methodology constraints); investigating beat synchronization, musicality, and  
465 cross-trait correlations in populations of non-European ancestry should be a future priority for capturing  
466 the spectra of musicality traits in a wider range of ethnic, cultural and socio-economic contexts (see<sup>100</sup>).  
467 Regrettably, early research on individual differences in musicality in the early 1900's was pursued not  
468 only using what we now recognize as highly culturally biased assessments, but also explicitly through the  
469 lens of eugenics (see<sup>101</sup>), similar to early research on individual differences in cognition. We strongly

470 condemn the intent and design of those studies, and emphasize that the value of this work arises not  
471 from the hypothetical ranking of interindividual differences in beat synchronization (indeed, genomic  
472 associations with beat synchronization cannot be used to make deterministic predictions about  
473 individual abilities or aptitudes<sup>102, 103</sup>). Rather the value arises from discovering that the shared  
474 experience of rhythm, different though it is across cultures, is, in part, hardwired into our human  
475 genome. Furthermore, new knowledge on the genetic basis of musicality must be used ethically and  
476 fairly for research discovery and never for harm (e.g., discouraging a child from accessing musical  
477 activities).

478  
479 We replicated previous findings implicating location 4q22.1 in musicality-related traits<sup>36,55</sup> (*CCSER1* was  
480 the top-associated gene in our MAGMA analysis), but did not find support for previous gene associations  
481 from a set of genes that was drawn from prior candidate-gene, linkage, and GWAS studies with  
482 relatively small samples<sup>54</sup>. This is potentially due to well-known methodological problems with these  
483 methods particularly when applied to complex traits in small samples<sup>104</sup>. Without a second comparably  
484 sized GWAS available within which to conduct replication of the loci discovered in the primary GWAS,  
485 we were still able to demonstrate generalizability of these results by showing that PGS for beat  
486 synchronization predicts a musical trait in a separate biobank sample. The GWAS results of beat  
487 synchronization were nearly identical even after conditioning the results on GWASs of educational  
488 attainment and general cognition (g-factor); these results align with twin findings of specific genetic  
489 effects of rhythmic aptitude over and above any common genetic influences between rhythm and non-  
490 verbal cognitive variables<sup>39,105</sup>. Moreover, given both the likely capturing of genetic variation related to  
491 SES<sup>106</sup> by the educational attainment GWAS summary stats, and the observation that our beat  
492 synchronization GWAS loci are robust to educational attainment, SES is unlikely to play a major role in  
493 our findings.

494  
495 Our cross-trait explorations revealed pleiotropic effects between beat synchronization and several  
496 breathing-related phenotypes (peak expiratory flow, forced vital capacity, forced expiratory volume, and  
497 shortness of breath). We demonstrated phenotypically that more accurate beat synchronization task  
498 performance was related to lower likelihood of shortness of breath, mirroring the genetic correlations  
499 between beat synchronization and breathing function. In light of our genetic correlation between beat  
500 synchronization and three categories of traits (breathing, motor, and cognitive functions) previously  
501 shown to be genetically interrelated during the aging process<sup>74,75</sup>, we used genomic SEM to uncover  
502 shared genetic variance among beat synchronization and enhanced breathing function, greater grip  
503 strength, faster walking pace, and faster processing speed. Poor beat synchronization could be tied to  
504 certain health risks during aging, in light of other genetic and epidemiological work showing that lung  
505 function decline predicts later declines in motor function and psychomotor speed in older adults<sup>107-110</sup>.

506  
507 The genetic correlation results suggest that beat synchronization shares common biology with a  
508 constellation of health traits, converging with the growing literature on the overlapping biomechanical  
509 and perceptual mechanisms of rhythms harnessed during synchronization, communication, muscle  
510 tensioning, and breathing; these relationships start very early in development<sup>111,112</sup>. The cerebellum in  
511 particular plays important roles in the control of coordinated movement, balance, respiration, dance,  
512 and even rhythm perception during passive listening to music<sup>33</sup>. Indeed, our rhythm-related traits multi-  
513 variate GWAS demonstrated enriched heritability of genes expressed in Cerebellar tissue, potentially of  
514 note in relation to experimental findings of functional synchronization of respiratory and upper limb  
515 movements during vocalization<sup>5</sup>. Moreover, “beat gestures” in speech involve the cerebellum<sup>113</sup> and are  
516 inextricably linked to respiration, upper limb movement, and postural control, all of which may be  
517 biomechanically related to tapping or clapping to music.

518  
519 Another dimension of biological chronometry was captured in the genetic correlation between  
520 chronotype and beat synchronization, which we replicated phenotypically (individuals who self-  
521 identified as ‘evening people’ tended to tap more accurately to music, even after removing professional  
522 musicians from the analysis). These results complement recent evidence of the increased prevalence of  
523 eveningness in musicians<sup>114</sup>, indicating that the relationship between chronotype and musicianship  
524 cannot solely be explained by environment (i.e., nocturnal job demands of professional musicians), but  
525 that also other shared biological factors may play a role. Given the genetic correlation between beat  
526 synchronization and lowered incidence of insomnia, the relationship between regulation of sleep,  
527 musicality, and rhythm represents an area for further exploration.

528  
529 Our GWAS effectively identified alleles at 69 separate loci differentially associated with typical vs.  
530 atypical beat synchronization, complementing existing evidence of underlying neural  
531 mechanisms<sup>77,79,80,99</sup>. Future genetic studies could study beat synchronization as a continuous trait,  
532 either through self-report or internet-based task paradigms (i.e., REPP<sup>47</sup>). Prior literature on liability  
533 threshold models has shown that case-control GWAS of complex traits yield similar results to those  
534 obtained through continuous phenotypic measures (e.g., the genetic architecture of continuous  
535 measures of psychiatric symptoms is highly similar to the genetic architecture of cases versus  
536 controls<sup>115</sup>). Moreover, the use here of a population-based control group that is not “super-normal”  
537 increases the likelihood that the genetic correlations that we uncovered are reliable and not biased  
538 upward<sup>116</sup>.

539  
540 Taken together, our results advance knowledge of the biological basis of beat synchronization by  
541 identifying genomic regions associated with individual differences in beat synchronization, estimating its  
542 cumulative SNP-based heritability, successfully applying a polygenic score model in a separate genetic  
543 sample, and exploring the enrichment of heritability in genes tied to central nervous system function.  
544 Movement in synchrony with a musical beat is a fundamental feature of music, and sensitivity to the  
545 beat emerges early in development, supporting childhood development in numerous ways<sup>3,11,27,30</sup> and  
546 with importance over the lifespan<sup>117</sup>. We have elucidated the genetic architecture of beat  
547 synchronization and revealed its health relevance through cross-trait analyses. This study also provides a  
548 solid foundation for future exploration of how specific genetic variants contribute to neural mechanisms  
549 of entrainment, prediction, and reward harnessed during musical interactions<sup>118</sup>.

550

## 551 **Methods**

### 552 **Phenotype validation studies**

#### 553 ***Phenotype Validation Experiment 1.***

554 *Overview.* Phenotype Validation Experiment 1 was designed to determine if self-reported rhythm  
555 abilities measured with the question used in the GWAS (i.e., ‘Can you clap in time with a musical beat?’)  
556 would be associated with task-based rhythm perception performance. The study was conducted in  
557 Amazon’s Mechanical Turk and received ethical approval from the Columbia University Institutional  
558 Review Board; participants gave their written informed consent, and the research complied with all  
559 relevant ethical regulations. We selected the Beat-based Advantage paradigm as a rhythm  
560 discrimination (perception) test due to its design of stimuli with simple and complex meter<sup>119</sup> and prior  
561 history investigating individual differences in rhythm perception in a variety of brain and behavioural  
562 studies in adults and children with typical and atypical development<sup>46,120–122</sup> as well as feasibility for

563 internet-based adaptation. A questionnaire (self-report questions) was administered prior to the  
564 perception task, to avoid biasing participant self-report responses by how they perceived their own task  
565 performance. See Supplementary Notes for additional details on procedure, compensation, and self-  
566 report questionnaire.

567  
568 *Participants.* The study sample was N=724 participants recruited anonymously in Amazon’s Mechanical  
569 Turk. All consented and passed a common headphone check<sup>123</sup> that guarantees good listening  
570 conditions and the ability to follow basic instructions; this test also effectively filters out bots.  
571 Participants (333 females; 387 males; 4 self-reported “other”) were 18-73 years old (mean = 36.1 years,  
572 SD=10.9) with 0-45 years of self-reported musical experience (mean 3.7 years, SD=5.7), representing an  
573 average degree of musical experience (see norms in<sup>43</sup>); demographics are reported in Table 1 (note that  
574 n=3 did not report their age).

575  
576 *Rhythm Perception Task.* Stimuli for the rhythm perception task consisted of 32 rhythms drawn from  
577 prior work<sup>46,119</sup>. For each participant, we randomized with probability of one half the occurrence of  
578 “simple” rhythms (strong beat-based metrical structure and generally easier to discriminate) and  
579 “complex” rhythms (weaker metrical structure due to syncopation and generally more challenging to  
580 discriminate). Each rhythm was presented using pure tone stimuli in one of 6 frequencies (294, 353, 411,  
581 470, 528, and 587 Hz, selected at random), and one of 4 durations (ISI of 220, 230, 240, and 250 ms).  
582 Each trial consisted of 3 rhythms separated by 1500 ms of silence; there were 32 trials of the task. The  
583 two first presentations were always identical, and in half of the trials (counterbalanced) the third rhythm  
584 was also identical (standard condition); in the other half of the trials, the rhythm differed by having one  
585 interval swapped (deviant condition). The pairings and structure of standard and deviant trials were  
586 taken from<sup>46</sup>. Participants were instructed that in each trial, they would listen to the series of three  
587 rhythms (the first two were always identical, and the third could be the same or different), and they had  
588 to indicate if the third rhythm was the same or different (see Supplementary Figure 2). Additional  
589 technical details are provided in the Supplementary Notes.

590  
591 *Data analysis.*

592 *Self-report.* Responses to the target question were as follows: n=654 (90.3%) participants answered  
593 ‘Yes’, n=25 (3.5%) answered ‘No’ and n=45 (6.2%) answered “I’m not sure.” Regarding an additional self-  
594 report question ‘Do you have a good sense of rhythm?’, n=503(67%) answered ‘Yes’, 102(14%)  
595 answered ‘No’ and n=117(16%) answered ‘I don’t know’. n=488 answered ‘Yes’ to both questions; the  
596 tetrachoric correlation between these two self-report questions was  $r=0.73$ .

597  
598 *Rhythm perception test.* Responses to the rhythm perception test were analysed using signal detection  
599 theory<sup>46,124</sup>; this method is appropriate for discrimination tasks where the participant has to categorize  
600 stimuli along some dimension with the resulting  $d'$  values the strength of detection of the signal relative  
601 to noise.  $d'$  values were calculated on the 32 test trials. As expected from prior work<sup>46,125</sup>, individuals  
602 performed better at discriminating simple rhythms (mean  $d'=1.98$ , SD =0.91) than complex rhythms  
603 (mean  $d'=1.43$ , SD =0.97) ( $t(724)=11.11$ ,  $p<0.001$ , Cohen’s  $d=0.58$ ).

604  
605 To examine whether the target question was related to the objective (experimenter-measured)  
606 performance on the rhythm perception test, we performed a logistic regression analysis in which the  
607 clap-beat target question (Yes vs. No) was the outcome and quantitative scores on the rhythm  
608 perception test ( $d'$  scores) were the predictor. Covariates included age, education, and sex. McFadden’s  
609  $R^2$  was also computed. We did not include ‘I’m not sure’ in the regressions, because this response was  
610 not available for data analysis in the GWAS. Given that the simple rhythms have a strong metrical



611 structure that is known to facilitate detection and synchronization of the beat<sup>46</sup>, we also tested whether  
612 performance on the simple rhythm trials predicted self-reported beat synchronization (i.e., those who  
613 responded Yes to the clap-beat question). See Supplementary Notes for additional analyses.

614

## 615 **Phenotype Experiment 2.**

### 616 *Overview.*

617 The aims of Phenotype Experiment 2 were two-fold: 1) to validate self-reported beat synchronization  
618 phenotype as a proxy for objectively measured beat synchronization ability, and 2) to explore  
619 phenotypic associations between rhythm/beat synchronization and assorted traits found to be  
620 genetically correlated with beat synchronization. Phenotype Experiment 2 was pre-registered with Open  
621 Science framework (<https://osf.io/exr2t>) on July 8, 2020, prior to data collection. This internet-based  
622 study consisted of a beat synchronization task to assess the accuracy of participants' tapping in time  
623 with musical excerpts, and a series of questionnaires assessing self-reported rhythm, musicality/music  
624 engagement, selected health traits, confidence as a personality trait, and demographics. We used  
625 REPP<sup>47</sup> to measure participants' tapping responses online with high temporal fidelity. The item from the  
626 GWAS study, "Can you clap in time with a musical beat?" with possible responses: Yes/No/I'm not sure,  
627 is referred to as the "target question."

628

629 We tested the following hypotheses: *H1*: Self-report responses to the target question will be correlated  
630 with beat synchronization task performance (i.e., accuracy of tapping to the beat of music), such that  
631 individuals who respond Yes to the "target question" are predicted to tap more accurately to the beat of  
632 musical excerpts (i.e., they will have lower standard deviation of asynchrony than individuals who  
633 respond No to the target question). *H1a*: Self-report on a highly similar self-report question ("I can tap in  
634 time with a musical beat") with responses on a 7-point agreement Likert scale are predicted to be  
635 correlated with tapping accuracy. *H2a*: The target question will be associated with broader rhythm  
636 ability/engagement (measured with a rhythm scale from seven other self-report questions). *H2b*: Beat  
637 synchronization task performance reflects broader self-reported rhythm ability/engagement. *H3*: To  
638 examine whether confidence (either as a personality trait or sureness in one's own task performance)  
639 affects the reliability of self-reported beat synchronization. *H4*: Selected traits found to be genetically  
640 correlated with beat synchronization in the GWAS will be phenotypically correlated with beat  
641 synchronization task performance and the Rhythm Scale. Specifically: better beat/rhythm is correlated  
642 with evening chronotype (*H4a*), less shortness of breath (*H4b*), more tinnitus and loud music exposure  
643 (*H4c*), and more smoking (*H4d*); and that these associations would survive controlling for age, sex, and  
644 education (*H4e*). *H5*. Responses to the target question will be positively correlated with musical  
645 engagement measured with the Gold-MSI. *H6*. The associations in *H4* would interact with being a  
646 musician, or more generally, with musical engagement.

647

648 *Participants*. A total of N=1,412 individuals met participation criteria outlined in the pre-registration  
649 (including passing the attention check item and not abandoning the study before completion). The study  
650 took place in Amazon Mechanical Turk and all participants provided informed consent in accordance  
651 with the Max Planck Society Ethics Council's approved protocol; the research complied with all relevant  
652 ethical regulations. Participants (728 females; 678 males; 6 prefer not answer) were 18-77 years old  
653 (mean=36.3 years, SD=11.9) and had of 1-2 years of self-reported musical experience (Table 1). To  
654 ensure that the tapping technology measured beat synchronization with high temporal fidelity, it was  
655 crucial that participants complied with instructions to perform the tapping task (e.g., using the laptop  
656 speakers instead of headphones, with minimal background noise, etc.), and also used hardware and  
657 software without any technical issues that would preclude the recording signal (e.g., malfunctioning  
speakers or microphones, or the use of strong noise cancellation technology; see<sup>47</sup>). Thus, several

659 precautions, including calibration tests and practice trials, were taken to make sure the tapping  
660 technology would work effectively, excluding cases that did not meet the requirements (see  
661 Supplementary Notes for details). A subset of  $n=542$  had appropriate hardware to complete all parts of  
662 the study (including the tapping tests). Questionnaires were administered in the full sample of  
663 participants. Sample demographics are reported in Table 1. Demographics of the participants that  
664 completed the tapping experiment was highly similar to the full sample, as shown in the table;  
665 furthermore, 65.3% of the full sample and 64.9% of tapping sample had a Bachelor's degree or higher.

#### 666 *Data collection for Phenotype Experiment 2.*

667 The first questionnaire included self-report items, including the "target question," and also covering a  
668 variety of musical, health, and interest phenotypes. The health phenotype questions were chosen from  
669 phenotypes (chronotype, smoking, shortness of breath, and tinnitus) found to be genetically correlated  
670 with beat synchronization in our genetic analyses. Rhythm questions were selected for their particular  
671 relevance to various aspects of interacting/engaging with musical rhythm. The order of the questions  
672 was fixed for all participants. In addition, we used an attention check item<sup>126</sup> between item 10 and 11, in  
673 order to exclude fraudulent responders, such as computer bots or disengaged participants responding  
674 randomly to the experiments. The end-questionnaire consisted of items covering the following  
675 additional self-report topics: another question about being a musician, a task confidence rating  
676 question, a Confidence scale, a 16-item short version of the Gold-MSI<sup>43</sup> (items were chosen due to their  
677 high reliability scores: reliability  $\omega = 0.92$ ), and a Demographic questionnaire. Questionnaire items  
678 for Phenotype Experiment 2 are listed in the Appendix of the Supplementary Notes.

680  
681 *Tapping technology.* Beat synchronization is particularly challenging to study with online research,  
682 where variability in participants' hardware and software can introduce delay in latency and jitter into  
683 the recorded time stamps<sup>127,128</sup>. Here we used REPP (see<sup>47</sup> for full details and a validation study of the  
684 technology), a robust cross-platform solution for measuring sensorimotor synchronization in online  
685 experiments that has high temporal fidelity and can work efficiently using hardware and software  
686 available to most participants online. To address core issues related to latency and jitter, REPP uses a  
687 free-field recording approach: specifically, the audio stimulus is played through the laptop speakers and  
688 the original signal is simultaneously recorded with participants' tapping responses using the built-in  
689 microphone. The resulting recording is then analyzed using signal processing techniques to extract and  
690 align timing cues with high temporal accuracy.

691  
692 *Beat synchronization task.* The beat synchronization task procedure consisted of three parts: calibration  
693 tests, practice phase, and main tapping phase. Participants started with the calibration tests, including a  
694 volume test to calibrate the volume of the laptop speakers to a level sufficient for detection by the  
695 microphone, a background noise test to make sure participants were in a quiet environment, and a  
696 tapping test to help participants practice how to tap on the surface of their laptop in the right level and  
697 location to be detected by the microphone. Participants were then presented with the practice phase,  
698 which consisted of four 15-second trials of isochronous tapping to a metronome beat (two with inter-  
699 onset interval of 500 msec and two with inter-onset interval of 600 msec). Following the practice phase,  
700 participants were presented with the main tapping task consisting of eight trials (4 musical excerpts,  
701 each played twice), with each trial 30 seconds long. The order of presentation of the practice trials and  
702 test trials was randomized for each participant.

703  
704 The musical excerpts were drawn from the MIREX 2006 Audio Beat Tracking database in which musical  
705 excerpts had been annotated for beat locations by 30 listeners who tapped along to the music<sup>129</sup>. We  
706 chose these four MIREX clips that represent different music genres with different tempos and tapping

707 difficulty: track 1 (“You're the First, the Last, My Everything” by Barry White), track 3 (“El Contrapunto”  
708 by Los Mensajeros de La Libertad), track 7 (“Le Sacre du Printemps” by Stravinsky), and track 19  
709 (“Possessed to Skate” by Suicidal Tendencies) of the MIREX training set (respectively). Based on the  
710 annotations in<sup>129</sup>, we identified the target beat locations from those consistently produced by the  
711 annotators. Additional technical details are provided in the Supplementary Notes, and Supplementary  
712 Figure 2 illustrates the instructions for participants.

713

714 *Data Analysis.*

#### 715 **Beat synchronization task performance: Tapping accuracy analysis**

716 Let  $S_t$  and  $R_t$  be the stimulus and response onsets, respectively. In case of the metronome  $S_t$  are the  
717 metronome onset (practice phase) and for music clips  $S_t$  is the target beat location based on the  
718 annotations. We define the asynchrony as  $a_t = R_t - S_t$ . Based on prior work<sup>130</sup>, we chose the standard  
719 deviation of the asynchrony ( $\text{std}(a_t)$ ) as our main target interest variable, as this appears to be a robust  
720 measure of individual performance and tightly linked to musical abilities<sup>131</sup>. We used metronome onsets  
721 to mark the beat metric level in an unambiguous way<sup>132</sup>. We emphasize that the metronome onsets  
722 were only physically present during the beginning and end of each clip. We used only the participant-  
723 produced asynchronies during the epoch at beats in which the guiding metronome was *not* present, in  
724 order to test the ability of the participants to synchronize to music without the metronome sounds  
725 (results were nearly identical when we included all onsets including the ones where physical metronome  
726 onsets were present). For the main test scores, we used the asynchronies computed relative to the  
727 virtual beat locations computed from prior human annotators in MIREX. We also computed vector  
728 length in order to confirm key associations of interest between the target question and beat  
729 synchronization accuracy (See Supplementary Notes).

730

#### 731 **Regression analyses**

732 In accordance with the OSF preregistration, we examined whether responses to self-reported beat  
733 synchronization phenotype were associated with objectively-measured tapping accuracy, other self-  
734 reported measures of rhythm ability, confidence, and/or musical sophistication using logistic regression  
735 and McFadden's  $R^2$  (for H1, H2a, H3, and H5) and linear regression (for H1a and H2b). Likewise, we used  
736 linear regression to examine potential replication of cross-trait associations uncovered by genetic  
737 analyses (H4a-d), to examine whether musical background interacted with the above associations (H6).  
738 Analyses were conducted in R version 3.5.1<sup>133</sup>. As described in our preregistration, individuals were  
739 recruited using MTurk and were included unless they failed an attention check item or abandoned the  
740 experiment before completing the study (N=1,412). Usable tapping data was available for n=542  
741 individuals. The majority of exclusions were due to technical reasons detected by REPP's signal  
742 processing pipeline during the practice trials (e.g., poor signal, noisy environment, wearing headphone,  
743 issues with laptop microphone, or people not tapping at all), but some additional subjects (n=19) were  
744 excluded for not having enough usable trials during data analysis. Missing covariates were handled using  
745 pair-wise deletion. Exclusion criteria are detailed in the Supplementary Notes.

746

#### 747 **GWAS of beat synchronization.**

748 Genome-wide association study summary statistics were generated from data acquired by personal  
749 genetics company 23andMe, Inc. Phenotypic status was based on responses to an English-language  
750 online questionnaire in which individuals self-reported “Yes” (cases) or “No” (controls) to the question  
751 ‘Can you clap in time with a musical beat?’. Individuals who responded “I'm not sure” were excluded  
752 from the genomic dataset as their data was not available. The GWAS included a total of 555,660 cases  
753 and 51,165 controls (total N=606,825, mean age(SD)=52.09(18.5), prevalence=92%), unrelated  
754 individuals of European ancestry; age range breakdown is provided in Table 1. All individuals provided

755 informed consent according to 23andMe's human subject protocol, which is reviewed and approved by  
756 Ethical & Independent Review Services, a private institutional review board  
757 (<http://www.eandireview.com>); the study complied with all relevant ethical regulations.

758  
759 GWAS was conducted using logistic regression under an additive genetic model, while adjusting for age,  
760 sex, the top five principal components estimated from genetic data in order to control for population  
761 stratification, and indicators for genotype platforms to account for batch effects. We excluded SNPs with  
762 Minor Allele Frequency (MAF) <0.01, low imputation quality ( $R^2 < 0.3$ ) and indels, resulting in 8,288,850  
763 SNPs in the GWAS summary statistics. Genotyping and QC details are provided in the Supplementary  
764 Notes.

#### 765 766 **Post GWAS enrichment analyses**

767 *FUMA-based analyses.* The FUMA<sup>58</sup> web application was used on the Genome-Wide Association  
768 summary statistics to identify genomic loci along with the "sentinel" SNPs that were independent in our  
769 analysis with a genome-wide significant P-value ( $< 5 \times 10^{-8}$ ) that are in approximate linkage  
770 disequilibrium (LD) with each other at  $r^2 < 0.1$  and to generate Manhattan plots and Quantile-Quantile  
771 plots. GWAS Catalogue associations for top loci were performed in FUMA (Supplementary Table 16).

772  
773 Next, using the GWAS summary statistics as input for MAGMA (v1.08), we conducted a gene-based test  
774 of association, a gene property enrichment test, and a gene-set enrichment analysis. Gene property  
775 analysis<sup>56</sup> utilized GTEx v8 data integrated in FUMA, with gene expression values log2 transformed  
776 average TPM per tissue type after winsorization at 50 based on GTEx RNA-seq data; this analysis was  
777 performed for 54 tissue types where the result of gene analysis was tested for one side while  
778 conditioning on average expression across all tissue types. We also performed exploratory GSA<sup>57</sup> in  
779 FUMA using 15,556 Gene Ontology gene sets from the MsigDB database<sup>134,135</sup>; a Bonferroni threshold of  
780  $3.2 \times 10^{-6}$  was used.

781  
782 *SNP-based heritability and partitioned heritability.*

783 SNP-heritability was computed with LD Score regression software<sup>60</sup>, and heritability estimates were  
784 adjusted to the liability scale based on population prevalence of atypical beat synchronization of 3.0%-  
785 6.5% (Supplementary Table 3, Supplementary Notes). We partitioned heritability of beat  
786 synchronization by 52 broad functional categories (Supplementary Table 7), using stratified LD score  
787 regression<sup>60,63</sup> (Bonferroni-corrected significance level of  $p = 9.6 \times 10^{-4}$ ). We hypothesized that SNPs falling  
788 into open chromatin regulatory regions (i.e., accessible to transcriptional machinery), and regions with  
789 human-specific variation, would be enriched for beat synchronization-associated variation.

790  
791 We further investigated (SNP-based) cell-type-specific and tissue-specific enrichments with LDSC-SEG  
792 (LDSC Specifically Expressed Genes)<sup>67</sup>, using a total of 697 gene sets (3 Cahoy gene sets, 205 Multi-tissue  
793 gene expression sets and 489 Multi-tissue chromatin sets from the RoadMap Epigenomics and ENCODE  
794 datasets); the Bonferroni-corrected significance level for this analysis was  $7.1 \times 10^{-5}$  (Supplementary Table  
795 8). The X chromosome was not included in these analyses or any subsequent analyses using LDSC, given  
796 that the file that is required for LDSC analysis (w\_hm3\_snplist) does not include chromosome X SNPs.

797  
798 *Evolutionary analyses.*

799 The set of human accelerated regions (HARs) was taken from<sup>65</sup>. All variants in perfect LD ( $r^2 = 1.0$  in 1000  
800 Genomes European participants) with variants in HARs were considered in the analysis. Similarly,  
801 variants tagging Neanderthal introgressed haplotypes were defined as in<sup>136</sup>. All variants in perfect LD  
802 with a Neanderthal tag SNP were considered Neanderthal variants. For each set, we performed

803 stratified LDSC (v1.0.0) with European LD scores and the baseline LD-score annotations v2.1. The  
804 heritability enrichment is defined as the proportion of heritability explained by SNPs in the annotation  
805 divided by the proportion of SNPs in the annotation. Standard effect size ( $\beta$ ), which quantifies the effects  
806 unique to the annotation, is the proportionate change in per-SNP heritability associated with a one  
807 standard deviation increase in the value of the annotation, conditional on other annotations in the  
808 baseline v2.1 model<sup>62</sup>. To determine the expected number of overlaps between the N loci significantly  
809 associated with beat synchronization and HARs, we computed all overlaps between these sets of  
810 genomic regions (in hg19 coordinates) using bedtools<sup>2137</sup>. We then randomly shuffled the locations of  
811 HARs around the genome choosing segments of equal lengths and avoiding gaps in the genome  
812 assembly. We repeated this process 10,000 times and for each iteration computed the number of  
813 overlaps observed with the significantly associated loci. Based on this empirical distribution created with  
814 no association between the region sets, we computed the enrichment and p-value for the observed  
815 number of overlaps.

816  
817 *Genetic correlations.* The genetic correlation method is designed to show whether there is shared  
818 genetic variation linked to a particular trait (here, our beat synchronization trait) and traits measured in  
819 other GWAS studies. We curated GWAS summary statistics for 64 complex traits representing a broad  
820 range of phenotypic categories: cognitive, psychiatric, neuro-imaging/other neurological, motor, other  
821 biological rhythms (circadian, heart, and breathing), overall health/well-being, and hearing (see  
822 Supplementary Table 10 and Supplementary Notes for details of the source studies). We estimated  
823 genetic correlations between beat synchronization and each of these traits using LDSC<sup>72</sup>, with a  
824 Bonferroni threshold of  $7.5 \times 10^{-4}$  (Supplementary Table 11).

825  
826 *Beat synchronization Polygenic Score (PGS) prediction of music engagement reported in health records*  
827 *Overview.* We examined whether beat synchronization polygenic scores (PGS) would be associated with  
828 music engagement reported in health records. Individuals who disclosed music engagement to their  
829 care providers (which was subsequently recorded by their provider) were drawn from a recent  
830 phenome-wide study of 9,803 musicians<sup>71</sup> identified from keyword searches of patient electronic health  
831 records (EHRs) in Vanderbilt University Medical Center's de-identified research database (Synthetic  
832 Derivative). The phenotyping method was based on mining of clinical notes, utilizing 4 keywords and 449  
833 regular expressions (i.e., "musician", "plays the piano"); see Supplementary Notes and<sup>71</sup> for details. The  
834 method was then validated with manually conducted chart review, with a positive predictive value (PPV)  
835 of 93%. Here we accessed the subset of n=1,259 musicians and 4,893 controls (matched for sex, median  
836 age (across the patients' medical record), ethnicity, race, and length of record) that were also part of the  
837 BioVU database and had genotyped data on file, to test the hypothesis that higher PGS for beat  
838 synchronization would be associated with musical engagement operationalized as a having musician-  
839 related keywords/regular expressions recorded in an individual's electronic health record.

840  
841 We only selected individuals of European ancestry with genetic data that met standard quality control  
842 thresholds due to the poor performance of PGS trained in individuals of one ancestry and applied to  
843 individuals of another. This resulted in n=1,259 individuals (553 (44%) females, mean median age of  
844 record (SD)=53.1(16.5)) as musician "cases" and 4,893 controls (1,963(40%) females, mean median age  
845 of record (SD)=53.2(16.3)). See Supplementary Notes for details on the phenotyping, the samples,  
846 genotyping, and QC.

847  
848 *Polygenic scores.* We used an IBD filter of 0.2 in order to include only unrelated European samples of  
849 BioVU. PGS were generated using the beat synchronization GWAS summary statistics, using software  
850 PRS\_CS<sup>138</sup>. Briefly, this method uses a Bayesian regression framework and places continuous shrinkage

851 (CS) prior on SNP effect sizes; this method outperforms previous methods in terms of prediction  
852 accuracy especially when the training sample size is large<sup>138</sup>, as is the case with the beat synchronization  
853 GWAS. The 1000genomes European reference set was used. The PGS was standardized to have a mean  
854 of 0 and SD of 1. Chromosome X was not included in the BioVU sample.  
855 Data analysis. We conducted a logistic multivariable regression where the outcome variable was  
856 musician vs. control, the predictor variable was PGS for beat synchronization, and covariates included  
857 median age across the patients' medical record, sex, top 10 principal components estimated from BioVU  
858 genetic data.  
859  
860 **Study FAQ:** A live FAQ for the study is at: [https://www.vumc.org/music-cognition-lab/news/faq-about-](https://www.vumc.org/music-cognition-lab/news/faq-about-beat-synchronization-gwas-study)  
861 [beat-synchronization-gwas-study](https://www.vumc.org/music-cognition-lab/news/faq-about-beat-synchronization-gwas-study)

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## 1166 **Author contributions**

1167  
1168 *Conceptualization of study:* RLG, LKD; *GWAS data acquisition and GWAS analyses:* JFS, 23andMe  
1169 Research Team, DH, PS, MN; *GWAS and post-GWAS study design:* LKD, RLG, JFS, MN, AJC, DH; *Data*  
1170 *visualization:* PS, MN, MAT, NJ, RLG, EE, DEG; *Post-GWAS analyses and interpretation:* MN, DEG, PS, RLG,  
1171 *EE, EM, JAC, JFS, MM, FU, NC; Phenotype studies design:* RLG, JDM, NJ, DEG, MAT; *Phenotype studies*  
1172 *data collection and analysis:* MAT, NJ, DEG, EB, PS, MN, RLG, MM; *Interpretation of results, writing,*  
1173 *editing, and reviewing drafts:* All authors; *Project Supervision:* RLG, LKD, NJ, DH.

## 1174 **Competing interests**

1175 JFS, DH, and members of the 23andMe Research Team are employees of 23andMe, Inc., and hold stock  
1176 or stock options in 23andMe. All other authors declare no competing interests.

## Tables

**Table 1. Sample demographics for each of the three study samples (GWAS and Phenotype Experiments 1 and 2).**

**GWAS Sample by Phenotype group (response to Clap-to-beat question)**

	<i>Cases (Yes)</i>	<i>Controls (No)</i>
Total	555660	51165
Males	226188	23998
Females	329472	27167
18 to 30 years old	57898	5186
30 to 45 years old	135168	12909
45 to 60 years old	150939	13312
60 years old and over	211655	19758

**Phenotype Validation Experiment 1 (rhythm perception)**

<i>Full sample who provided demographics</i>	<i>N</i>	<i>Mean Age in years (for N=722 who reported demographics)</i>	<i>SD Age</i>
Total	722	36.08	10.90
Males	386	34.95	10.60
Females	332	37.49	11.07

**Phenotype Validation Experiment 2 (beat synchronization and cross-trait phenotypic replication)**

<i>Full sample (questionnaires)</i>	<i>N</i>	<i>Mean Age in years</i>	<i>SD Age</i>
Total	1412	36.34	11.93
Males	678	35.53	11.12
Females	728	37.15	12.61
<i>Subset with valid tapping data</i>	<i>n</i>	<i>Mean Age in years</i>	<i>SD Age</i>
Total	542	35.24	11.39
Males	241	35.02	10.62
Females	300	35.43	12.00

**Table 2. Genomic loci and sentinel SNPs significantly associated with beat synchronization in the primary GWAS.** Further details (e.g., chromosomal location) are provided in Supplementary Table 2.

<b>Genomic Locus</b>	<b>Sentinel SNP</b>	<b>chr</b>	<b>A1</b>	<b>MAF</b>	<b>p-value</b>	<b>gene symbol</b>
11	rs848293	2	G	0.42228	9.23E-18	VRK2
26	rs62340585	4	G	0.20695	1.81E-14	GPM6A
13	rs10168817	2	G	0.49299	1.94E-14	NA
20	rs10779987	3	T	0.38175	2.21E-14	GBE1
28	rs28392605	5	G	0.33904	8.93E-14	NA
45	rs1832909	9	T	0.40687	1.78E-13	NA
2	rs34762587	1	T	0.31379	2.25E-13	FOXO6
60	rs7542	16	G	0.46184	2.41E-13	MAPK3
5	rs10875125	1	C	0.15305	2.61E-13	DPYD
35	rs9400241	6	C	0.28851	4.49E-13	FOXO3
64	rs4792891	17	T	0.34013	7.07E-13	MAPT

39	rs1468701	7	G	0.29172	3.62E-12	<i>SND1</i>
50	rs10848650	12	G	0.42192	6.04E-12	<i>SLC6A13</i>
29	rs2635634	5	T	0.45317	9.54E-12	<i>CDH12</i>
67	rs9626920	22	G	0.41282	1.04E-11	<i>MIRLET7BHG</i>
16	rs764299	2	G	0.26719	1.47E-11	<i>PLEKHM3</i>
43	rs10984506	9	T	0.36558	1.66E-11	<i>ANP32B</i>
53	rs1426371	12	G	0.25919	1.67E-11	<i>WSCD2</i>
58	rs12913592	15	T	0.3596	6.13E-11	<i>NA</i>
6	rs72700870	1	G	0.14377	1.42E-10	<i>MCL1</i>
34	rs9388171	6	G	0.47595	2.16E-10	<i>NA</i>
55	rs6572878	14	T	0.39477	3.48E-10	<i>HAUS4</i>
4	rs11210206	1	T	0.31286	3.93E-10	<i>NA</i>
28	rs72633496	5	T	0.43224	6.21E-10	<i>NA</i>
10	rs7586405	2	G	0.30559	7.19E-10	<i>PPP1CB</i>
63	rs3024293	17	T	0.23528	8.26E-10	<i>C1QL1</i>
1	rs2061843	1	G	0.4001	1.19E-09	<i>CSMD2</i>
19	rs1349028	3	T	0.25977	1.54E-09	<i>EIF4E3</i>
25	rs4443239	4	T	0.2463	1.68E-09	<i>C4orf27</i>
33	rs1901739	5	T	0.47772	2.14E-09	<i>NA</i>
7	rs55678522	1	G	0.21629	2.25E-09	<i>LRRN2</i>
61	rs8079923	17	T	0.25309	2.88E-09	<i>AKAP10</i>
62	rs7501911	17	T	0.18191	3.34E-09	<i>NLK</i>
66	rs6087848	20	G	0.44304	3.40E-09	<i>POFUT1</i>
54	rs10744255	12	G	0.23229	4.24E-09	<i>NA</i>
31	rs13163173	5	C	0.16597	4.51E-09	<i>MEF2C</i>
3	rs2819333	1	T	0.37068	4.54E-09	<i>PTPRF</i>
51	rs2453873	12	G	0.22254	5.17E-09	<i>NA</i>
27	rs67264739	5	G	0.27395	5.54E-09	<i>ADCY2</i>
69	rs4898322	X	T	0.14076	5.90E-09	<i>NA</i>
56	rs2284901	14	G	0.37485	6.48E-09	<i>AKAP6</i>
32	rs1596431	5	T	0.19182	7.42E-09	<i>NA</i>
44	rs10978661	9	T	0.12006	7.74E-09	<i>ZNF462</i>
23	rs4263335	4	G	0.49483	8.74E-09	<i>JAKMIP1</i>
48	rs7939759	11	T	0.23981	1.23E-08	<i>CTSF</i>
65	rs9710427	19	G	0.41536	1.32E-08	<i>TECR</i>
21	rs12638746	3	G	0.33546	1.37E-08	<i>EPHA3</i>
59	rs12909047	15	G	0.48251	1.49E-08	<i>UBL7</i>
46	rs2505344	10	G	0.17674	1.51E-08	<i>EPC1</i>
24	rs67816799	4	C	0.38188	1.56E-08	<i>CCSER1</i>
15	rs10932201	2	G	0.46351	1.59E-08	<i>CREB1</i>
49	rs526904	11	T	0.34865	1.60E-08	<i>PICALM</i>
68	rs764935655	X	T	0.23454	1.83E-08	<i>NA</i>
9	rs6548147	2	T	0.4402	2.05E-08	<i>TSSC1</i>

52	rs10877461	12	G	0.29968	2.44E-08	NA
41	rs11996434	8	G	0.27037	2.61E-08	NA
40	rs1996148	8	G	0.31961	2.69E-08	PEBP4
47	rs10885458	10	G	0.28314	2.69E-08	NA
17	rs191373913	2	T	0.43899	2.74E-08	NGEF
38	rs12056186	7	C	0.42875	2.93E-08	ORC5
42	rs7856850	9	C	0.22184	3.07E-08	PTPRD
36	rs13197257	6	T	0.27444	3.23E-08	PTPRK
14	rs10497355	2	T	0.46078	3.43E-08	UBR3
12	rs11692449	2	T	0.37522	3.45E-08	XPO1
30	rs4704043	5	T	0.2827	3.65E-08	TNPO1
18	rs43182	3	T	0.13443	3.80E-08	PTPRG
57	rs62014217	15	G	0.20132	3.91E-08	HERC1
8	rs476141	1	T	0.49868	4.49E-08	NA
37	rs2849543	6	G	0.41591	4.60E-08	PARK2
22	rs571760466	3	C	0.27511	4.81E-08	LSAMP

**Abbreviations:** SNP=Single Nucleotide Polymorphism, chr=Chromosome, A1=effect allele, MAF=Minor Allele Frequency, OR=Odds Ratio, Notes: Gene symbol is based on HUGO (HGNC). These are all genes annotated to SNPs in  $r^2 > 0.1$  with the lead SNP; Sentinel SNP in a given locus refers to independent SNP from FUMA. The SNPs were mapped to genes based on ANNOVAR annotation and on being physically located inside a Protein coding gene using 10kb window. NA=when the SNP is not within the 10kb window of a gene. For presentation reasons we only included one gene per SNP. For the full list of genes see Supplementary Table 2.