

1 Title:

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4 Schizophrenia-associated variation at *ZNF804A* correlates with

5 altered experience-dependent dynamics of sleep slow-waves and

6 spindles in healthy young adults

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29

30 **ABSTRACT**

31 **Background**

32 The rs1344706 polymorphism in *ZNF804A* is robustly associated with schizophrenia (SZ), yet
33 brain and behavioral phenotypes related to this variant have not been extensively
34 characterized. In turn, SZ is associated with abnormal non-rapid eye movement (NREM) sleep
35 neurophysiology. To examine whether rs1344706 is associated with intermediate
36 neurophysiological traits in the absence of disease, we assessed the relationship between
37 genotype, sleep neurophysiology, and sleep-dependent memory consolidation in healthy
38 participants.

39 **Methods**

40 We recruited healthy adult males, with no history of psychiatric disorder, from the Avon
41 Longitudinal Study of Parents and Children (ALSPAC) birth cohort. Participants were
42 homozygous for either the SZ-associated 'A' allele (N=25) or the alternative 'C' allele (N=22)
43 at rs1344706. Actigraphy, polysomnography (PSG) and a motor sequencing task (MST) were
44 used to characterize daily activity patterns, sleep neurophysiology and sleep-dependent
45 memory consolidation.

46 **Results**

47 Average MST learning and sleep-dependent performance improvements were similar across
48 genotype groups, but with increased variability in the AA group. CC participants showed
49 increased slow-wave and spindle amplitudes, plus augmented coupling of slow-wave activity
50 across recording electrodes after learning. Slow-waves and spindles in those with the AA

51 genotype were insensitive to learning, whilst slow-wave coherence decreased following MST
52 training.

53 **Conclusion**

54 We describe evidence that rs1344706 polymorphism in *ZNF804A* is associated with changes
55 in experience- and sleep-dependent, local and distributed neural network activity that
56 supports offline information processing during sleep in a healthy population. These findings
57 highlight the utility of sleep neurophysiology in mapping the impacts of SZ-associated variants
58 on neural circuit oscillations and function.

59 **INTRODUCTION**

60 Schizophrenia (SZ) is a debilitating psychiatric disorder with a lifetime prevalence of up to 4%
61 (1). SZ etiology is complex and heterogenous, but an estimated heritability of up to 80%
62 reflects critical genetic contributions to SZ liability (2,3). Recent efforts in cataloguing the
63 genetic architecture of SZ have generated a list of over 100 loci thought to contribute in some
64 way to the development of the disease (4,5). Despite most of these risk variants having small
65 individual effects and acting in combination with other genetic and environmental factors,
66 elucidating the neuronal changes downstream of genetic liability remains crucial for
67 understanding normal brain development and the etiology of psychiatric disorders.

68 The single nucleotide polymorphism (SNP) rs1344706 within the second intron of *ZNF804A*
69 was the first SNP to show genome-wide significant association for psychosis diagnosed in both
70 bipolar disorder and SZ (6). This finding has been replicated in subsequent genome wide
71 association studies (GWAS) (4,7–9) including a fine-mapping study which confirmed
72 rs1344706 as the most strongly associated variant at the locus, with an OR for SZ of 1.10 [1.07
73 – 1.14] (10). *ZNF804A* is expressed in the brain and is predicted to encode a protein with a
74 C2H2 zinc finger domain, indicating a role in transcriptional regulation (8,10) and thus likely
75 complex biological functions (11). rs1344706 has been linked to a number of behavioral and
76 neuronal phenotypes (12,13), correlating with altered neuroanatomy (14,15) (but see (16) for
77 a null result), abnormal neurophysiology (17–19) and cognitive phenotypes (20–22). In
78 particular, *ZNF804A* genotype has been associated with cortico-hippocampal functional
79 connectivity in healthy control subjects (23,24) and also in SZ patients and their unaffected
80 siblings (17,25).

81 Whilst cognitive deficits are an established feature of SZ (26,27), links have recently been
82 made between cognitive symptom dimensions and abnormal sleep. Sleep disturbances are a
83 core feature of SZ (28,29) and include increased sleep latency and decreased total sleep time,
84 independent of neuroleptic treatment (30). At the level of neural network activity, sleep in
85 patients also features changes in characteristic electroencephalography (EEG) oscillations,
86 particularly during NREM sleep. Thalamo-cortical spindle oscillations are a defining feature of
87 NREM and are reduced in patients with SZ (31–34). Consistent with the roles of spindle
88 oscillations in memory consolidation in healthy participants (35–38) spindle deficits in SZ have
89 been linked to cognitive deficits in patients (39,40). More recently, slow oscillations and their
90 coordination with spindles have also been implicated in contributing to deficits in sleep-
91 dependent memory consolidation in patients (41–43).

92 Overall, there is convergent evidence that circuit abnormalities in SZ are reflected by changes
93 in sleep physiology that, in turn, may be important for cognitive symptoms (44). In principle,
94 linking specific genetic variations with sleep neurophysiology phenotypes holds the promise
95 of illuminating a broader understanding of genetic effects and potential mechanisms of
96 neural circuit dysfunction in SZ. Here we used a recall-by-genotype approach (45) to recruit
97 healthy individuals who were homozygous at rs1344706 in order to reduce the issues of
98 confounding and reverse causality that commonly effect traditional observational
99 case/control studies. In this case, the availability of genetic data in a large and engaged cohort
100 study allowed for efficient and balanced recruitment of participants into a detailed
101 examination of sleep architecture and neurophysiology. We aimed to test the hypothesis
102 that, in the absence of disease, rs1344706 genotype would associate with the facets of
103 abnormal sleep neurophysiology and sleep-dependent memory consolidation seen in SZ.

104 **METHODS AND MATERIALS**

105 The study design and protocol was published in advance in (46); raw and processed data and
106 metadata are available upon application to the Avon Longitudinal Study of Parents and
107 Children (ALSPAC) Executive Committee through a standard application process (see
108 <http://www.bristol.ac.uk/alspac/researchers/access/>).

109 **Participants**

110 Healthy males aged 21-23 years and of European ancestry were recruited from ALSPAC, a
111 prospective birth cohort allowing the study of health and development across the life course
112 (47,48). Participants were invited based on homozygosity either for the rs1344706 allele
113 previously associated with increased liability for SZ (AA group), or for the alternative allele
114 (CC group).

115 Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee (ref.
116 9224). The data collection protocol was previously approved by The University of Bristol
117 Faculty of Science Human Research Ethics Committee as part of a pilot study (ref. 8089). All
118 participants provided informed consent to participate in the study following the
119 recommendations of the ALSPAC Ethics and Law Committee. For a detailed description of the
120 cohort and recruitment see Supplemental Methods.

121 **Procedures**

122 Data were collected from each participant over approximately two weeks, beginning and
123 ending with a night of polysomnography (PSG, including 9-channel EEG) at the Clinical
124 Research and Imaging Centre at the University of Bristol (Figure 1). Both researchers and
125 participants were blind to participant genotype throughout data collection. During visits,
126 participants completed sleep-based questionnaires in order to assess self-rated sleep quality

127 and collect information about subjective experience of their night in the sleep laboratory (see
128 a detailed description of all procedures in Supplemental Procedures).

129 **Analysis**

130 *Behavioral data*

131 All paper questionnaires were manually scored and transcribed to spreadsheets. MST
132 performance was quantified using the number of correct sequences and the reaction time
133 during correct sequences. These variables were used to calculate average values for trial 10-
134 12 of the evening session ('training performance') and average values for trials 1-3 of the
135 morning session ('test performance'). Overnight improvement was calculated as the
136 percentage change in each outcome measure from training to test (49). Actigraphy data were
137 manually annotated in MotionWare (CamNtech, UK) to derive sleep architecture and
138 circadian rhythm measures.

139 *Polysomnography data*

140 Polysomnography was scored by an experienced expert (blinded to participant genotype)
141 based on AASM criteria (50) using REMLogic software (Natus Europe GmbH, Germany). Sleep
142 architecture was quantified using standard variables including total sleep time (TST) and sleep
143 onset latency (SOL) (see Polysomnography Analyses in Supplemental Methods). EEG traces
144 were analyzed using automatic detection of characteristic NREM sleep events - slow waves
145 (SW), delta waves, slow and fast spindle events as described earlier (43,51). Characteristic
146 NREM events were further characterized using multitaper spectra and coherence using the
147 Chronux toolbox (www.chronux.org).

148 **Statistical methods**

149 A detailed description of all analysis and statistical methods can be found in Supplemental
150 Methods; Tables S1, S2 show a full record of methods and their alignment to analytical

151 arguments. In brief, behavioral measures were analyzed either by a comparison of means
152 across groups (two-sample two-sided t-test or Wilcoxon rank-sum test) or by fitting a linear
153 mixed model with genotype and MST session (training versus testing) fitted as fixed effects
154 (using Stata v14.2 (52)). PSG-derived sleep architecture measures were analyzed in a linear
155 mixed model with genotype and recording night (night 1: baseline, night 2: learning) fitted as
156 fixed effects. PSG-derived event properties, power and coherence measures were compared
157 across genotype groups, electrodes, recording nights (night 1: baseline, night 2: learning) and
158 sleep stages (N2, N3) using a linear mixed model framework and a stepwise reduction
159 procedure implemented using the lme4 (53) and lmerTest (54) packages in R. We built a full
160 model of the general form [$y \sim genotype + night + electrode + sleep_stage + (genotype * night) + (1/ID)$], where y is any derived sleep variable, and then applied backward elimination
161 of non-significant model terms using the R function step which is part of the R package
162 lmerTest (54). Results presented are mean \pm standard error (SE) unless stated otherwise.

164 **RESULTS**

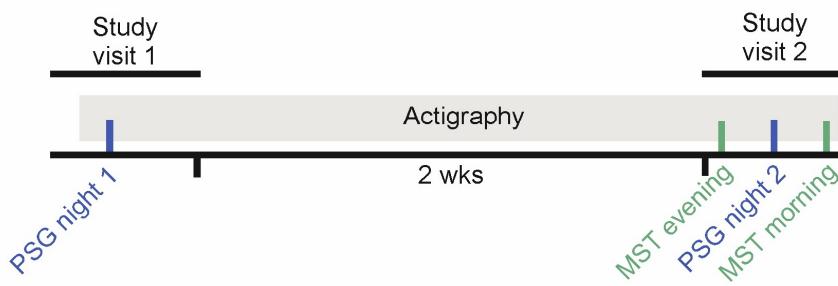
165 Data were collected from 47 participants (25 AA and 22 CC). The two genotype groups did not
166 differ in maternal education, social class, psychosis-like symptoms at age 18, or in the
167 Wechsler Abbreviated Scale of Intelligence at age 15 (Table S3). Data from seven participants
168 were excluded due to missing or corrupted data (see Supplemental Results for further
169 explanation); we therefore present results for 40 participants (Figure S1).

170

171

172

Figure 1: Study design



173

174 The study included two study visits to the sleep lab at the Clinical Research & Imaging Centre in Bristol with two
175 weeks of actigraphy monitoring between visits. Participants visited the sleep lab for a baseline polysomnography
176 (PSG) recording night on their first visit (night 1). They were also issued an actigraphy watch which they wore
177 until the end of the second study visit. During the second visit, participants were trained on the motor sequence
178 task (MST) in the evening and tested in the morning, with an intervening second PSG recording (night 2).

179 Increased variability in Motor Sequence Task performance in the rs1344706 AA group

180 Overall performance levels for practice-dependent increases in the number of correct
181 sequences (NCS) – and corresponding decreases in button press latency within correct
182 sequences ('reaction time', RT) – were comparable between genotype groups. Figure 2,
183 panels A, D show the MST learning curves for both genotype groups and Figure 2, panels B, E
184 show the averages of the last 3 trials in the evening and first 3 trials in the morning that are
185 used to calculate overnight improvement. Participants in both groups improved overnight in
186 mean NCS (overnight change in NCS, CC: 16.9% with standard deviation (SD): 9.6, AA: 15.9%
187 SD: 16.8, Figure 2C, Table 1) and RT (overnight change in absolute RT, CC: 10.5% (SD: 6.2), AA:
188 8.3% (SD 11.9), Figure 2F, Table 1).

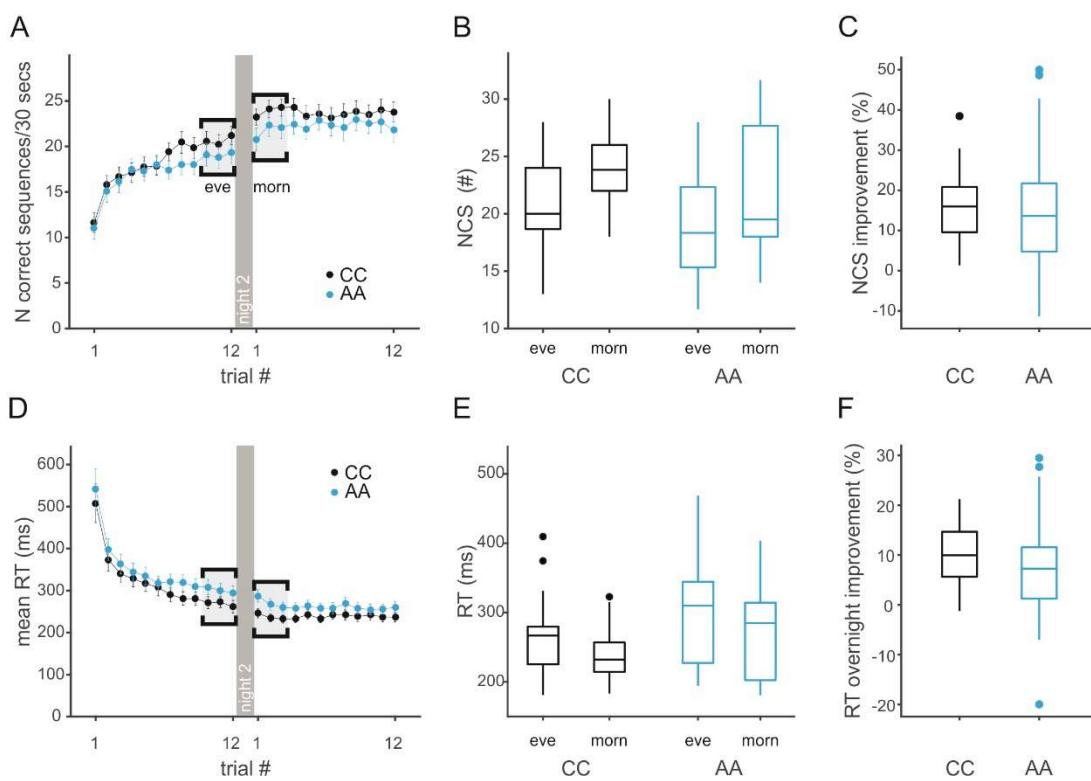
189 Linear mixed modelling of the MST performance data confirmed effects of session (training
190 vs. test) on NCS (session: $F(1, 39) = 79.1, p = 6.38e-11$) and RT (session: $F(1, 39) = 28.8, p =$
191 $3.93e-06$, Table 2), suggesting sleep-dependent consolidation of motor memory in both
192 genotype groups. There was no strong evidence for an effect of genotype on task

193 performance, but point estimates suggested that AA group participants produced fewer
194 correct sequences ($F(1, 38) = 1.61, p = 0.21$) and had slower reaction times ($F (1, 38) = 3.0, p =$
195 0.09, Table 2).

196 Interestingly, the AA group showed higher variance in overnight improvement in NCS (SD CC:
197 9.6, AA: 16.8, two-sample variance comparison $p = 0.02$, Table 1) and RT (SD CC: 6.2, AA: 11.9,
198 two-sample variance comparison $p = 0.01$). This higher variance was particularly pronounced
199 during the morning test session (SD NCS, CC: 3.6, AA: 5.5, Levene's test $p = 0.02$; SD RT, CC:
200 41 ms, AA: 62 ms, Levene's test $p = 0.02$).

201

202 **Figure 2: Average MST learning curves and overnight improvement by genotype group**



203
204 Black: CC group (N=18); Blue: AA group (N= 22).

205 A) MST learning curves showing the number of correct sequences per trial. Night 2 is indicated by a dark grey
206 separator, the last 3 and first 3 trials used to calculate the average for the evening (eve) and morning (morn)
207 performance are highlighted in light grey.
208 B) Box plot showing median number of correct sequences (last 3 trials in the evening v first 3 trials in the
209 morning) for each MST session and genotype group. (Plots indicate the median, with boxes showing the 25th
210 and 75th percentile of data, whiskers indicate the range of values inside 1.5* interquartile range, extreme values
211 (outside 1.5 IQR) are plotted as individual data points, see Statistical Methods for details).
212 C) Boxplot showing the median of overnight improvement in number of correct sequences/30 s trial as
213 percentage change from evening to morning performance.
214 D) Learning curves as in A but for the mean reaction time (RT, button press latency within a correct sequence)
215 per trial.
216 E) Boxplot showing the median RT during correct sequence button presses (last 3 trials in the evening v first 3
217 trials in the morning) for each MST session and genotype group.
218 F) Boxplot of median overnight improvement in RT measured as absolute percentage change from evening to
219 morning performance
220

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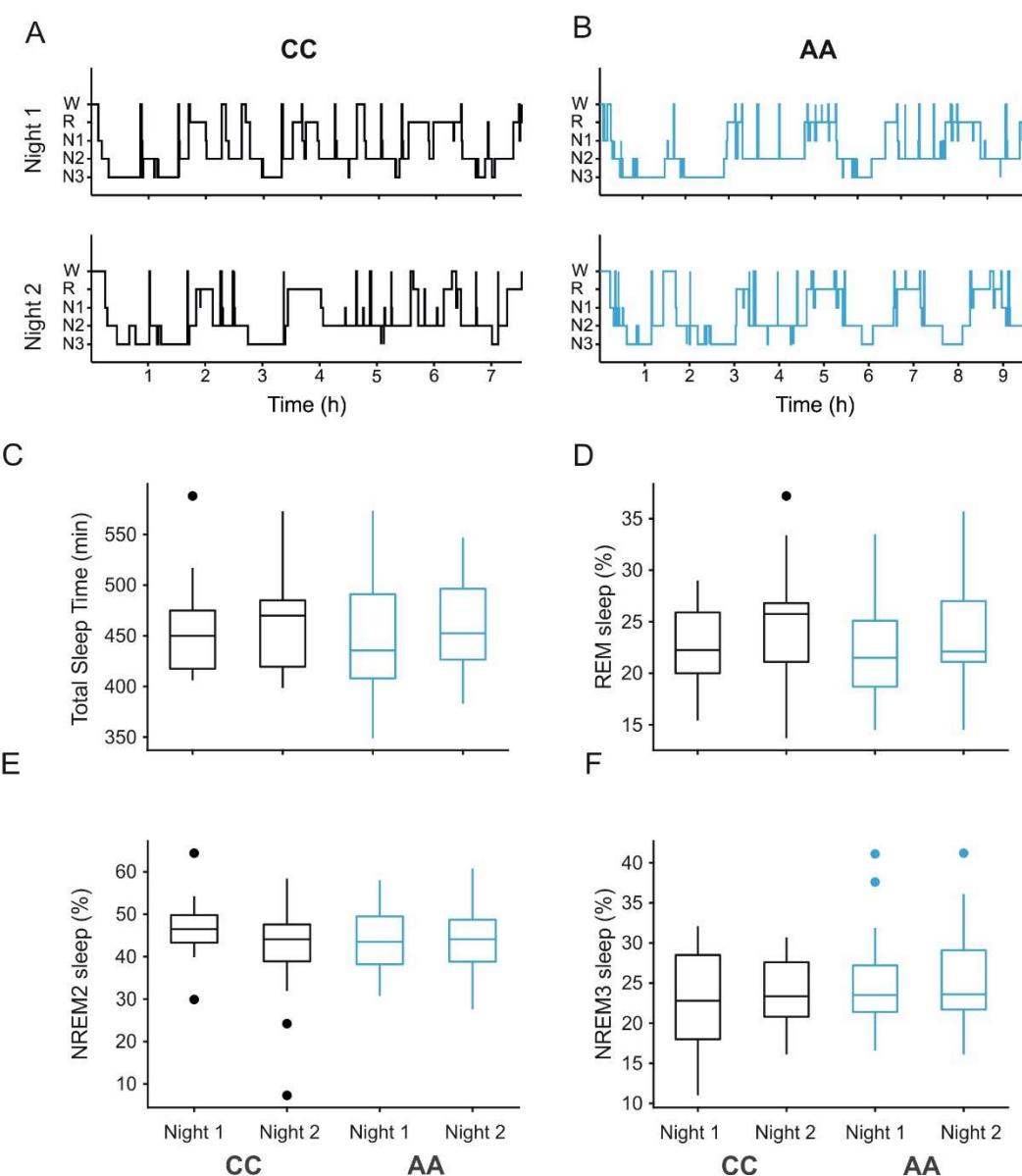
222 **Sleep timing, architecture and quality appear unaffected by rs1344706 genotype**

223 We found no evidence for consistent effects of genotype on diurnal rhythmicity (Table S4),
224 sleep architecture derived from the PSG (Figure 3 and Table S5) or subjective/objective sleep
225 quality (Table S6).

226

227

Figure 3: Example hypnograms and sleep architecture variables from polysomnography



228

229 A) Hypnogram examples from a CC individual for nights 1 and 2, x- axis shows time from lights off. Sleep
230 stages are Wake (W), REM (R), NREM1 (N1, NREM2 (N2), NREM3 (N3).
231 B) Hypnogram examples from an AA individual for nights 1 and 2, x- axis shows time in hours from lights off
232 C-F) Boxplots of PSG derived variables of sleep architecture by genotype group (CC, black; AA, blue) and
233 recording night. Outlier (outside the 25th and 75th percentile) are included as individual data points (o symbol).
234 We observed no significant effects of night or genotype using linear mixed model approach for C) Total Sleep
235 Time (min), D) Percentage of REM sleep, E) Percentage of stage 2 NREM sleep or F) Percentage of stage 3 NREM
236 sleep.
237

238 **rs1344706 genotype is associated with experience dependent changes in NREM sleep EEG**
239 **oscillations**

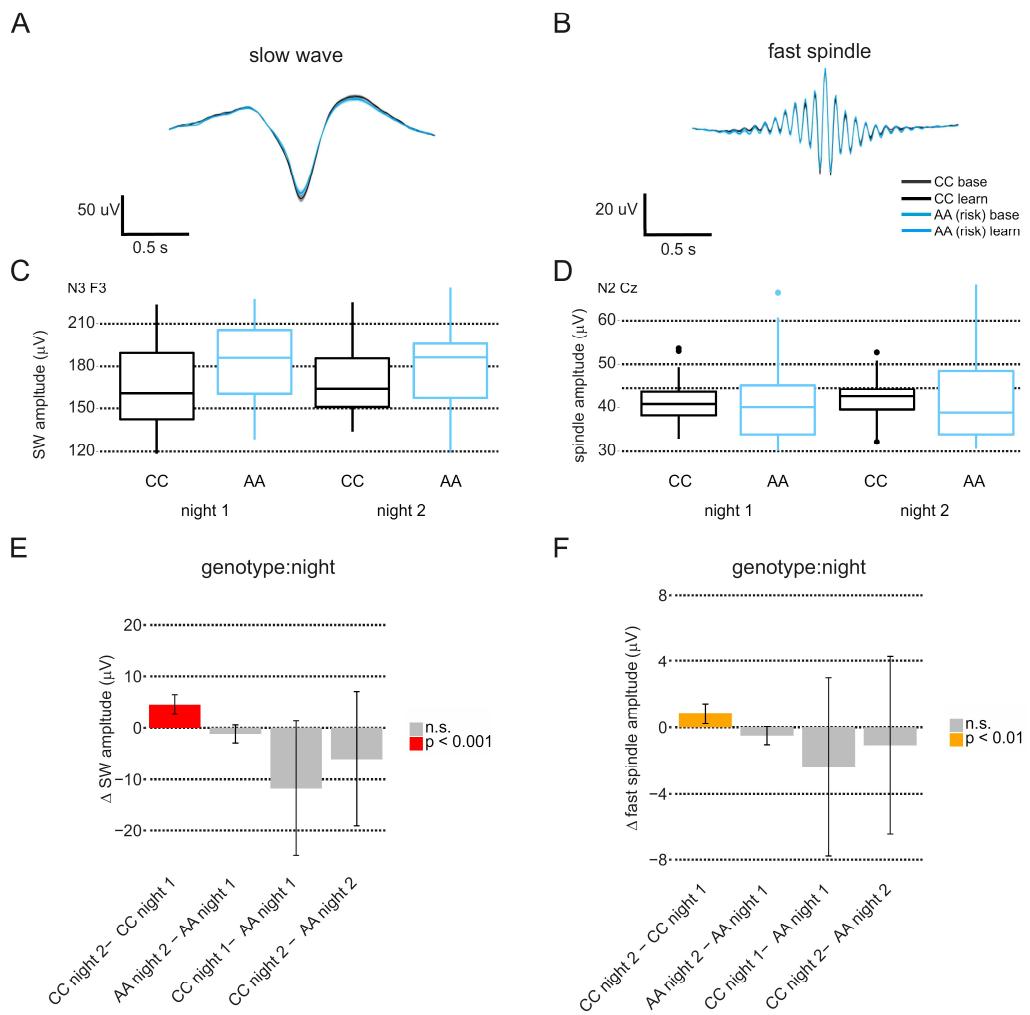
240 To assess potential neurophysiological correlates of variance in MST performance, we used
241 custom detection algorithms to extract slow and delta waves (0.5-4Hz), and slow (9-12Hz)
242 and fast spindles (13-16Hz). Figure 4, panels A and B show wave-triggered averages, revealing
243 the morphologies of slow waves and fast spindles recorded at electrodes F3 and Cz:
244 waveforms appeared similar across genotype group and recording night at these electrode
245 locations. Panels C and D show average extracted amplitude values for each event at the
246 electrode locations F3 and Cz. (For a complementary spectral analysis of power in
247 corresponding frequency bands see Supplementary Results and Tables S7, S8.)

248 *Slow-wave amplitudes depend on experience, but only in the CC group*

249 We did not detect differences in density of slow-wave events between nights or genotypes
250 (Table S9). However, a linear mixed model analysis of slow-wave amplitudes from N2 and N3
251 sleep from all electrode locations suggested a main effect of night and an important
252 interaction term (night by genotype) in the initial full model. After stepwise reduction, the
253 night by genotype interaction remained ($F(1, 1356.05) = 18.67, p = 1.67e-05$, Table S9). Figure
254 4E shows the differences in estimated marginal means between nights, demonstrating an
255 increase in slow-wave amplitudes from night 1 (baseline) to night 2 (learning) in CC
256 participants (night 1: $100 \pm 4.80 \mu\text{V}$; night 2: $105.12 \pm 4.78 \mu\text{V}, p < 0.001$, Table S10). In contrast,
257 slow-wave amplitudes in the AA group remained similar across nights (night 1: $112 \pm 4.34 \mu\text{V}$,
258 night 2: $111 \pm 4.34 \mu\text{V}$, n.s.). These SW event results were supported by very similar results for
259 delta wave event properties (Tables S11, S12) and separate Fourier analyses of 0.5-1.5Hz
260 power, which showed the same pattern of experience and genotype-dependent changes
261 (Tables S7 and S8). Collectively, these analyses suggest that the coordinated firing of cortical

262 populations during SW events may be modulated following learning in a genotype-dependent
263 manner.

264 **Figure 4: Slow wave and spindle properties**



265
266 A) SW wave triggered average at F3 for all genotype groups and both recording nights. CC, baseline night, grey,
267 CC, learning night, black, AA baseline night, light blue, AA learning night, dark blue. We found no significant
268 difference for any time bin ($p < 0.05$, Wilcoxon ranksum test, no correction).
269 B) Spindle wave triggered average at Cz for all genotype groups and both recording nights, same colors as in A.
270 We found no significant difference for any time bin ($p < 0.05$, Wilcoxon ranksum test, no correction).
271 C) Estimated marginal means for SW amplitude values for SW recorded at F3, during N3 sleep by genotype group
272 and by recording night.

273 D) Estimated marginal means of fast spindle amplitude values for spindles recorded at Cz, during N2 sleep for
274 both genotypes and both recording nights.
275 E) Estimated marginal means differences for the factors genotype and night estimated from a linear mixed model
276 analysis of all detected SW amplitudes (using the R package lmerTest (see **Supplemental Methods** for details)).
277 CC individuals show an increase in SW amplitude in night 2, but AA's do not. Error bars indicate 95% confidence
278 intervals.
279 F) Same as E for all detected fast spindle amplitudes. Like SW amplitudes, CC individuals show an increase in fast
280 spindle amplitude in night 2, but AA's do not. Error bars indicate 95% confidence intervals.
281

282 *Spindle properties depend on experience, with differential effects of genotype*
283 A linear mixed model analysis of 9-12Hz (slow) spindle event properties revealed night and
284 genotype dependent associations with amplitude (Table S13), with a trend for an increase
285 after learning in the CC group ($31.1 \pm 2.0 \mu\text{V}$ during night 1 vs. $31.7 \pm 2.0 \mu\text{V}$ during night 2,
286 $p=0.05$), but a decrease in the AA group (from $33.8 \pm 1.8 \mu\text{V}$ to $33.2 \pm 1.8 \mu\text{V}$, $p=0.03$, Table S14).
287 We also observed a main effect for night-dependent associations with slow spindle
288 frequency, with small decreases in slow spindle frequency after motor learning in both groups
289 (from $11.36 \pm 0.05 \text{ Hz}$ to $11.31 \pm 0.05 \text{ Hz}$ in CC and from $11.33 \pm 0.04 \text{ Hz}$ to $11.31 \pm 0.04 \text{ Hz}$ in AA,
290 $p=0.005$, Table S14).

291 We also detected a night by genotype interaction for fast spindle amplitude ($F(1, 1356.05) = 10.24, p=0.001$, Table S15), with differences in estimated marginal means shown in
292 Figure 4F: amplitudes increased from night 1 to night 2, but again only in the CC group
293 participants (from $31.8 \pm 2.0 \mu\text{V}$ to $32.6 \pm 2.0 \mu\text{V}$, $p=0.007$, Table S16). Fast spindle frequency did
294 not vary across nights or genotype, but fast spindle duration showed a similar pattern to fast
295 spindle amplitude: a genotype by night interaction ($F(1, 1356.53) = 7.24, p=0.0072$), driven by
296 shorter spindles in CC group during night 1 ($795 \pm 8 \text{ ms}$ vs. $819 \pm 8 \text{ ms}$ in AA, $p=0.02$, Table S16)
297 and an increase in spindle length from night 1 to night 2 only in the CC group (from $795 \pm 8 \text{ ms}$
298 to $800 \pm 8 \text{ ms}$, $p=0.03$, Table S16). We found no strong evidence for an effect of genotype or

300 night on slow or fast spindle density (Table S13, 15). These fast spindle event-based analyses
301 were supported by spectral analyses of fast sigma power, which showed differential patterns
302 of experience-dependent changes between genotypes (Tables S7, S8).

303 To summarize these NREM EEG event analyses, only the CC genotype group showed slow-
304 wave and spindle properties – particularly event amplitudes – that were sensitive to
305 experience, sustaining increases on night 2 (post-MST learning) relative to night 1 (baseline).
306 It is possible, then, that attenuated experience-dependent changes in thalamocortical activity
307 contributed to more variable MST performance in the AA group. However, since recent work
308 has highlighted the importance of temporal interrelationships between these thalamocortical
309 oscillations for sleep-dependent memory consolidation (42,55–57), we next tested whether
310 slow-wave coordination also varied across nights and participants.

311 **Slow wave mediated cortical connectivity during NREM sleep**

312 We analyzed slow wave synchronization during NREM sleep for both genotype groups and
313 nights using multi-taper spectral coherence. Figure 5A illustrates all EEG electrode positions
314 and Figure 5B shows raw EEG traces surrounding a single SW event detected at electrode Fz.
315 To illustrate SW-associated temporal covariance in frontal and occipital EEG, we used Fz SW
316 events (trough times) as triggers to extract +/-2s windows of EEG surrounding each event
317 across both channels, averaging across all windows for each recording night. Figure 5C shows
318 Fz SW event triggered averages at Fz and O1 from one participant of the CC group. Here we
319 can see highly stereotypical SW events detected at Fz (with low variance) during both
320 recording nights, but different average waveforms at O1. During night 1, Fz SW coincide with
321 highly variable activity at O1, where a SW-like waveform is hardly separated from surrounding

322 background activity (Figure 5, C1); in contrast, during night 2 a distinct average SW waveform
323 coordinated with Fz, manifests at O1 (Figure 5, C2).

324 Figure 5, panels D1-4 show group-averaged coherograms for the electrode pair Fz-O1 for both
325 recording nights and genotype groups: the most coherent frequency ranges are 0.5-1.5 Hz
326 (SW) and fast spindle coherence (12-15 Hz). We used the average SW coherence (0.5-1.5Hz)
327 during 1s windows surrounding each SW for each electrode pair to construct a cortex-wide
328 SW connectivity matrix. Figure 5, E1-4 show matrices of group averaged coherence values for
329 both genotypes and both recording nights during N3 sleep. All matrices show a gradient of
330 coherence, with highest values between frontal and central electrodes and lowest values
331 between the most distant pairs, i.e. frontal and occipital electrodes.

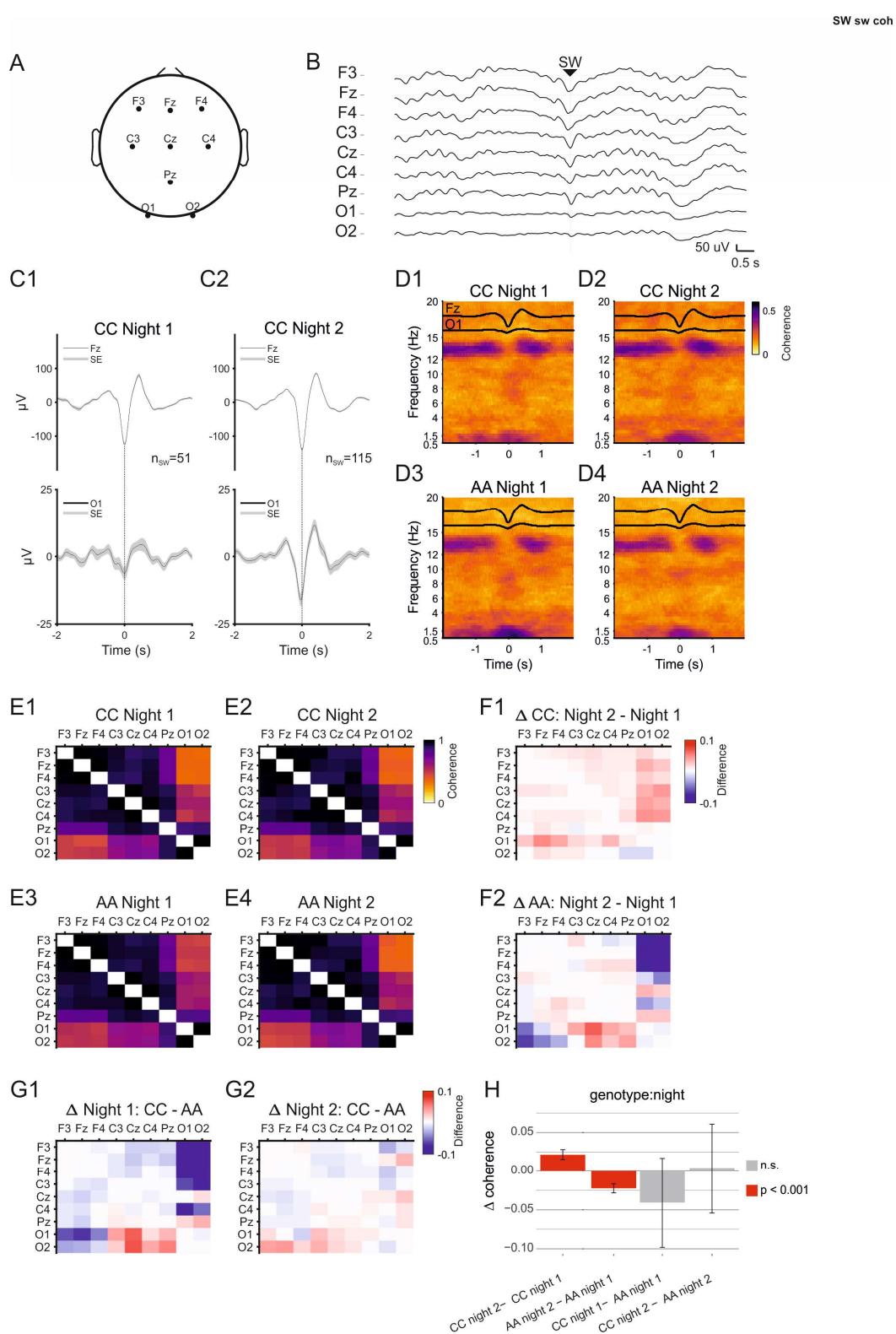
332 We calculated the difference between all coherence values and plotted them in the same
333 matrix layout to illustrate differences in slow-wave coherence between nights (Figure 5, F1-
334 2) and genotypes (Figure 5, G1-2). Consistent differences in slow-wave coherence are
335 apparent between recording nights. Slow wave coherence increases in those in the CC group
336 from night 1 (baseline) to night 2 (learning, Figure 5, F1) - but a decrease in the AA group can
337 be seen in the difference matrices for this genotype group (Figure 5, F2). Slow-wave
338 coherence is higher in the AA group on night 1 (mainly frontal to occipital coupling between
339 electrodes F3, Fz, F4 to O1, O2), compared to the CC group (Figure 5, G1). Furthermore, a
340 linear mixed model with subsequent stepwise reduction revealed a genotype by night
341 interaction, indicating a differential effect of learning on slow-wave coherence in CC vs. AA
342 genotypes (genotype x night: $F(1, 11182) = 97.37, p < 2e-16$, Table S17). Both genotypes show
343 changes in slow-wave coherence upon motor learning but a least squares estimation of group
344 marginal means reveals that those in the CC group show a post-learning increase in slow-

345 wave coherence (CC night 1 0.85 ± 0.021 , CC night 2 0.87 ± 0.019 , $p < 0.001$, Table S18),
346 whereas the AA group show a decrease in overall slow-wave coherence (genotype by night:
347 AA night 1 0.89 ± 0.019 - AA night 2 0.86 ± 0.021 , $p < 0.001$, Table S18) after learning. These
348 results are confirmed when using SW coherence of whole noise free NREM sleep epochs (see
349 Supplemental Results and Tables S19, S20). Thus, the CC group showed the increased SW
350 coherence predicted by previous studies (43,58), whereas SW coordination was attenuated
351 following learning in the AA participants.

352

353

Figure 5: Slow wave triggered coherence



354

355 A) A head diagram showing sleep EEG electrode positions.

356 B) Raw data example showing all EEG traces surrounding a typical detected SW event at Fz.

357 C) SW triggered averages from one participant from band pass filtered (0.5-4 Hz) and EEG traces. Individual SW
358 event traces were averaged in windows of +/- seconds with the SW trough time set t=0. C1) SW triggered
359 average at Fz and O1 for 51 SW events detected during night 1 N2 sleep in one participant (CC, Night 1), C2) SW
360 triggered averages as described in C1 using, 115 SW events during night 2 from the same participant ('CC', Night
361 2)
362 D) Average SW triggered coherograms. SW triggered data windows (SW trough time at Fz, t = 0) from the seed
363 electrode (Fz) and target electrode (O1) were used to calculate multitaper coherograms for each data window
364 pair. Coherograms were averaged for each participant and then averaged for each group and recording night.
365 In the coherogram darker colors indicate higher coherence. Overlaid black traces are SW wave triggered
366 averages for seed and target electrode (Fz, top and O1, bottom).
367 D1) Average coherogram for CC night1, D2) Average coherogram for CC night 2, D3) Average coherogram for AA
368 night 1, D4) Average coherogram for AA night 2.
369 E) Average SW-triggered coherence values (0.5-1.5 Hz, -0.5 -0.5 s) for all electrode pairs for each genotype group
370 during N2 sleep for both recording nights. E1) CC, during (baseline) night 1; E2) CC, during (learning) night 2, E3)
371 AA, during (baseline) night 1, E4 AA, during (learning) night 2.
372 F) Differences in SW coherence between nights in each genotype group CC (F1), and AA (F2).
373 G) Differences between genotype groups on each night, night 1: CC-AA (G1), night 2: CC-AA (G2).
374 H) Estimated marginal means differences for the factors genotype and night estimated from a linear mixed
375 model analysis of SW event coherence. CC individuals show an increase in SW coherence during night 2, but
376 AA's show an overall decrease in coherence. Error bars indicate 95% confidence intervals.
377

378 DISCUSSION

379 We performed a recall-by-genotype study (45) to investigate the potential contributions of
380 an SZ-associated SNP, rs1344706, to sleep-dependent memory processing and sleep
381 neurophysiology in healthy volunteers. In summary, 1) all participants showed normal
382 wake/sleep rhythms and there was no evidence for an effect of genotype on any variable
383 describing macro sleep architecture; 2) we observed greater variance in learning and sleep-
384 dependent memory consolidation following a motor task in AA participants homozygous for
385 the variant associated with increased SZ liability; 3) we detected genotype- and learning-
386 dependent effects on SW and fast spindle amplitudes, with the AA group showing attenuated

387 changes in SW and spindle amplitudes after learning; 4) the AA group failed to exhibit the
388 learning-dependent increase in SW coherence evident in the CC genotype group.

389 **Behavior**

390 Using a motor learning task previously shown to be impaired in SZ patients, we did find
391 evidence for greater variability in overnight improvement and other variables derived from
392 MST in those with the AA genotype at rs1344706, suggesting that rs1344706 may associate
393 with subtle changes motor learning and consolidation.

394 Motor learning (59) and its sleep-dependent memory consolidation are impaired in patients
395 diagnosed with SZ (60). The key brain areas involved in motor learning and its sleep
396 dependent consolidation, including the neocortex, striatum, thalamus, hippocampus and
397 cerebellum (61,61–64), have all been implicated in the etiology of SZ (65–67). *ZNF804A* has
398 been shown to be highly expressed in these brain regions, particularly the thalamus,
399 hippocampus and cortex (68), hence altered *ZNF804A* function may contribute to changes in
400 brain development and plasticity that influence motor learning and its consolidation (69).
401 Previous studies have shown that variability between individuals during early phases of
402 learning a motor task is higher in patients diagnosed with SZ compared to healthy controls
403 (70), potentially reflecting higher variability in brain anatomy or functional connectivity
404 patterns (71). Whether this variability and the associations of *ZNF804A* derive from
405 neurodevelopmental effects or altered adult neural plasticity remains an open question.

406 **NREM sleep and neurophysiology**

407 Although we did not observe consistent evidence for an effect of genotype on diurnal
408 rhythmicity or sleep architecture, detailed analyses of overnight EEG did unveil relationships
409 between rs1344706, corticothalamic activity during NREM sleep and neural correlates of

410 motor memory consolidation. We observed several interaction effects between genotype
411 and recording night, where NREM sleep activity appears to be differentially affected by the
412 acquisition of a motor task in AA and CC participants.

413 *Spindle oscillations*

414 Previous studies have shown that sleep dependent motor memory consolidation correlates
415 with spindle oscillations (56,72–75). Indeed, a substantial body of work has demonstrated
416 correlations between N2 sleep or spindles with motor memory in healthy participants (76–
417 79), although contradictory studies do exist (80,81). In particular, the individual contributions
418 of slow and fast spindles to memory consolidation are still debated.

419 We found some evidence supporting a role for slow spindle oscillations (9-12 Hz) in motor
420 memory consolidation, since slow spindle amplitudes appeared to be increased in CC
421 genotype participants during the learning night, whilst decreasing in the AA group. However,
422 we found no evidence of an effect of genotype or night on either slow or fast spindle density.
423 Despite fast spindle density being reduced in first episode (34,82,83) and chronically ill
424 patients (32,33,39) and their first-degree relatives (29,34,82), and the association of spindle
425 properties with polygenic risk scores for SZ (84), our results imply that rs1344706 alone does
426 not impact directly on fast spindle density. Given established polygenic effects in SZ, multiple
427 genetic variants and their interactions are likely to impact cortico-thalamic circuit
428 development. In particular, SNPs linked to ion channel genes like *CACAN1C* (84) are likely to
429 interact with other SNPs to impact corticothalamic development and maturation which might
430 have causal effects on cortico-thalamic oscillatory signatures or NREM sleep (40).

431 *Slow oscillations*

432 On average, slow-wave amplitudes increased during the sleep after learning only in the CC
433 genotype group. In addition, SW coherence appears to be differentially modulated after

434 learning between the genotype groups: those in the CC group show an increase in slow-wave
435 coherence, but participants with the AA genotype show a decrease in slow wave coherence
436 during the night that followed motor learning. Previous studies have shown that during early
437 sleep, after motor learning, slow-wave event amplitudes are locally increased in central and
438 parietal areas (85). Slow wave coherence has also been shown to increase during sleep after
439 a declarative memory task (58), and our recent work has demonstrated slow wave coherence
440 increased after motor learning in a control group, but not in patients diagnosed with SZ (43).
441 Our results in individuals homozygous for the 'A' allele at rs1344706 seem to be line with
442 these findings and provide a genetic correlate for slow wave phenotypes related to psychosis
443 and SZ.

444 Recent studies on the rodent homologue of *ZNF804A* suggest it has both a role during
445 development and in adult plasticity (69,86). Our own work in a rodent neurodevelopmental
446 model of SZ has demonstrated that interference in cortico-thalamic development causes
447 severe disruption of slow wave coordination between remote cortical areas and simultaneous
448 desynchronization of spindle and hippocampal ripple oscillations (51). Given the suggested
449 role of *ZNF804A* in cortical and thalamic development we speculate that rs1344706 may have
450 a role in corticothalamic development which itself would be related to impaired coordination
451 of SW activity during sleep. These deep characterizations of genotypic association motivate
452 future mechanistic studies in animal models that enable high-resolution phenotyping
453 corticothalamic circuit development and plasticity.

454 **Limitations**

455 Currently, we are only beginning to understand complex genotype-phenotype relationships
456 related to SZ. Quantifying brain activity and function directly related to identified neuronal

457 circuits in combination with a Recall-by-Genotype approach is critically advancing our
458 understanding of underlying biological mechanisms. Here we characterized the impact of the
459 rs1344706 variant on sleep neurophysiology but have not directly quantified the effect of the
460 variant on *ZNF804A* gene expression and/or function. Indeed, no consensus has been reached
461 on the function of *ZNF804A* itself yet, although a recent study suggests that *ZNF804A* may
462 regulate RNA synthesis (89). The rs1344706 variant may then reduce the expression of a
463 *ZNF804A* splice variant during prenatal development (87) leading to reduced spine density in
464 cortical excitatory neurons (69,88) - although the exact impact of rs1344706 on cortico-
465 thalamic development remains to be investigated. Moreover, recent studies show that the
466 impact of rs1344706 on brain function may depend on the carriage of other SZ-associated loci
467 (e.g. in genes *CACNA1C* (90) and *COMT* (91,92)) and environmental risk factors such as
468 cannabis use (93). Thus, the relationship between rs1344706 and its downstream
469 consequences is not easily determined. Furthermore, whilst the intention here was to
470 understand the role of *ZNF804A* in the absence of disease, further work is needed to show
471 that the phenotypes we observed here, are indeed relevant to SZ.

472 Finally, the small sample size and lack of replication within this study (due to the labor and
473 cost intensive nature of sleep laboratory experiments) naturally limit the strength of our
474 conclusions. Future work will look to improve the efficiency and reach of genetic sleep studies
475 by developing protocols that implement wearable technology to monitor sleep
476 neurophysiology at-home, over extended periods of time and in much larger samples.

477 **Conclusions**

478 Given the complex network of events linking genetics to brain-wide connectivity and function,
479 how can we best map genomic information to a neurobiological understanding of SZ? Here

480 we show that sleep neurophysiology presents a uniquely powerful opportunity to bridge
481 different levels of analysis: relating genotype to sleep-dependent physiology and
482 environmental factors such as learning, constitutes a rational, neurobiologically-informed
483 approach to delineating causal mechanisms of thalamocortical circuit dysfunction (44). Future
484 translational studies should investigate the influence of *ZNF804A* on slow wave and spindle
485 properties and their coordination in genetic rodent models and patient populations to further
486 elucidate genetic and circuit mechanisms of psychosis and their impacts on sleep, cognition
487 and novel therapies.

488

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522

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