



Letter to the Editor

The effects of positive schizotypy and sleep deprivation on prepulse inhibition



Prepulse inhibition (PPI) of the startle response is a measure of sensorimotor gating (Graham, 1975). PPI deficits have been reliably reported in schizophrenia patients, their first-degree relatives, and in schizotypal individuals (Braff, 2010). Reduced PPI has also been observed in rodent and human experimental model systems of psychosis, such as acute sleep deprivation (Ettinger and Kumari, 2015). In this study, we aimed to replicate (1) lower PPI in people with high, relative to low, positive schizotypy (Simons and Giardina, 1992; Takahashi et al., 2010), (2) sleep deprivation-induced disruption of PPI (Petrovsky et al., 2014), and, in addition, examined, for the first time, potential interactions between schizotypy and sleep deprivation on PPI.

The study involved 24 healthy participants, 12 with high (HS; 7 women) and 12 with low positive schizotypy (LS; 9 women), selected from a larger pool (Supplementary Tables 1–2). Schizotypy was measured using the German translation of the Oxford-Liverpool Inventory of Feelings and Experiences short form (O-LIFE; Grant et al., 2013). HS participants were required to score ≥ 1.25 standard deviation above (score ≥ 9) and LS to score ≤ 0.5 standard deviation below the mean (score ≤ 3) on Unusual Experiences. Both groups were required to (i) score ≤ 0.5 standard deviations below the mean on Introverted Anhedonia (score ≤ 2) to avoid confounding effect of negative schizotypy, (ii) be native German speakers, and (iii) be free of any diagnoses of psychotic disorders among first-degree relative, hearing impairment, prescription or over-the-counter medication, sleep disorder, irregular sleep-wake-rhythm, shift-working, any current Axis I disorder diagnosis and any current or history of psychotic disorders, and alcohol or drug abuse. All participants were assessed after nights of normal sleep and 24-h total sleep deprivation, one week apart, using a randomized counterbalanced within-subjects design (Meyhöfer et al., 2017). PPI paradigm was identical to that used previously (Petrovsky et al., 2014) and included prepulse + pulse trials with stimulus-onset-asynchrony (SOA) of 30 ms, 60 ms, 120 ms. Psychotomimetic states were quantified as in Meyhöfer et al. (2017). The study was approved by the local ethics committee (Department of Psychology, University of Bonn). Participants provided written informed consent and were reimbursed with €80 or course credits.

Data were analyzed using IBM Statistical Package for Social Sciences (Version 23) and R (R Core Team, 2016). Startle amplitude data (log transformed to reach approximate normality) were subjected to mixed model analysis of variance (ANOVA) with *Condition* (normal sleep, sleep deprivation) and *Block* (five blocks of pulse-alone trials) as within-subjects factors and *Group* (HS, LS) as between-subjects factor. Habituation measures were analyzed in a *Condition* \times *Group* ANOVA. PPI was evaluated using a mixed ANOVA with *Condition* and SOA

(30 ms, 60 ms, 120 ms) as within-subjects factors and *Group* as between-subjects factor; significant interactions involving *Group* were followed up by one-tailed *t*-tests and evaluated using Bonferroni-Holm-correction. Correlational analyses investigated whether pulse-alone startle amplitude and PPI are correlated. Lastly, to consider the effect of sleep deprivation here relative to that reported previously (Petrovsky et al., 2014), Cohen's *d* (Gibbons et al., 1993) was calculated separately for the three SOAs in each of the two studies. The current PSI results (Supplementary Materials) were analyzed similarly and corresponded to those in Meyhöfer et al. (2017).

We found lower startle amplitude in HS than LS participants (*Group*, $F[1,19] = 6.46$, $p = .02$, $\eta_p^2 = 0.25$) and significant startle habituation (*Block*, $F[4,76] = 55.02$, $p < .001$, $\eta_p^2 = 0.74$) from block 1 to 2 ($p = .004$, $d = 1.32$) and block 2 to 3 ($p = .004$, $d = 1.53$) (Table 1). Habituation measures did not differ between HS and LS participants, or between normal sleep and sleep deprivation (Table 1). For PPI, *Group* interacted significantly with SOA ($F[2,44] = 4.00$, $p = .03$, $\eta_p^2 = 0.15$), indicating lower PPI in HS than LS participants at 60 ms ($p = .03$, $d = 0.94$) and 120 ms ($p = .03$, $d = 1.04$) SOAs but not at 30 ms SOA ($p = .30$, $d = 0.22$) (Table 1; Supplementary Fig. 1). The main effect of sleep deprivation was in the expected direction but not formally significant ($F[1,22] = 3.60$, $p = .07$, $\eta_p^2 = 0.14$) and there were no interaction effects involving sleep deprivation or *Group* (*Condition* \times *SOA*: $F[2,44] = 0.22$, $\epsilon = 0.65$, $p = .71$, $\eta_p^2 = 0.01$; *Condition* \times *Group*: $F[1,22] = 0.21$, $p = .65$, $\eta_p^2 = 0.01$; *Condition* \times *Group* \times *SOA*: $F[2,44] = 0.29$, $\epsilon = 0.65$, $p = .65$, $\eta_p^2 = 0.01$). Lower startle amplitude associated with lower PPI at 30 ms SOA ($p = .03$), 60 ms SOA ($p = .003$), and 120 ms SOA ($p = .004$) after normal sleep but not after sleep deprivation ($p > .09$) in HS participants (Supplementary Fig. 2); no significant associations occurred in LS participants (see Supplementary Tables 3–5 for full summaries of the ANOVA and correlation analyses).

Our results confirmed the effect of schizotypy on PPI. The effect of sleep deprivation, however, was nonsignificant ($p = .07$) and weaker, especially at 30 ms and 60 ms SOAs (Cohen's *d* 0.19, 0.31 and 0.50 for 30 ms, 60 ms and 120 ms SOAs, respectively) than in our previous study (Cohen's *d* 0.54, 1.12, and 0.38 for 30 ms, 60 ms and 120 ms SOAs, respectively, in Petrovsky et al., 2014). Possible reasons for this may include a higher probability of undetected subtle sleep problems and thus relatively less PPI disruption by sleep deprivation in HS (Cohen's *d* 0.07 and 0.25 for 30 ms and 60 ms SOAs, respectively) compared to LS participants (Cohen's *d* 0.29 and 0.38 for 30 ms and 60 ms SOAs, respectively) which weakened the overall sleep deprivation effect but was insufficient to emerge as a sleep deprivation by schizotypy interaction. This study, unlike our previous study, also had mostly female participants in both groups. Notably, the overall pattern of results indicates that schizotypy and sleep deprivation may affect PPI by different cognitive mechanisms. We and others (Simons and Giardina, 1992) have found lower PPI accompanied with lower startle amplitude in high schizotypes while sleep deprivation reduces PPI in humans without affecting startle amplitude (Petrovsky et al., 2014). This would also explain the loss of startle amplitude-PPI correlation in HS

Table 1
Descriptive statistics of startle amplitude, habituation, and % PPI in High (HS) and Low Positive Schizotypy (LS) groups.

Study group	Block 1	Block 2	Block 3	Block 4	Block 5
Startle amplitude over pulse-alone trials: normal sleep					
LS	867.68 (560.28)	650.56 (450.64)	472.11 (471.57)	493.11 (467.02)	530.91 (560.79)
HS	398.98 (257.32)	261.07 (237.27)	169.56 (157.43)	147.31 (130.05)	139.83 (93.36)
Startle amplitude over pulse-alone trials: sleep deprivation					
LS	673.84 (516.07)	498.35 (484.26)	432.70 (603.89)	362.85 (389.79)	399.68 (475.69)
HS	415.81 (264.67)	235.42 (190.07)	137.75 (83.66)	107.93 (74.44)	117.29 (88.40)
Habituation measures					
Normal sleep			Sleep deprivation		
Early	Total	Coefficient	Early	Total	Coefficient
25.74 (32.16)	51.25 (23.99)	−81.99 (67.02)	27.68 (52.96)	58.21 (23.88)	−78.55 (71.81)
	30 ms		60 ms		120 ms
PPI (%): normal sleep					
LS	30.13 (25.17)		72.25 (19.40)		77.90 (14.14)
HS	20.80 (25.40)		53.32 (23.47)		56.98 (23.32)
PPI (%): sleep deprivation					
LS	18.57 (33.08)		64.97 (16.28)		66.87 (21.41)
HS	18.69 (27.23)		46.96 (29.06)		47.20 (27.57)

Notes. Data represent untransformed means (standard deviations). Startle amplitude is depicted in arbitrary units (1 unit = 2.62 μ V). Startle amplitude over pulse-alone trials: $N_{LS} = 9$, $N_{HS} = 12$. PPI, total habituation, and habituation coefficient b: $N_{LS} = 12$, $N_{HS} = 12$. Early habituation: $N_{LS} = 11$, $N_{HS} = 12$.

participants following sleep deprivation. In animals too, distinct schizophrenia-relevant manipulations (tail pinch stress, sleep deprivation) can selectively affect responsiveness to the pulse or information-filtering capabilities (PPI) (Liu et al., 2011). If our assumptions concerning different mechanisms for schizotypy and sleep deprivation effects in PPI are found to be supported, a combination of schizotypy and sleep deprivation would allow pro-cognitive effects of drugs on different cognitive (and associated neural) processes to be investigated concurrently.

Conflicts of interest statement

The authors report no conflicts of interest.

Contributors

U.E., N.P., and V.K. designed research; I.M. and E.F. performed research; I.M., U.E., and V.K. analyzed the data; I.M., U.E., and V.K. wrote the paper. All authors contributed to and have approved the final manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.schres.2019.05.017>.

References

- Braff, D.L., 2010. Prepulse inhibition of the startle reflex: a window on the brain in schizophrenia. *Curr. Top. Behav. Neurosci.* 4, 349–371.
- Ettinger, U., Kumari, V., 2015. Effects of sleep deprivation on inhibitory biomarkers of schizophrenia: implications for drug development. *Lancet Psychiatry* 2, 1028–1035. [https://doi.org/10.1016/S2215-0366\(15\)00313-2](https://doi.org/10.1016/S2215-0366(15)00313-2).
- Gibbons, R.D., Hedeker, D.R., Davis, J.M., 1993. Estimation of effect size from a series of experiments involving paired comparisons. *J. Educ. Stat.* 18, 271–279. <https://doi.org/10.2307/1165136>.
- Graham, F.K., 1975. The more or less startling effects of weak prestimulation. *Psychophysiology* <https://doi.org/10.1111/j.1469-8986.1975.tb01284.x>.
- Grant, P., Kuepper, Y., Mueller, E.A., Wielpuetz, C., Mason, O., Hennig, J., 2013. Dopaminergic foundations of schizotypy as measured by the German version of the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE)—a suitable endophenotype

- of schizophrenia. *Front. Hum. Neurosci.* 7, 1–11. <https://doi.org/10.3389/fnhum.2013.00001>.
- Liu, Y.P., Tung, C.S., Chuang, C.H., Lo, S.M., Ku, Y.C., 2011. Tail-pinch stress and REM sleep deprivation differentially affect sensorimotor gating function in modafinil-treated rats. *Behav. Brain Res.* 219 (1), 98–104. <https://doi.org/10.1016/j.bbr.2010.12.012>.
- Meyhöfer, I., Steffens, M., Faiola, E., Kasparbauer, A.-M., Kumari, V., Ettinger, U., 2017. Combining two model systems of psychosis: the effects of schizotypy and sleep deprivation on oculomotor control and psychotomimetic states. *Psychophysiology*, 1–15. <https://doi.org/10.1111/psyp.12917>.
- Petrovsky, N., Ettinger, U., Hill, A., Frenzel, L., Meyhöfer, I., Wagner, M., Backhaus, J., Kumari, V., 2014. Sleep deprivation disrupts prepulse inhibition and induces psychosis-like symptoms in healthy humans. *J. Neurosci.* 34, 9134–9140. <https://doi.org/10.1523/JNEUROSCI.0904-14.2014>.
- R Core Team, 2013. A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria URL. <http://www.R-project.org/>.
- Simons, R.F., Giardina, B.D., 1992. Reflex modification in psychosis-prone young adults. *Psychophysiology* 29, 8–16. <https://doi.org/10.1111/j.1469-8986.1992.tb02004.x>.
- Takahashi, H., Iwase, M., Canuet, L., Yasuda, Y., Ohi, K., Fukumoto, M., Iike, N., Nakahachi, T., Ikezawa, K., Azechi, M., Kurimoto, R., Ishii, R., Yoshida, T., Kazui, H., Hashimoto, R., Takeda, M., 2010. Relationship between prepulse inhibition of acoustic startle response and schizotypy in healthy Japanese subjects. *Psychophysiology* 47, 831–837. <https://doi.org/10.1111/j.1469-8986.2010.01000.x>.

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