Age-dependent role of pre- and perinatal factors in interaction with genes on ADHD symptoms across adolescence

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A B S T R A C T

Little is known about the effects of risk factors on attention-deficit/hyperactivity disorder (ADHD) symptom over time. Here, we longitudinally studied the role of candidate genes, pre- and perinatal factors, and their interactions on ADHD symptoms between ages 10 and 18 years. Subjects were part of the general population or clinic-referred cohort of the TRacking Adolescents’ Individual Lives Survey (n = 1667). At mean ages of 11.1 (T1), 13.4 (T2), and 16.2 years (T3), ADHD symptoms were assessed with the Child Behavior Checklist. Linear Mixed Models were used to examine the association of candidate genes (i.e., DRD4, DRD2, 5-HTTLPR, COMT, and MAOA), pre- and perinatal factors (i.e., index measure of various pregnancy and delivery complications, maternal smoking, maternal drinking, and low birth weight), and their interactions with ADHD symptoms across adolescence. Pregnancy and delivery complications were associated with a higher level of ADHD symptoms across all time points, but with a significantly declining influence over time (p = 0.006). We found no main effects of the candidate genes on ADHD symptoms throughout adolescence. The simultaneous presence of the low activity MAOA genotype and low birth weight (p < 0.001) and of the 5-HTTLPR LL-allele and respectively pregnancy and delivery complications (p = 0.04) and maternal smoking (p = 0.04) were associated with more ADHD symptoms particularly during early adolescence, and these influences significantly decreased over time. Findings suggest an age-dependent role of gene-environment interactions on ADHD symptoms across adolescence.

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1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a childhood-onset disorder with age-inappropriate symptoms of inattention and hyperactivity/impulsivity (American Psychiatric Association, 2013), which tend to decrease over time (Faraone et al., 2006), but with a highly variable long-term course (van Lier et al., 2007). Although genetic (Faraone and Mick, 2010; Gizer et al., 2009), pre- and perinatal factors (most notably maternal smoking during pregnancy and low birth weight; Banerjee et al., 2007), and gene-environment (G×E) interactions (Neuman et al., 2007) have been implicated in the etiology of ADHD, their possibly changing effect over time on ADHD symptoms remains largely unknown. Recent research in twins indicated that inter-individual differences in the overall decline in ADHD symptoms could be explained by genetic and environmental influences that are largely distinct from those influencing the onset of symptoms (Pingault et al., 2015). This is consistent with the idea that the role of risk factors for ADHD may change over time (Thapar et al., 2007).

In contrast to the wealth of cross-sectional studies that investigated genes in association with ADHD (Faraone and Mick, 2010;
Gizer et al., 2009; Brookes et al., 2006), few studies have examined the role of genetic factors during the course of ADHD symptoms. The dopamine D4 receptor gene (DRD4) 7-repeat was found to be associated with a more persistent course of ADHD symptom severity over time (Biederman et al., 2009; Langley et al., 2009), whereas the presence of the long version of the serotonin transporter gene (5-HTTLPR) was not associated with the course of ADHD (Biederman et al., 2009).

It is reasonable to assume that pre- and perinatal factors have a long lasting role on ADHD symptoms, given that unfavorable perinatal conditions were linked to persistently high trajectories of ADHD symptoms from infancy to middle childhood (Galera et al., 2011), and were associated with a diagnosis of ADHD, even up to 40 years after birth (Halmøy et al., 2012). However, no studies are available that examined the role of pre- and perinatal variables on ADHD symptom levels during the course of adolescence.

The aim of the current study was to investigate the association of a number of ADHD candidate genes (DRD4, 5-HTTLPR, dopamine D2 receptor [DRD2], catechol-O-methyl transferase [COMT], and monoamine oxidase A [MAOA]), a set of pre- and perinatal factors (an index of various pregnancy and delivery complications, maternal smoking during pregnancy, maternal drinking during pregnancy, and low birth weight), and their interactions with changing levels of ADHD symptom from early to late adolescence.

2. Material and methods

2.1. Study sample

The present study contained 1667 adolescents (92.0% Dutch descent) of whom genetic information was available and who participated in the first (T1; \( M_{age} = 11.09 \)), second (T2; \( M_{age} = 13.37 \)), and/or third (T3; \( M_{age} = 16.16 \)) wave of the Tracking Adolescents’ Individual Lives Survey (TRAILS). TRAILS consists of a general population cohort (\( n = 2230 \) at T1) and a parallel clinic-referred cohort (\( n = 543 \) at T1; see Oldehinkel et al., 2015; de Winter et al., 2005 for more sample characteristics). Children from the clinic-referred cohort had been referred to the Groningen university child and adolescent outpatient clinic at least once. The child’s parents or legal guardian and adolescents (\( \geq 12 \) years) provided both written informed consent prior to each wave, whereas younger participants provided verbal assent. The TRAILS study was approved by the Central Committee on Research Involving Human Subjects (Dutch CCMO).

2.2. Procedure

At T1, T2, and T3 parents filled out a questionnaire on adolescent’s ADHD symptoms. At T1, trained interviewers used the TRAILS Family History Interview (Ormel et al., 2005) to assess pre- and perinatal variables by interviewing one of the parents or guardians (preferably the mother, 95.6%). Blood or buccal cells were collected for DNA analysis (see further below).

2.3. Measures

2.3.1. ADHD symptoms

The DSM-IV-Oriented subscale Attention-Deficit/Hyperactivity Problems of the CBCL (Achenbach, 1991; Verhulst and Achenbach, 1995) consisting of 7 items was used as outcome measure of ADHD symptoms at all three waves. Items were scored by parents on a 3-point Likert-scale ranging from 0 = not true to 2 = very true or often true, over the past six months. For descriptive purposes, ASEBA cut-off scores (Achenbach, 1991) were used to categorize adolescents with clinical (>Percentile97 [P97]), subclinical (between P90—P97), and normal (<P90) ADHD symptom levels.

2.3.2. Pre- and perinatal factors

Based on Buschgens et al. (2009), we created an index score of the total number of 31 possible complications (observed range 0–12, mean = 1.83, SD = 2.10) related to pregnancy (e.g., physical, social, or psychological problems during pregnancy), delivery (e.g., breech presentation, Caesarean section), and neonatal hospitalization of the child (e.g., lack of oxygen, blood transfusion, jaundice) or the mother, as an overall score of a suboptimal pre- and perinatal environment. Three groups were created based on the number of events: 0 = no complications (35.9%), 1 = few complications (between 1 and 4 complications, 52.6%), and 2 = many complications (\( \geq 5 \) complications, 11.4%).

Maternal smoking at any time during pregnancy was categorized as 0 = nonsmokers (71.4%), 1 = mild smokers (daily use of 1–10 cigarettes or occasional smoking; 22.5%), and 2 = moderate smokers (daily use of >10 cigarettes; 6.1%, cut-off based on Maughan et al., 2004). Maternal alcohol use at any time during pregnancy was divided into 0 = nonusers (80.7%), 1 = mild drinkers (<1 glass a week; 14.1%), and 2 = moderate drinkers (\( \geq 1 \) glass a week; 5.2%). A birth weight less than 2500 g (standard clinical cut-off) was categorized as a low birth weight (4.2%). Correlations between the pre- and perinatal factors showed positive associations between maternal smoking and alcohol use during pregnancy (r = 0.07, p < 0.001), and between the pregnancy and delivery complication index and low birth weight (r = 0.17, p < 0.001).

2.4. Candidate genes

We selected all ADHD neurotransmitter-related candidate genes from recent meta-analyses (Brookes et al., 2006; Gizer et al., 2009) that were available in TRAILS; unfortunately, the dopamine transporter gene (DAT1) was not available.

2.4.1. Genotyping

Genotyping of the length polymorphisms (LP) DRD4, 5HTTLPR including SNP rs25331 (A/G SNP in 5 HTTLPR), and MAOA was done at the Radboud University Nijmegen Medical Centre in Nijmegen, The Netherlands. The DRD2 TaqA (rs1800497), and the COMT val158met (rs4680) were genotyped by the Golden Gate Illumina BeadStation 500 platform (Illumina Inc., San Diego, CA) according to the manufacturers protocol. Genotyping procedures are documented elsewhere (Stavrakakis et al., 2013).

2.4.2. Genotype model

We considered the 7-repeat of DRD4, the A1 allele of DRD2, the long version of 5HTTLPR, the Val-allele of COMT, and the high activity alleles of MAOA as ‘risk’ alleles for a more persistent course of ADHD, based on the etiological literature. We used dominant models for DRD4 and COMT, an additive model for the tri-allelic classification of 5HTTLPR, and a recessive model for DRD2. The functional status of heterozygous females is uncertain given that MAOA is X-linked. Based on previous findings (Reif et al., 2014), heterozygous females carrying at least one long allele (3.5, 4 or 5 repeats; Deckert et al., 1995) were categorized in the high transcription group. Table 1 shows the genotype distribution. For a description of genotyping methods see Additional Supporting Information (Appendix S1, available online).

2.5. Data analysis

We applied Linear Mixed Models (LMMs) using data from T1, T2, and T3 to investigate the role of (1) five candidate genes in separate models (i.e., two-way interactions between the respective
Table 1

Sample characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1667</td>
<td>1583</td>
<td>1458</td>
</tr>
<tr>
<td>Male gender</td>
<td>51.1%</td>
<td>50.6%</td>
<td>50.8%</td>
</tr>
<tr>
<td>Age in years, M (SD)</td>
<td>11.1 (0.55)</td>
<td>13.47 (0.61)</td>
<td>16.2 (0.68)</td>
</tr>
<tr>
<td>COMT (SS; LS; LL)</td>
<td>419 (25.1%)</td>
<td>828 (49.8%)</td>
<td>420 (25.1%)</td>
</tr>
<tr>
<td>MAOA (low activity; high activity)</td>
<td>426 (25.6%)</td>
<td>1241 (74.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Note: ADHD = Attention-Deficit/Hyperactivity Disorder; DRD4 = Dopamine D4 Receptor; DRD2 = Dopamine D2 Receptor; 5-HTTLPR = Serotonin Transporter; MAOA = Monoamine oxidase A gene.

3. Results

3.1. Sample descriptives

Table 1 presents sample characteristics and the genotypic distributions. ADHD symptom severity decreased in a similar pattern in both sexes, with a stronger decline from T1 to T2 than from T2 to T3. ADHD symptom levels in the clinical range were observed for 176 (10.6%) of the adolescents at T1, 118 (7.1%) at T2, and 71 (4.3%) at T3. Subclinical levels were found for 135 adolescents (8.1%) at T1, 137 (8.7%) at T2, and 126 (8.6%) at T3.

3.2. Candidate genes during the course of ADHD symptoms

None of the candidate genes were related to ADHD symptoms over time (p-values 0.06 to 0.97), although the DRD2 gene was marginally significant (p = 0.06). Subsequent pairwise comparisons showed that A-allele carriers had significantly lower ADHD symptom severity at T1, T2, and T3 (p-values < 0.001 to 0.006) compared to G-allele homozygotes of DRD2.

3.3. Pre- and perinatal factors during the course of ADHD symptoms

Of the four two-way interactions between pre- and perinatal factors and time, that of pregnancy and delivery complications was significantly related to ADHD symptoms across adolescence (b = −8.10, p = 0.006; see Additional Supporting Information for details...
Appendix S2 and S3, available online). There was a similar, albeit marginally significant effect of maternal smoking during pregnancy ($b = -6.13, p = 0.06$). The slopes of the three levels of pregnancy and delivery complications (none, few, and many) differed significantly from each other ($p$-values < 0.001 to 0.04). Adolescents with many complications had significantly higher ADHD symptom levels at each wave compared to adolescents with few or no complications. Also, those with few complications had significantly higher ADHD symptom levels than those with no complications (all $p$-values < 0.001).

3.4. GXE interactions during the course of ADHD symptoms

Because DRD4 and low birth weight ($r = -0.05, p < 0.05$), and MAOA and maternal drinking during pregnancy ($r = 0.05, p < 0.05$) showed significant GxEs, unstandardized residuals of DRD4 and MAOA were used in the respective GxE analysis. The LMMs (Table 2) showed three significant three-way interactions related to ADHD symptoms across adolescence: 5-HTTLPR × pregnancy and delivery complications × time ($b = -9.08, p = 0.04$), 5-HTTLPR × maternal smoking during pregnancy × time ($b = -9.82, p = 0.04$), and MAOA × low birth weight × time ($b = 85.72, p < 0.001$). No significant GxE interactions were found for DRD2, DRD4, and COMT.

3.4.1. 5-HTTLPR × index score of pregnancy and delivery complications

Fig. 1 (upper panel) shows that L-allele carriers had distinct ADHD symptom levels across adolescence depending on the number of pregnancy and delivery complications, with strongest effects for L-allele homoyzogotes. GEE analyses indicated that the slope of L-allele homozygotes with many pregnancy and delivery complications showed the steepest decline of ADHD symptoms from T1 to T3 compared to all other slopes ($\Delta b = 14.57$ to 29.74, $p$-values < 0.001 to 0.004), except for the slope of L-allele heterozygotes with many complications which was marginally significant ($\Delta b = 10.00, p = 0.08$). Moreover, the pairwise comparisons showed that L-allele homozygotes with many complications had the most severe ADHD symptoms compared to those with few or no complications, both within and across the allelic variation of the 5-HTTLPR, not only at T1 ($p$-values < 0.001 to 0.008), but also at T2 ($p$-values < 0.001 to 0.02) and T3 ($p$-values < 0.001 to 0.02). However, L-allele homozygotes with many complications did not differ to S-allele carriers with many pregnancy and delivery complications at T2 and T3 and a few other exceptions ($p$-values between 0.07 and 0.82). Thus, for L-allele homozygotes, larger differences in ADHD severity between adolescents with no, few, or many pregnancy and delivery complications were found in early than in late adolescence. This pattern was also found for L-allele heterozygotes, albeit to a lesser extent; also here, differences in ADHD symptom levels remained significantly different between L-allele homozygotes with no, few, or many complications at all three waves (all $p$-values < 0.001).

Finally, the pairwise comparisons showed that S-allele homozygotes without pregnancy and delivery complications had less severe ADHD symptoms than those with few or many complications at all waves (all $p$-values < 0.001). S-allele homozygotes with few or many complications also differed in ADHD symptom levels from each other at T2 ($p = 0.006$) and T3 ($p = 0.03$), but not at T1 ($p = 0.12$).

3.4.2. 5-HTTLPR × maternal smoking during pregnancy

Fig. 1, lower panel shows the three-way interaction between 5-HTTLPR × maternal smoking during pregnancy × time, similar to the results for pregnancy and delivery complications. Again, the significantly steepest decline of ADHD symptoms was found for L-allele homozygotes with moderate levels of maternal smoking ($\Delta b = 25.58$ to 46.97, $p$-values ≤ 0.001), with the highest ADHD symptom levels compared to all other adolescents at T1 ($p$-values < 0.001 to 0.002). However, at T3, these moderately exposed L-allele homozygotes had similar ADHD symptom levels as moderately exposed adolescents carrying at least one S-allele of the 5-HTTLPR genotype ($p$-values of 0.75 and 0.77). Thus, L-allele homozygotes exposed to severe levels of maternal smoking during

\begin{table}[h]
\centering
\begin{tabular}{lccc}
\hline
Parameter & 5-HTTLPR Estimate$^a$ & SE$^b$ & $p$ \tabularnewline
\hline
Intercept$^c$ & 474.40 & 48.96 & <0.001 \tabularnewline
Time & $-33.71$ & 6.95 & <0.001 \tabularnewline
Genotype$^d$ & $-53.47$ & 38.74 & 0.168 \tabularnewline
MSDP$^e$ & 57.45 & 47.41 & 0.226 \tabularnewline
MDDP$^f$ & 5.92 & 53.34 & 0.912 \tabularnewline
PDCs$^g$ & 45.24 & 45.62 & 0.322 \tabularnewline
LBW$^h$ & 118.25 & 153.69 & 0.442 \tabularnewline
Genotype$^d$ × Time & 8.30 & 5.28 & 0.116 \tabularnewline
MSDP × Time & 5.76 & 6.44 & 0.371 \tabularnewline
MDDP × Time & $-3.24$ & 6.91 & 0.639 \tabularnewline
PDCs × Time & 1.88 & 6.04 & 0.756 \tabularnewline
LBW × Time & 2.64 & 1.96 & 0.893 \tabularnewline
Genotype$^d$ × MSDP × Time & $-9.82$ & 4.84 & 0.043 \tabularnewline
Genotype$^d$ × MDDP × Time & $-1.55$ & 4.75 & 0.745 \tabularnewline
Genotype$^d$ × PDCs × Time & $-9.08$ & 4.31 & 0.035 \tabularnewline
Genotype$^d$ × LBW × Time & $-3.73$ & 1.34 & 0.669 \tabularnewline
\hline
\end{tabular}
\caption{Three-way interactions between respectively the 5-HTTLPR and MAOA genes × pre- and perinatal factors × time during the course of ADHD symptoms across adolescence.}
\end{table}

Note: MSDP = Maternal smoking during pregnancy; MDDP = Maternal drinking during pregnancy; PDCs = Index of pregnancy and delivery complications; LBW = Low birth weight, see further Table 1.

\begin{itemize}
\item[$a$] Adjusted for sex and ADHD medication.
\item[$b$] Values multiplied by 1000 to increase readability.
\item[$c$] Significant variability ($p < .001$) in intercept for ADHD symptoms for both 5-HTTLPR (var $u_{0j} = 197.53, \chi^2(1) = 22.14$) and MAOA (var $u_{0j} = 198.14, \chi^2(1) = 22.11$).
\item[$d$] 5-HTTLPR coded as SS-carriers (0), LS-carriers (1), or LL-carriers (2); MAOA as low (0) or high activity (1).
\item[$e$] MSDP and MDDP coded as no (0), mild (1), or moderate (2).
\item[$f$] PDCs coded as no (0), few (1), or many (2).
\item[$g$] LBW coded as yes (0) or no (1).
\end{itemize}
pregnancy conveyed the greatest risk for the most severe ADHD symptoms in early but not late adolescence.

3.4.3. MAOA

Fig. 2 indicates that adolescents with the low activity MAOA and low birth weight showed the steepest decline in ADHD symptom levels from T1 to T3 (Δb = 74.71 to 84.94, all p-values < 0.001) and the highest ADHD symptom levels at T1 compared to all other adolescents (all p-values < 0.001). Notably, ADHD symptom levels at T3 of adolescents with low activity MAOA and a low birth weight approached those of adolescents without low birth weight (p = 0.05), and adolescents with high activity MAOA with and without low birth weight (p < 0.001). Interestingly, adolescents with the high activity MAOA without low birth weight had the least severe ADHD symptoms at all three waves compared to all other adolescents (all p-values < 0.001). Of note, given that MAOA is a sex-linked gene, we performed additional post-hoc exploration of results, which indicated similar patterns for boys and girls (due to small cell sizes for girls, statistics for only boys are presented in Additional Supporting Information Appendix S4).

4. Discussion

This study investigated the role of several ADHD candidate genes, pre- and perinatal adversities, and their interactions on ADHD symptom levels across three time points in a pooled population and clinic-referred sample of adolescents from age 10–18 years. Our results indicate age-dependency of a number of G × E interactions on ADHD symptom levels across adolescence; G × E interactions were primarily apparent in early adolescence and tended to level off over time. In line with the literature (Pingault et al., 2015), we observed a general decline of ADHD symptoms.

More specifically, we observed an age-dependent interaction of MAOA with birth weight. Adolescents with low activity MAOA and low birth weight appeared most at risk for elevated levels of ADHD symptoms during early adolescence. Similarly, age-dependent G × E interactions were found for 5-HTTLPR with an index of pregnancy and delivery complications and maternal smoking, respectively. Results showed that L-allele carriers (particularly L-allele homozygotes) are more vulnerable to pre- and perinatal adversities than S-allele carriers particularly during early and middle adolescence. Taken together, these findings suggest that MAOA and 5-HTTLPR...
genotypes moderate the influence of pre- and perinatal adversities on ADHD symptoms primarily during the earlier phases of adolescence, an association that diminishes as adolescents grow towards adulthood.

It should be noted that the results of this study are best considered as preliminary and are in need of replication given the paucity of similar studies on G×E interactions. A field that is often hampered by non-replication (Dick et al., 2015; Duncan and Keller, 2011). Only the G×E interaction of MAOA with low birth weight above the significance threshold corrected for multiple testing, hence, especially the findings regarding the 5-HTTLPR genotype should be considered with caution.

An important finding was a distinct role of the low activity MAOA genotype in relation to a more unfavorable course of ADHD as opposed to the high activity MAOA genotype that has been linked to ADHD etiology (Gizer et al., 2009), thus providing support for the existence of factors that are specifically related to the course of ADHD symptoms as previously suggested (Pingault et al., 2015; Thapar et al., 2007). Interestingly, the high activity MAOA genotype appeared to play a protective role specifically in the absence of a low birth weight, as opposed to the low activity MAOA genotype.

The possible involvement of the long but not the short version of the 5-HTTLPR interacting with pre- and perinatal adversities in relation to more severe ADHD symptoms is consistent with previous studies (Gizer et al., 2009). Yet, in a recent study S-allele carriers of the 5-HTTLPR genotype were shown to be more sensitive to psychosocial stress in relation to ADHD symptoms (van der Meer et al., 2014). The 5-HTTLPR genotype may thus differentially interact with the type of environmental stressor. Underlying mechanisms of pre- and perinatal adversities are unclear but fetal hypoxia may be at play (Allen et al., 1998). However, we would like to stress that our suggested associations between the pre- and perinatal factors and ADHD symptom levels are no proof of causality (see Langley et al., 2012).

We did not find support for an independent role of candidate genes on ADHD symptom levels across adolescence, although there was a marginally significant effect of DRD2 genotype. Negative findings of the 5-HTTLPR genotype in relation to the course of ADHD symptoms have been previously reported (Biederman et al., 2009), although the DRD4 7-repeat was found to be associated with a more persistent course of ADHD in two studies (Biederman et al., 2009; Langley et al., 2009). Discrepant findings may be due to methodological differences between the studies (e.g., age, sex, the use of continuous measures of ADHD symptoms versus clinical diagnosis, investigation of subtypes of ADHD, or study design). In addition, overall genetic influences as well as the impact of specific genes (independent from environmental factors) may vary across development, for example, being more evident during either childhood (Kuntsi et al., 2005) or young adulthood (Dick et al., 2006). However, we did find an age-dependent role of pregnancy and delivery complications across adolescence independent of genotype.

In sum, our results emphasize the importance of G×E interactions during the course of ADHD symptoms (Thapar et al., 2007), in line with previous evidence that a large proportion of the genetic variation is specific to the developmental course, not necessarily shared with the onset of symptoms (Pingault et al., 2015). Further, our findings corroborate the evidence that genetic influences may change over time (Chang et al., 2013), resulting in G×E interactions being more evident at some points during development than at others. Moreover, our study is consistent with the finding that prenatal adversities heighten the likelihood of persistently high ADHD symptom levels from infancy to middle childhood (Galera et al., 2011), yet points to a declining influence during adolescence.

4.1. Strengths and limitations

This prospective study provides novel evidence on the role of
G×E interactions on ADHD symptoms within a large sample of adolescents in the transition into adulthood, an understudied area in ADHD research so far. Clearly, replication of our findings is needed. While retrospective recall of pre- and perinatal factors may have been a limitation of this study, retrospective recall of maternal smoking during pregnancy and of low birth weight have been found to be accurate (Rice et al., 2007). Moreover, we used a pooled sample of a population and clinic-referred cohort to increase power to detect significant G×E effects. However, this limits generalizability to pure population or clinical samples.

5. Conclusions

This study supports the notion that genetic factors in interaction with exposure to pre- and perinatal adversities have a changing role during the course of ADHD symptoms beyond childhood. Importantly, our findings suggest that the here reported G×E interactions on ADHD symptom severity decrease over time and may not carry over into adult age. This highlights the importance of taking developmental age into account when studying risk factors for ADHD, especially in cross-sectional studies with wide age ranges. Future studies are necessary to extend our preliminary findings to other age ranges. Particularly, investigating age-dependent effects of genetic and perinatal risk factors from the very onset of ADHD symptoms would be important up into adulthood. Such studies may also focus on epigenetic mechanisms.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2017.02.014.

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