Dopamine Transporter Gene Polymorphism Moderates the Effects of Severe Deprivation on ADHD Symptoms: Developmental Continuities in Gene–Environment Interplay

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Early institutional deprivation is a risk factor for Attention-Deficit/Hyperactivity Disorder (ADHD) symptoms. However not all individuals are affected. We tested the hypothesis that this heterogeneity is influenced by gene x environment (GxE) interaction and that genetic polymorphisms involved in dopamine neurotransmission moderate the effects of severe early institutional deprivation on symptoms of ADHD (sADHD). Using a prospective-longitudinal design sADHD were measured at ages 6, 11, and 15 years in a sample of individuals who experienced severe institutional deprivation (up to 42 months of age) in Romanian orphanages and a non-institutionalized comparison group. Individuals were genotyped for polymorphisms in the dopamine D4 receptor (DRD4 48-bp VNTR in exon 3) and dopamine transporter gene (DAT1) haplotypes combining a 40-bp VNTR in 3'UTR and a 30-bp VNTR in intron 8). The risk for sADHD associated with early institutional deprivation was moderated by the DAT1 but not the DRD4 genotypes; an effect that was first apparent in early-, and persisted to mid-adolescence. The results (i) provide evidence for developmental continuities in G x E interaction, (ii) explain some of the heterogeneity in ADHD outcomes following institutional deprivation and, (iii) add to our understanding of environmental determinants of sADHD. © 2009 Wiley-Liss, Inc.

Key words: gene–environment interaction; DAT1 gene; longitudinal study; attention-deficit/hyperactivity disorder

INTRODUCTION

Early institutional deprivation impacts negatively on a number of areas of psychological functioning [Fisher et al., 1997; Rutter et al., 2000, 2007a; Zeanah et al., 2003; Vorria et al., 2006; Gunnar and van Dulmen, 2007]. This is the case for those children raised in the institutions of the Ceaușescu regime in Romania who were adopted into UK families at the time of the fall of the regime. Follow-up studies suggest that while this lead to a dramatic improvement in general functioning in many cases [O’Connor et al., 2000], significant residual problems persisted in some specific domains including inattention, overactivity and impulsivity (i.e., symptoms of Attention-Deficit/Hyperactivity Disorder; sADHD), quasi-autism,
disinhibited attachment and intellectual impairment [Beckett et al., 2006; Rutter et al., 2007b,c; Stevens et al., 2008]. These effects were more likely in children who experienced extended periods of deprivation [i.e., over 6 months; Kreppner et al., 2007]. Despite persisting impairments in a substantial minority (about one third of the extended deprivation group), there is marked variation in these outcomes, even amongst children exposed to similar degrees of adversity [Kreppner et al., 2007]. One explanation for this variation is that adoptees’ characteristics or aspects of their environment (pre- or post-adoption) act as modifiers; protecting some children from poor outcomes while leaving others at risk [Rutter, 2006]. In the light of previous research highlighting the potential that genetic factors have to serve this function in relation to early adversity in general [e.g., Caspi et al., 2002; Laucht et al., 2007], including early deprivation [Kumsta et al., 2009], the current study sets out to test the hypothesis that this variation in outcome is in part due to gene × environment (G × E) interactions in which genetic factors moderate the association between institutional deprivation and outcomes.

The current analysis concerns sADHD, one of a limited number of specific, negative sequelae associated with early institutional deprivation [Rutter et al., 2007a]. Like other outcomes it varies greatly within groups of deprived individuals, even those experiencing marked adversity: Stevens et al. [2008] found that although many children who experienced over 6 months institutional deprivation had significant sADHD the majority were in the normal range. While it may be distinctive in some ways [e.g., its overlap with disinhibited attachment behavior; Kreppner et al., 2001, 2007], it also appears to share elements with the non-deprivation-related clinical phenotype [e.g., an association with conduct problems; Stevens et al., 2008]. Therefore the genetic factors implicated in sADHD in the general population may also be relevant to the study of sADHD in deprived samples.

Twin studies suggest that in the non-deprived population sADHD involves a strong genetic influence [Biederman and Faraone, 2005], and molecular genetics studies have identified a number candidate genes; although these are all of only small effect [Mick and Faraone, 2008]. Genetic factors have been shown to moderate the effects of both pre- and post-natal environmental risk to determine sADHD levels [Brookes et al., 2006; Laucht et al., 2007]. The current article focuses on the possible moderating role of two genes implicated in the regulation of dopamine neurotransmission, which appears to play a role in the pathophysiology of ADHD in the non-deprived population [Pliszka, 2005]: the dopamine transporter gene (SLC6A3, DAT1) and the dopamine D4 receptor gene (DRD4; DiMaio et al., 2003; Li et al., 2006). Meta-analyses support an association between ADHD and the 10-repeat (10R) allele of a 40-base pair (bp) variable number tandem repeat (VNTR) polymorphism within the 3′-untranslated region (UTR) of DAT1 [chromosome 5p15.3; Yang et al., 2007]. The overall effects are small and highly variable across populations [OR = 1.17; Li et al., 2006; Yang et al., 2007]. This variability may be because this polymorphism is merely a marker for a functional polymorphism elsewhere on the gene or because the functionality of this gene may be especially susceptible to environmental risk factors [Brookes et al., 2006]. In keeping with this, a common DAT1 haplotype (comprised of the 10R allele of the 40-bp VNTR in 3′-UTR and a 6 repeat (6R) allele of the 30-bp VNTR in intron 8) has been shown to moderate the effects of exposure to environmental risk, with elevated rates of ADHD observed in children that carried this haplotype and had been exposed to post-natal psychosocial adversity [Laucht et al., 2007] or prenatal maternal smoking [Brookes et al., 2006]. The association between ADHD and the DRD4 7-repeat (7R) allele of a 48-bp VNTR in exon 3 located within chromosome 11p15.5 has been found across studies [DiMaio et al., 2003; Li et al., 2006]. The effects are larger and more homogeneous than for DAT1, although still small [pooled OR = 1.34; Li et al., 2006]. Several potential gene by environment interactions involving the DRD4 polymorphism have been reported: Maternal insensitivity was associated with preschool externalizing disorders only in children carrying the 7R allele [Bakermans-Kranenburg and van Ijzendoorn, 2006] and parental warmth was protective against externalizing disorders only in the absence of the 7-repeat allele [Propper et al., 2007].

Despite the focus on G × E in the causes of ADHD and other childhood disorders [e.g., Caspi et al., 2002, 2003; Eley et al., 2004; Van Ijzendoorn and Bakermans-Kranenburg, 2006; Sonuga-Barke et al., 2009] little is known about the extent of the developmental continuities of these effects [Uher and McGuffin, 2008]. Moreover, studies of G × E interaction and early adversity are often reliant on retrospective accounts of environmental experiences and are therefore open to possibility that individual differences in personality and recall bias may the confound the effects [Bradburn et al., 1987; Krueger et al., 2003]. Longitudinal analyses of objectively measured risk and prospectively measured outcome factors at multiple time points seem crucial to: (i) properly establish the robustness of the G × E hypothesis and (ii) to test developmental G × E mechanisms. Here we addressed these limitations by using objectively measured early environmental adversity and longitudinal data on sADHD. More specifically, we examine the moderating effect of DRD4 and DAT1 functional polymorphisms on the effects of deprivation on sADHD at 6, 11, and 15 years.

MATERIALS AND METHODS

Participants

The article utilizes the sample (total: N = 217; male: n = 108; female: n = 109) from the English and Romanian Adoptees (ERA) longitudinal study (for a full description see: Rutter and ERA Study Team, 1998). The ERA study comprises a large sample of Romanian children (n = 165) who were reared during infancy in extremely deprived conditions before being adopted into families in the UK before 43 months of age. The children experienced profound psychosocial and nutritional deprivation in the state institutions in Romania (note: n = 21/165 adopted from deprived family settings). The conditions in the institutions ranged from poor to abysmal. Staffing levels were very low (about 1 staff per 30 children), there were virtually no toys or educational activities, staff to child interaction and communication was minimal, feeding was mainly by means of propped up bottles with large teats, and washing involved being hosed down with cold water. A comparison sample of 52 “within-country” (UK) adoptees was selected, who were all aged less than 6 months when adopted but who had not
experienced deprivation. Ethical approval for the ERA study as a whole, and for DNA collection separately was given by the Institute of Psychiatry (King’s College London) and the Bethlem and Maudsley NHS Trust. Parents gave informed consent for their children to be studied and children gave assent at age 15.

Measures

ADHD symptoms. The analysis includes mothers’ and fathers’ ratings of sADHD, obtained at age 6 (n=210), 11 (n=199), and 15 years (n=184). At age 6 and 11 these were based on the Revised Rutter Parent Scales for school-age children [Elender and Rutter, 1996], with supplementary questions from Behar and Stringfield [Behar and Stringfield, 1974; Hogg et al., 1997], while at age 15 years the Difficulties Questionnaire was employed with comparable items and scaling to the Rutter scales [SDQ; Goodman, 1997]. Mother and father ratings were combined to form a composite. At age 15 assessments of sADHD were also available for 195 individuals from the parent Child and Adolescent Psychiatric Assessment (CAPA) interview [Lifetime version developed for use in the English and Romanian Adoptees Study: Rutter et al., 2004, based on Angold et al., 1995]. The CAPA is an interviewer-based diagnostic interview focused on symptoms that occurred since the age of 11 years. The analysis of rates of ADHD at age 15 was based on classification using a diagnostic algorithm which comprised four main criteria: symptom count, age of onset, presence of symptoms across settings and clinically significant impairment. These criteria correspond broadly to those required for a diagnosis of ADHD using the DSM-IV-TR and all four criteria had to be met in order for a research diagnosis of ADHD to be assigned. Longitudinal data from teacher reports of sADHD were available for only sub-group of the sample (70% of the sample for the G × E analyses) and were therefore not included in this analysis.

Cognitive function. The McCarthy Scales of Children’s Abilities [McCarthy, 1972], and the short form of the Wechsler Intelligence Scales for Children [WISC III UK: Wechsler, 1992], were administered at age 6, and 11/15 years respectively.

Assessment of DAT1 and DRD4 genotype. DNA was collected using buccal swabs and extracted following standard procedures outlined by Freeman et al. [2003]. Systematic analyses conducted on the total ERA sample to compare the group whom we received DNA from (n=129) with the group we did not receive DNA from (n=88) revealed no significant differences between the groups in terms of age at adoption (P=0.12); weight at adoption (index of subnutrition; Romanian sample only: P=0.96); developmental level at adoption (P=0.67) or sADHD levels (age 6: P=0.37; age 11: P=0.84; age 15: P=0.72). The genotyping of the VNTR markers followed standard polymerase chain reaction (PCR) protocols, using 30 cycles of annealing 64°C (DAT1 intron 8); 60°C (DAT1 3’UTR) or 55°C (DRD4 exon 3) for 1 min and extension at 72°C for 1 min. PCR products were genotyped on 2% agarose gel, checked and repeated whenever the band pattern was not clear [Mill et al., 2001; Brookes et al., 2006]. Genotyping of the markers was successful for over 97% of samples (DAT1 3’UTR: 98.43%; DAT1 Intron 8: 98.43%; DRD4 exon 3: 97.64%).

High and low genetic risk (g’risk) groups were established for the genotypes of interest. The DAT1 haplotype combining the 40-bp VNTR (3’UTR) and the 30-bp VNTR (intron 8) was constructed following the approach used by Brookes et al. [2006] and there was no deviation from Hardy–Weinberg equilibrium for either DAT1 marker (DAT1 40-bp (3’UTR): P=0.72; DAT1 30-bp (intron 8): P=0.96). There were haplotype data available on 125 study participants. The high risk haplotype group comprised the individuals who were homozygous for both the 10R 40-bp VNTR and the 6R 30-bp VNTR (n=62, 49.6%). The low risk haplotype group comprised all other haplotype combinations (n=63, 50.4%). For DRD4, the high g’risk group consisted of the children who possessed at least one 7-repeat allele of the 48-bp VNTR in exon 3 of DRD4 (n=30, 24%). The low g’risk group consisted of those who possessed no 7-repeat alleles (n=96, 76%). Again, there was no deviation from Hardy–Weinberg equilibrium (P=0.94).

Analytical Strategy

The longitudinal effects of duration of institutional deprivation, genotype group and the G × E interactions at different ages (rated on the Rutter Scales/SDQ) were studied using three-way repeated-measures analysis of variance tests, with IQ and gender controlled to take account of their association with ADHD. Separate cross sectional analyses at each age were performed when a three-way interaction between deprivation group, genotype and assessment age was detected. Symptom data from both the questionnaire and the interview measurement tools were utilized for the cross sectional analysis at age 15. Institutional deprivation risk was based on a binary classification of the duration of institutional care experienced by the individual before adoption. This was based on a 6 months threshold used in previous ERA study analyses [Kreppner et al., 2007; Stevens et al., 2008]. Children who spent less than 6 months or no time in institutions (including all the UK adoptees and the non-institution reared Romanians) made up the low environmental risk (e’risk) group (total ERA sample: N=119; genetic analyses: n=74–75). Those who experienced 6 months or more deprivation were included in a high e’risk group (total ERA sample: N=98; genetic analyses: n=51). The 6-month cut-off was selected for the risk threshold as previous findings have shown that there was no difference in sADHD for the Romanian adoptees with less than 6 months exposure to deprivation and the UK adoptees, that these two groups differed significantly from those with more than 6-month deprivation and that there was no further increase in risk per additional month of deprivation in this over 6-month group [Beckett et al., 2006; Kreppner et al., 2007; Stevens et al., 2008].

RESULTS

Figure 1 plots the level of sADHD as measured using the Rutter/SDQ scales at each age as a function of the duration of deprivation. Moreover, at age 15 years 16% of the group who experienced 6 months or more deprivation received a research diagnosis of ADHD from the CAPA interview, compared with 4% in the low environmental risk group (χ²(1, N=195) = 8.83; P=0.003). This confirms the 6-month threshold linking duration of deprivation to sADHD.

There was no evidence for genotype by environmental risk correlations, that is, no detectable differences in genotype frequency
between adoptee groups for the DAT1 haplotype ($\chi^2 (1, N = 125) = 0.70, P = 0.40$). In the low e’risk group 53% (n = 39) possessed the high risk 10R-6R haplotype and 47% (n = 35) carried one of the low risk haplotypes. In the high e’risk sample 45% (n = 23) were high risk 10R-6R haplotype carriers and 55% (n = 28) possessed one of the low risk haplotypes. Likewise for the DRD4 exon 3 marker no differences in genotype frequencies were detected between the e’risk groups ($\chi^2 (1, N = 126) = 0.13, P = 0.72$). In the low e’risk group 23% (n = 17) carried at least one 7R allele and 77% (n = 58) carried no 7R alleles. In the high e’risk sample 25% (n = 13) possessed at least one 7R allele and 75% (n = 96) possessed no 7R alleles. Nor was there a correlation between DAT1 and DRD4 ($\chi^2 (1, N = 123) = 1.79, P = 0.18$).

### Dopamine Transporter (DAT1)

Table I shows the results of the longitudinal analysis of the sADHD data from childhood to mid-adolescence. A repeated measures analysis of variance test showed that exposure to extended periods of institutional deprivation was associated with elevated levels of sADHD irrespective of age of testing ($P = 0.04$). Levels of sADHD were also higher in those individuals with the DAT1 10R-6R haplotype ($P = 0.02$). There was a significant G x E interaction between DAT1 haplotype and early institutional deprivation ($P = 0.02$), with elevated levels of sADHD for those children who were both exposed to extended deprivation and carried the “risk” haplotype (Fig. 2). The three-way interaction with assessment age ($P = 0.02$) suggested developmental change in the moderating effect of the genotype: Figure 2 suggests that the effects grew stronger with age.

The G x E interaction involving this genotype was significant at age 11 ($P = 0.04$) and age 15 ($P = 0.01$) but not age 6. When age 15 sADHD CAPA interview data were the outcome the G x E interaction was similar (see Fig. 3) but fell short of significance ($P = 0.095$). The highest levels of sADHD were found for those exposed to extended deprivation and carrying the risk genotype, across both measurement types and all assessment ages (see Table II). The G x E interaction was especially apparent in the large effect size of haplotype status, at age 15, in individuals in the high e’risk group (SDQ: $d = -0.92$; CAPA: $d = -0.64$) compared with in the low e’risk group (SDQ: $d = 0.07$; CAPA: $d = -0.002$). A similar pattern of results was found when the two DAT1 markers (40-bp 3’UTR and 30-bp intron 8) were analyzed separately.

### Dopamine Receptor (DRD4)

Tables III and IV show the data and results for DRD4. There was no evidence of a G x E interaction between DRD4 genotype and duration of institutional deprivation at any age.

### DISCUSSION

In the current study we showed that the effect of institutional deprivation on the risk for sADHD was moderated by a DAT1

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**Table I. Results of Longitudinal Analysis of Main Effects and Interactions Between DAT1 Haplotype, Institutional Deprivation and Assessment Age on sADHD Over Time**

<table>
<thead>
<tr>
<th>Source</th>
<th>$F$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early deprivation</td>
<td>4.22</td>
<td>0.04</td>
</tr>
<tr>
<td>DAT1 haplotype</td>
<td>5.69</td>
<td>0.02</td>
</tr>
<tr>
<td>Early deprivation x DAT1 haplotype</td>
<td>5.24</td>
<td>0.02</td>
</tr>
<tr>
<td>Early deprivation x DAT1 haplotype x age</td>
<td>4.26</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Denominator degrees of freedom: 104.
haplotype. Carriers of the DAT1 10R-6R haplotype within the group of children that experienced over 6 months institutional deprivation had significantly higher sADHD scores from childhood to mid-adolescence than those with the low risk haplotype and those not exposed to extended early deprivation in either haplotype group. The G × E interaction between risk factors was significant from early adolescence onwards. The results are important in a number of ways. First, they provide compelling evidence for the potential of genetic variability to moderate the effects of severe early institutional deprivation on the development of ADHD symptoms. They provide an insight into why some children suffer long term impairment while others seem to show few long term ill effects despite the same degree of environmental risk. Data from the ERA study are striking in that they provide the first evidence that genetic factors can alter the impact of even the most extreme social environmental factors. Previous studies with mental health outcomes have looked at extreme variations of risk within the normal range of experiences—the moderating effect of the genes regulating serotonin function on the impact of everyday life events being a case in point [Caspi et al., 2003]. Given the profound and extended nature of the environmental adversity reported in this article one might have speculated that any genetic effects would be overwhelmed. Interestingly, recent research on effects of early deprivation and serotonin transporter (5-HTT) genotype in predicting emotional problems within the ERA study sample has revealed a similar pattern of effects to the current DAT1 results [Kumsta et al., 2009].

The current results are also important as they extend the previous literature of G × E effects to explore continuities across development by taking a longitudinal perspective. Most striking in this regard is the relative increase over time in the G × E effect in explaining sADHD. One explanation for this could be that the degree of heterogeneity (as indicated by the range of sADHD scores) is increasing as children get older with a larger spread of sADHD scores. This is an unlikely explanation of the current finding as the variance in extended deprivation groups stays fairly constant over time. The second possibility is that, although the degree of heterogeneity to be explained is the same at all ages, the DAT1 polymorphism plays an increasingly important role; Either the DAT1 genotype is asserting its influence more and more or other factors, independent of duration of deprivation are more important in determining outcomes at 6 years relative to 11 and 15 years. Such factors could be related to pre-, peri-, and post-natal risk or the early adoptive environment. These questions are beyond the scope of the current article.

The current results also help us to further characterize sADHD as a specific outcome of deprivation [Kreppner et al., 2001]. A previous study has suggested that the deprivation-specific outcome shares a number of clinical features in common with ADHD in the general population who have not experienced deprivation or institutional care [Stevens et al., 2008]. The current results take this one step further by implicating genetic factors that are associated with dopamine function. The fact that the effects were limited to DAT1 rather DRD4 may in hindsight not be surprising given the previous suggestion that DAT1 seems especially sensitive to environmental factors and the findings that ADHD symptoms are only elevated for children who also experience an adverse environment [Brookes et al., 2006; Laucht et al., 2007]. Meta-analysis of the association between the DAT1 10R polymorphism and ADHD highlights the heterogeneity of effects across samples [Yang et al., 2007]. The current study provides further evidence that G × E interplay may help to account for the discrepancy in DAT1 effects. Previous studies suggest that the effects of DRD4 on ADHD are more consistent across studies and so may not be so dependent on the adverse effect of adversity and environmental risk factors [Altink et al., 2008; Mick and Faraone, 2008].

It is quite possible that genetic effects will play a smaller role in determining other outcomes of institutional deprivation and, if they do, different genes are likely to be involved. Candidate genes for these outcomes are less obvious than for sADHD. This is partly because the specific phenotypes perhaps share less in common with similar, but non-deprivation-related outcomes [e.g., Rutter et al., 1999, 2009] and partly because, even where there is possible overlap in phenotype, the relevant molecular genetic studies for autism and cognitive impairment, for example, have thus far found the identification of susceptibility genes somewhat elusive [Veenstra-Vanderweele et al., 2004; Plomin et al., 2006]. An alternative strategy for searching for candidates is to focus on putative mechanisms of action of effects, rather than common phenotypic elements [Moffitt et al., 2005]. Adopting such a strategy might lead us to explore the role polymorphisms in the glucocorticoid receptor genes known to alter an individual’s psychological physiological stress response [Wust et al., 2004; Kumsta et al., 2007; Ising et al., 2008] and which animal models suggest may have long term implications for the
regulation of the HPA axis [Plotsky and Meaney, 1993; Meaney, 2001].

At present we can only speculate on the underlying neurobiological mechanisms responsible for the interaction reported. One possibility is that the presence of the DAT1 10R-6R haplotype alters dopaminergic functioning in such a way to make the child differentially susceptible to the influence of the environment, whether that be in a positive or a negative manner [Belsky et al., 2009], perhaps by altering the temperamental disposition of the child toward their environment [Kim et al., 2006]. Such effects could then perhaps alter long term dopamine function. Indeed, the functional significance of DAT1 polymorphisms is supported by neuroimaging studies and animal models [Rubinstein et al., 1997; Dougherty et al., 1999]. The second possibility is that extended environmental adversity has epigenetic effects leading to differential expression of the DAT1 gene within those brain regions involved in the regulation of attention, activity and impulse control through dopaminergic mechanisms. Although the investigated DAT1 polymorphism is not located in the regulatory region of the gene, epigenetic modification might interact with genetic variability, that is, changes in gene expression might have the largest impact on dopamine neurotransmission in presence of the DAT1 10R-6R haplotype. It is not possible in non-experimental studies to tease apart the operative biological gene–environment mechanisms. However, the current study goes some way to providing an understanding of the developmental trajectory of the interplay between risk factors in explaining the heterogeneity in sADHD outcome following early institutional deprivation. The limitations of the study should be acknowledged. The study relied on a restricted sample for the genetic analyses. However, no differences were found on a range of background and outcome measures between those who participated from the wider ERA sample and those who did not. There was very limited information available on the pre- and peri-natal risk factors, which may hold particular relevance for the current investigation, as pre-natal adversity has been implicated in the etiology of non-deprivation-related sADHD. A further limitation is the increase in risk associated with multiple testing strategies in terms of capitalising on chance and detecting false positive results. In the current study we tested for the effects of two genetic polymorphisms in separate longitudinal models (DAT1 and DRD4). However, the judicious selection of genes and environmental risk factors, alongside the consistency of the results with theory and past research goes some way to limit this possibility. One-off positive results were

| Table III. Results of the Longitudinal Analysis of the Main Effects and Interactions Between DRD4 Genotype, Institutional Deprivation and Assessment Age on sADHD Over Time |
|----------------------------------|---------|---------|
| Source                           | F       | P       |
| Early deprivation                | 1.89    | 0.17    |
| DRD4 genotype                    | 0.02    | 0.90    |
| Early deprivation × DRD4 genotype | 0.01    | 0.92    |
| Early deprivation × DRD4 genotype × age | 1.38    | 0.26    |

Denominator degrees of freedom: 105.
treated with caution, with more confidence being placed in significant results that were reflected across DAT1 genotype/haplotype and analytical models. The DAT1 G × E interaction effect in the longitudinal model remained significant after adjusting for multiple testing across two genotypes (P = 0.02). The main effects did not.

In summary, the current results confirmed the potential of DAT1 polymorphisms to moderate the effects of early adversity associated with institutional deprivation on sADHD and provided evidence for longitudinal emergence and continuity in G × E effects across childhood and adolescence.

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REFERENCES


