Gulf War illness (GWI) as a neuroimmune disease

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Abstract  Gulf War illness (GWI) is a chronic disease characterized by the involvement of several organs, including the brain (Christova et al., Exp Brain Res doi: 10.1007/s00221-017-5010-8, 2017). In a previous study (Georgopoulos et al., J Neural Eng 4:349–355, 2015), we identified six protective alleles from Class II human leukocyte antigen (HLA) genes, and more recently, we investigated the brain correlates of this protection (James et al., EBioMedicine 13:72–79, 2016). Those and other studies (Israeli, Lupus, 21:190–194, 2012) suggested an involvement of the immune system in GWI. In a recent study (Engdahl et al., EBioMedicine doi:10.1016/j.ebiom.2016.08.030, 2016), we showed that the brain pattern of synchronous neural interactions (SNI; Georgopoulos et al., J Neural Eng 4:349–355, 2007) in GWI is distinctly different from that in healthy controls. Here we focused on the SNI itself, as a basic measure of neural communication (irrespective of specific connections) and compared it between GWI and seven other diseases that cover a broad spectrum of etiology and pathophysiology. Specifically, we sought to determine which, if any, of those diseases might resemble GWI SNI, overall and within the HLA protective domain, and thus gain further knowledge regarding the nature of GWI brain abnormality. We studied a total of 962 participants from a healthy control population (N = 583) and eight different diseases, including GWI (N = 40), schizophrenia (SZ; N = 21), Alzheimer’s disease (AD; N = 66), posttraumatic stress disorder (PTSD; N = 159), major depressive disorder (MDD; N = 10), relapsing–remitting multiple sclerosis (RRMS; N = 43), Sjögren’s syndrome (SS; N = 32), and rheumatoid arthritis (RA; N = 8). They all underwent a resting-state magnetoencephalographic (MEG) scan to calculate SNIs. Data were analyzed using analysis of covariance (ANCOVA) with disease as fixed factor, and sex and age as covariates. We found that GWI SNIs differed significantly from control SZ, AD, PTSD and MDD but not from RRMS, SS and RA. In addition, we compared GWI to RRMS, SS and RA with respect to SNIs of MEG sensor pairs that were related to the HLA alleles protective for GWI (James et al., EBioMedicine 13:72–79, 2016). We found that GWI SNIs did not differ significantly from any of these three diseases but they did so from control SZ, AD, PTSD and MDD. These findings indicate that (a) GWI brain synchronicity does not differ significantly from that of known immune-related diseases (RRMS, SS, RA), and (b) that this SNI similarity is present within the HLA-related SNIs. In contrast, GWI SNIs differed significantly from those of the other diseases. We conclude that altered brain communication in GWI likely reflects immune-related processes, as postulated previously (James et al., EBioMedicine 13:72–79, 2016). By extension, these findings also indicate...
that functional brain abnormalities in RRMS, SS and RA might be, in part, due to lack of protective HLA alleles as documented for GWI (Georgopoulos et al., EBioMedicine 3:79–85, 2015).

Keywords Gulf War illness (GWI) · Magnetoencephalography · Human leukocyte antigen (HLA) · Veterans · Schizophrenia · Alzheimer’s disease · Posttraumatic stress disorder · Major depressive disorder · Relapsing–remitting multiple sclerosis · Sjögren’s syndrome · Rheumatoid arthritis

Introduction

Gulf War illness (GWI)

Twenty-five years after the 1990–1991 Persian Gulf War, approximately 250,000 veterans continue to suffer from Gulf War illness (GWI), a condition characterized by chronic and diffuse physical and mental health symptoms that are not readily explained (White et al. 2016). Typical symptoms of GWI include widespread pain, fatigue, mood disruption, cognitive impairment and neurological abnormalities as well as skin rashes, respiratory complaints, and gastrointestinal problems (Fukuda et al. 1998; Steele 2000). The etiology of GWI remains unknown and definitive pathophysiological markers have not been identified. Recently, however, several lines of research suggest a clear explanation, specifically, that GWI involves immune system disruption (Georgopoulos et al. 2015; Parkitny et al. 2015; Skowera et al. 2004; Whistler et al. 2009) which is reflected (in part) in altered brain function (Engdahl et al. 2016; James et al. 2016) in genetically vulnerable individuals (Georgopoulos et al. 2015). Here we seek to extend that line of research and clarify GWI’s relation to other immune-related conditions by comparing brain synchronicity in veterans with GWI to various immune- and non-immune-related diseases.

Synchronous neural interactions (SNI)

Several magnetic resonance imaging studies have identified brain abnormalities associated with GWI (White et al. 2016), although various methodological differences have hampered identification of definitive GWI-related brain biomarkers. We have taken a different approach, focusing on SNIs derived from task-free magnetoencephalography (MEG). Healthy brain functioning is characterized by patterns of synchronized neural communications that are conserved across individuals (Langheim et al. 2006). In contrast, diseases involving the brain manifest characteristic aberrations in neural synchrony. To that end, we have demonstrated that SNIs successfully discriminate various brain disorders including schizophrenia, chronic alcoholism, Sjögren’s syndrome, multiple sclerosis, Alzheimer’s disease temperomandibular joint disorder (Georgopoulos et al. 2007) and posttraumatic stress disorder (Georgopoulos et al. 2010; Engdahl et al. 2010) from each other and from healthy brain functioning. More recently, we demonstrated highly accurate discrimination of veterans with GWI from healthy controls based on regional SNI distributions (Engdahl et al. 2016), further substantiating the discriminatory power of SNI. In the current study, we compare SNI in GWI with that of healthy brain functioning and seven other diseases and to determine which, if any, resemble GWI.

Rationale of the study

In the present study, we test our hypothesis that GWI is a neuroimmune disorder by comparing GWI SNI, irrespective of its regional brain distribution, to seven other diseases with neurological-cognitive-mood (NCM) symptoms of diverse etiology: schizophrenia, Alzheimer’s disease, posttraumatic stress disorder, major depressive disorder, relapsing–remitting multiple sclerosis, Sjögren’s syndrome, and rheumatoid arthritis. We hypothesized that GWI SNI would be similar to the latter three known immune-related diseases but not to the other conditions. Based on our prior work demonstrating HLA- and non-HLA-related brain effects on GWI symptoms (James et al. 2016), we also compared SNI across diseases with regard to HLA status.

Materials and methods

Study participants

A total of 962 human subjects participated in this study as paid volunteers. The study protocol was approved by the relevant institutional review boards and informed consent was obtained prior to the study. Exclusionary criteria included cardiac pacemakers or implanted ferrous metal, central nervous system disorders (e.g., Parkinson’s disease, cerebrovascular accidents, a history of traumatic brain injury, etc.), and current alcohol or drug dependence. There were eight groups, including healthy controls (HC), patients with GWI, schizophrenia (SZ), Alzheimer’s disease (AD), post-traumatic stress disorder (PTSD), major depressive disorder (MDD), relapsing–remitting multiple sclerosis (RRMS), Sjögren’s syndrome (SS), and rheumatoid arthritis (RA). Demographic information (age and sex) and counts per group of zero-lag partial cross-correlations (synchronous neural interactions, SNI) are given in Table 1. The diagnoses for each patient group were made by a specialist in the respective field of medicine at the time of the study, as follows. GWI patients met both Centers for Disease Control
(Fukuda et al. 1998) and Kansas (Steele 2000) criteria. SZ patients were diagnosed based on DSM-IV criteria (APA 2000), had no history of electroconvulsive therapy, no past substance dependence, no current substance/alcohol dependence or abuse, and no medical conditions that effect the central nervous system (e.g., epilepsy). AD patients were diagnosed based on an interdisciplinary consensus diagnosis conference and determined to meet criteria for (1) a diagnosis of dementia according to DSM-IV (APA 2000) and (2) possible or probable AD according to NINCDS-ARDA criteria (McKhann et al. 1984). PTSD was diagnosed using the Clinician-Administered PTSD Scale for DSM-IV (CAPS; Blake et al. 1995). MDD was diagnosed using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID; First et al. 2002). RRMS patients met the modified McDonald criteria (Polman et al. 2005), had greater than or equal to 10 T2 cerebral lesions, were at least 30 days post relapse or steroid burst, and had a clear relapsing–remitting MS subtype. SS patients were diagnosed based on the classification criteria by the American-European consensus group for Sjögren’s syndrome (Vitali et al. 2002). They complained of cognitive dysfunction verified clinically by their physicians and by neuropsychological measurements. RA patients had their diagnosis established at the rheumatology clinic. Finally, the control group comprised age-matched subjects to the patient groups, as well as additional healthy subjects. Patients were receiving medications relevant to their brain illness; some of these medications were psychotropic.

**Data acquisition**

All participants underwent a magnetoencephalographic (MEG) scan. As described previously (Georgopoulos et al. 2007, 2010), subjects lay supine within the electromagnetically shielded chamber and fixated their eyes on a spot ~65 cm in front of them, for 45–60 s. MEG data were acquired using a 248-channel axial gradiometer system (Magnes 3600WH, 4-D Neuroimaging, San Diego, CA), band-filtered between 0.1 and 400 Hz, and sampled at 1017.25 Hz. Data with artifacts (e.g., from non-removable metal or excessive subject motion) were eliminated from further analysis.

**Data analysis**

Standard statistical methods were used to analyze the data, including analysis of covariance (ANCOVA). The following packages were employed: IBM-SPSS statistical package, version 23, Matlab (version R2015b), and ad hoc Fortran computer programs employing the International Mathematics and Statistics Library (IMSL; Rogue Wave Software, Louisville, CO, USA) statistical and mathematical libraries. Prewhitening of the raw MEG series (see below) was performed using programs in Python (Mahan et al. 2015).

Single trial MEG time series from all sensors underwent ‘presh whitening’ (Box and Jenkins 1976; Priestley 1981) using a (50,1,3) ARIMA model (Mahan et al. 2015) to obtain innovations (i.e., residuals). All possible pairwise zero-lag cross-correlations (N = 30,628, given 248 sensors) were computed between the prewhitened MEG time series. Finally, the partial zero-lag cross-correlations $PCC^0_{ij}$ (SNI) between $i$ and $j$ sensors were computed for all sensor pairs. $PCC^0_{ij}$ was transformed to $z^0_{ij}$ using Fisher’s (Fisher 1958) $z$ transformation to normalize its distribution:

$$\text{SNI} = z^0_{ij} = \text{atanh}(PCC^0_{ij})$$

An analysis of covariance (ANCOVA) was used to evaluate SNI differences between GWI and the remaining eight groups. For that purpose, SNIs were pooled from all subjects in each group; the number of SNIs per group are given in Table 1. Since age and sex differed among groups (Table 1), and since the objective was to test whether GWI SNIs differed significantly from those of the other groups, eight

**Table 1** Demographic and SNI information for study groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (years)</th>
<th>SD</th>
<th>N (participants)</th>
<th>N (men)</th>
<th>N (women)</th>
<th>N (SNI)</th>
<th>N (HLA-SNI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>52.1</td>
<td>17.6</td>
<td>583</td>
<td>446</td>
<td>137</td>
<td>1553181</td>
<td>1501287</td>
</tr>
<tr>
<td>GWI</td>
<td>50.0</td>
<td>7.7</td>
<td>40</td>
<td>36</td>
<td>4</td>
<td>997227</td>
<td>961726</td>
</tr>
<tr>
<td>SZ</td>
<td>45.0</td>
<td>9.4</td>
<td>21</td>
<td>17</td>
<td>4</td>
<td>537775</td>
<td>520457</td>
</tr>
<tr>
<td>AD</td>
<td>78.3</td>
<td>7.4</td>
<td>66</td>
<td>61</td>
<td>5</td>
<td>1600581</td>
<td>1556639</td>
</tr>
<tr>
<td>PTSD</td>
<td>50.9</td>
<td>14.8</td>
<td>159</td>
<td>139</td>
<td>20</td>
<td>4109160</td>
<td>3973161</td>
</tr>
<tr>
<td>MDD</td>
<td>50.5</td>
<td>11.9</td>
<td>10</td>
<td>9</td>
<td>1</td>
<td>193048</td>
<td>186546</td>
</tr>
<tr>
<td>RRMS</td>
<td>41.3</td>
<td>10.3</td>
<td>43</td>
<td>12</td>
<td>31</td>
<td>1195130</td>
<td>1148449</td>
</tr>
<tr>
<td>SS</td>
<td>55.3</td>
<td>11.0</td>
<td>32</td>
<td>4</td>
<td>28</td>
<td>867689</td>
<td>838534</td>
</tr>
<tr>
<td>RA</td>
<td>63.2</td>
<td>15.5</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>215331</td>
<td>206581</td>
</tr>
</tbody>
</table>
ANCOVAs were carried out, one between GWI and each of the eight groups, where the SNI was the dependent variable, GWI and a specific disease were the Group fixed factor, and sex and age were covariates.

Additional analyses were performed to assess differences between GWI and other diseases in a subset of sensor pairs ($N = 29219$) the SNIs of which were found previously to possess a significant relation to the presence of any one (or more) HLA alleles protective for GWI (James et al. 2016; Georgopoulos et al. 2015) with respect to NCM symptom severity. Therefore, eight additional ANCOVAs as above were performed for this HLA-related SNI subset.

### Results

#### All sensor pairs (Fig. 1)

GWI SNIs differed significantly from those in the control group ($P = 0.001$, $F$ test in ANCOVA; Table 2). The results of the comparisons of GWI with the other seven disease groups are given in Table 2 and shown in Fig. 2. Of the seven diseases, GWI SNIs were highly significantly different from SZ, AD, PTSD, and MDD (the mental health disorders) but not so from RRMS, SS and RA, i.e., the three immune-related disorders.

#### HLA-related sensor pairs

The location of sensors related to HLA protection (James et al. 2016) is shown in Fig. 3. HLA-related GWI SNIs (i.e., SNIs of all sensor pairs in Fig. 3) differed significantly from those in the control group ($P < 0.001$, $F$ test in ANCOVA; Table 3). The results of the comparisons of GWI with the other seven disease groups are given in Table 3 and shown in Fig. 4. Of the seven diseases, GWI SNIs were highly significantly different from SZ, AD, PTSD, and MDD (the mental health disorders) but not so from RRMS, SS and RA, i.e., the three immune-related disorders.

### Adjustment for multiple comparisons

The experimental design was for planned two-group comparisons (GWI vs. another group); the number of the ANCOVAs ($=16$ in total) reflected the number of groups compared (eight: GWI vs. control and seven disease groups) $\times$ the two sets of sensor pairs (all and HLA-related). Thus, there were no multiple comparisons within each ANCOVA, and from this viewpoint, the probability values given in Tables 2 and 3 are valid at face value. However, it could be argued that an adjustment would be appropriate to account for the fact that 16 overall...
comparisons were performed. For that purpose, we computed an adjusted $P$ value using the Bonferroni correction. We found that for control SZ, AD, PTSD and MDD, all corrected values were $P \leq 0.02$, whereas for RRMS, SS and RA they were $P = 1$. Therefore, the essence of the results regarding the comparison of GWI SNIs against control, mental health disorders and immune-related disorders remains the same with or without Bonferroni correction.

Discussion

Neural synchronicity: SNI

In the present study, we evaluated brain synchronicity in GWI relative to seven other diseases and healthy brain functioning to test the hypothesis that GWI is a neuro-immune disease. For that purpose, we focused on the SNI itself, the basic measure of neural synchronicity,
irrespective of its regional brain distribution. This approach complements our previous one that focused on differences of brain patterns of SNI (Georgopoulos et al. 2007, 2010; Engdahl et al. 2010, 2016). As expected, the results highlight similarities in brain synchronicity between GWI and known immune-related conditions and point to genetically mediated mechanisms underlying similarities between GWI and other immune-related diseases.

An asset of this study is the use of a fine-rain physiological measure of neural synchronicity (SNI) derived from high-fidelity (MEG) measurements to compare GWI with other diseases. SNIs (~30628/brain) come from a dense MEG sensor array (248 sensors) and cover most of the brain, thus providing a detailed background dataset on which comparisons are made. A reduction of this rich dataset to single values (e.g., mean SNI/brain) would eliminate all meaningful information and be, therefore, unwise. Indeed, use of individual SNIs as predictors has proved very innovative during the past 10 years in discriminating various diseases (Georgopoulos et al. 2007, 2010; James et al. 2014; Engdahl et al. 2016); in fact, it is on the basis of subsets of such single SNIs that classification of subjects to various diseases has been made. Finally, it could be argued that use of SNIs would tend to yield “significant” results due to the large number of degrees of freedom. However, the results of this study show that using SNIs did not just find or amplify “significant” effects: the outcomes (“significant” or “nonsignificant”) followed the nature of disease (immune-related or not) compared to GWI and did not just yield universally “significant” results.

A different issue concerns the neurobiological significance of neural synchronicity, which is measured by SNI. In general, neural synchronicity has been shown to be an important aspect of brain function in health and disease by many studies (see Singer 1999, and Uhlhaas and Singer 2006 for reviews). This is not surprising, since the essence of brain function as a massive communication network lies exactly in the interactions between neuronal populations. During the past decade, we have validated the clinical value of SNIs in several different ways. First, we showed that the brain pattern of SNI is very similar and robust across healthy subjects (Langheim et al. 2006). Second, we found that this pattern is distinctly different in brain disease, such as PTSD (Engdahl et al. 2010), GWI (Engdahl et al. 2016), and fetal alcohol syndrome (Lewis et al. 2016). Third, we showed that small subsets of SNIs can correctly classify with >90% accuracy healthy subjects and a number of brain diseases, including schizophrenia, Alzheimer’s disease, multiple sclerosis, Sjögren’s syndrome, temporomandibular joint disorder and chronic alcoholism (Georgopoulos et al. 2007), PTSD (Engdahl et al. 2010; James et al. 2014; Christova et al. 2015, using SNI from functional magnetic resonance data), and GWI (Engdahl et al. 2016). Finally, we have shown that neural synchronicity can be modulated in an orderly fashion by various, diverse factors, including trauma (James et al. 2012), pathological personality traits (James et al. 2015), posttraumatic growth (Anders et al. 2015), apolipoprotein E genotype (Leuthold et al. 2013), and HLA genes (James et al. 2016). Altogether, those studies have documented the importance of neural synchronicity as a fundamental aspect of brain network function and as an effective measure to

Fig. 4 Results for HLA-related sensor pairs to show means (±2SEM) of SNI differences between stated disease group and GWI, adjusted for age and sex (ANCOVA). An asterisk denotes a statistically significant result, as detailed in Table 3.
differentiate, quantify and evaluate the effects of disease and behavioral factors on integrative brain function.

**Immune basis of GWI**

A number of researchers have implicated immune system disruption in GWI (Hotopf et al. 2000; Israeli 2012; Moss 2013; Parkitny et al. 2015; Skowera et al. 2004; Toubi 2012; Whistler et al. 2009). To that end, we recently demonstrated genetic vulnerability involving human leukocyte antigen (HLA) genes in veterans with GWI (Georgopoulos et al. 2015). HLA genes, which are located in the Major Histocompatibility Complex of chromosome 6, play a central role in immune system functioning (Meuer et al. 1982). We reported that six Class II HLA alleles discriminate veterans with GWI from healthy controls and are inversely related to GWI symptom severity, suggesting a protective effect (Georgopoulos et al. 2015). That is, veterans with GWI lack protection, thereby increasing the likelihood of immune-related reactions and other aberrant immune responses when exposed to environmental triggers. We also demonstrated that these HLA alleles interact with brain function to influence symptoms of GWI including NCM (James et al. 2016). There, we concluded that in the absence of HLA protection, immune-related brain abnormalities develop in GWI, perhaps via the development of antibodies to brain antigens resulting in cellular abnormalities, anomalies in neural communication, and symptomatology.

**Brain dysfunction in GWI and other disorders with immune involvement**

GWI is associated with structural brain abnormalities, notably subcortical brain atrophy (Christova et al. 2017). Functionally, more than half of veterans with GWI report at least moderate neurological/cognitive/mood (NCM) impairment (Steele 2000). Typical symptoms include memory and concentration difficulty, word-finding trouble, headaches, blurred vision, tremors, numbness, and mood alterations among others. Similar cognitive and neuropsychiatric symptoms have been associated with various conditions characterized by disruptions in immune functioning including rheumatoid arthritis (Hanly et al. 2005; Shin et al. 2012, 2013; de Melo and Da-Silva 2012), systemic lupus erythematosus (Ainala et al. 2001; Antonchak et al. 2011; Carbotte et al. 1986; de Melo and Da-Silva 2012; Ginsburg et al. 1992; Hanly et al. 1994, 2005; Hay et al. 1992) Sjögren’s syndrome (Alexander and Provost 1987; Lafitte et al. 2001; Martinez et al. 2010; Segal et al. 2012, 2014), and multiple sclerosis (Amato et al. 2006; Chiara-valloti and DeLuca 2008; Denney et al. 2005; Rao et al. 1991). Although estimates vary, some studies have found that two thirds of patients with these disorders exhibit cognitive impairment (Ainala et al. 2001; Hamed et al. 2012; Carbotte et al. 1986; Alexander and Provost 1987; Heaton et al. 1985). These deficits are observed in individuals with no prior cognitive or psychiatric history and have been shown to be associated with markers of inflammation or autoimmunity (Alexander and Provost 1987; Kozora et al. 2001; Hamed et al. 2012). Thus, like GWI, these conditions appear to exhibit interacting effects on the nervous system and immune system that result in both NCM impairment and immune system disruption.

**GWI SNI differences from other diseases**

We have previously demonstrated the power of SNI brain patterns derived from task-free MEG in successfully discriminating various brain diseases (Georgopoulos et al. 2007, 2010; Engdahl et al. 2010, 2016; James et al. 2014). In the present study, we compared average GWI SNI, irrespective of its brain distribution, to healthy brain functioning and other diseases of varied etiology, all of which involve NCM-related impairments. Results demonstrated that GWI SNI did not differ significantly from that of three immune-related diseases (SS, RRMS, and RA) but differed significantly from healthy brain functioning and from brain functioning in non-immune-related diseases (SZ, AD, PTSD, MDD), supporting our hypothesis that GWI is a neuroimmune disease. Although many researchers have recently surmised that GWI is an immune-related condition, this is the first study to empirically demonstrate brain-related similarities between GWI and known immune diseases.

**GWI differences within protective HLA-related SNIs**

In previous studies, we demonstrated HLA-involvement in GWI (Georgopoulos et al. 2015) as well as HLA-related neural influences on GWI symptoms (James et al. 2016). Here we sought to further evaluate SNI differences between GWI and the three immune-related diseases with regard to HLA status. The vast majority of SNIs (29219 out of 30628) were significantly related to HLA with respect to GWI NCM severity (James et al. 2016), highlighting robust interactions of neural and immune systems in GWI. The SNIs involved were widespread although entirely absent in the right temporal region (Fig. 3) and sparse in the right temporal region. Within this subset of HLA-related SNIs, there were no significant differences between GWI and the three immune-related diseases: RA, RRMS, and SS, in contrast to significant differences present between GWI and the four non-immune-related diseases (SZ, AD, PTSD, MDD).
Implications for possible HLA protective involvement in other diseases

The results of the present study highlight neuroimmune involvement in GWI and indicate brain-based similarities with other immune disorders, particularly with regard to HLA-related neural synchrony. Here, the focus is on disease and, with regard to HLA-related SNI, GWI is indistinguishable from RRMS, RA, and SS. However, in as much as the absence of certain HLA alleles has been linked to enhanced vulnerability for GWI, the presence of those alleles confers protection (Georgopoulos et al. 2015). This suggests the possibility that these same alleles may confer protection for brain involvement in other neuroimmune diseases as well. Interestingly, DRB1*13:02, one of our six GWI protective alleles (Georgopoulos et al. 2015), has been found to confer protection to a wide variety of immune-related disorders (Furukawa et al. 2017). This adds further support to the link between GWI and lack of HLA protection (Georgopoulos et al. 2015).

Limitation of the study

The main limitation of the study is the relatively small number of participants in the disease groups. Although the number of SNIs was large and allowed valid comparisons, the representation of adequate variety across participants with various diseases is important. Another possible limitation concerns the criteria used for diagnosis. In the present study, disease diagnosis was made by expert clinician at the time of study but such criteria may change over time. This limitation holds for many clinical studies and trials.

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Compliance with ethical standards

Conflict of interest

The authors do not report any financial disclosures or conflicts of interest.

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