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Intraindividual variability in Systemic Lupus Erythematosus

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Increased intraindividual reaction time variability in persons with neuropsychiatric manifestations of Systemic Lupus Erythematosus.

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Running title:
Intraindividual variability in Systemic Lupus Erythematosus
Abstract

Systemic Lupus Erythematosus (SLE) can affect multiple organ systems, including the central (CNS) and/or peripheral nervous system. Patients with Neuropsychiatric SLE (NPSLE) (defined as SLE affecting the nervous system) can present with non-specific symptoms such as cognitive dysfunction. It is difficult to ascertain whether this is a direct consequence of lupus disease activity on the brain. Intraindividual variability, measured through trial-to-trial reaction time variation, has been proposed as a behavioural marker of CNS integrity. We compared 14 NPSLE, 20 non-NPSLE, and 27 age-matched healthy participants using multiple variability metrics. Variability was increased in NPSLE compared to non-NPSLE participants, and was increased throughout the distribution rather than there being a selective increase in extreme reaction times. Variability metrics were strongly intercorrelated providing convergent evidence that the different metrics are tapping similar processes. The results suggest there is ongoing disruption to cognitive processing in NPSLE and may indicate small fluctuations in attention.

Key words; Intraindividual variability; Reaction time variability; Ex-Gaussian; Neuropsychiatric Systemic Lupus Erythematosus (NPSLE).
Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, inflammatory, immune mediated disease. It can affect multiple organ systems, including the central nervous system (CNS) and/or peripheral nervous system. The American College of Rheumatology define 19 neuropsychiatric manifestations of SLE (NPSLE) to allow classification of nervous system involvement (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999). This includes cognitive dysfunction, which is acknowledged to affect a sizable proportion of individuals with NPSLE (Ainiala, Loukkola, Peltola, Korpela, & Hietaharju, 2001; Brey et al., 2002). However, prevalence rates of cognitive dysfunction of 15-55% have been shown in individuals with SLE without overt neuropsychiatric symptoms (non-NPSLE) (Denburg & Denburg, 2003). Deficits are commonly found in attention, information processing speed, executive function and memory (Benedict, Shucard, Zivadinov, & Shucard, 2008; Denburg & Denburg, 2003), with greater severity in persons with NPSLE (e.g. Kozora, Ellison, & West, 2004). Mechanisms for cognitive dysfunction include vascular or inflammatory injury to the nervous system (Hanly, 2014), but dysfunction may also be unrelated to direct effects of SLE on the brain, and may stem from mood disorders, fatigue and medications. Associations have been found between cognitive performance and Magnetic Resonance Imaging metrics in both NPSLE (e.g. Jung et al., 2012) and non-NPSLE participants (Filley et al., 2009), suggesting there may be similar mechanisms for cognitive dysfunction in the two groups. Further investigation is needed to characterise cognition in NPSLE and non-NPSLE populations and whether this is linked to CNS integrity.

Previously published studies investigating cognition in SLE have used paradigms that rely on measures of within-person central tendency, or average group performance. In recent years some researchers in cognitive neuropsychology have focussed on the measurement of intraindividual variability (IIV) as an alternative metric of cognitive functioning, which refers to the within person
Intraindividual variability in Systemic Lupus Erythematosus fluctuation in performance. This can be on a single measure, such as the variability in reaction time (RT) across multiple trials of a single task. Other measures include variability across testing sessions or across tasks in a test battery. One proposal is that increased variability reflects fluctuations in attentional or executive control, which increase the RTs on intermittent trials and thus increase the overall variability index (Bunce, MacDonald, & Hultsch, 2004; Bunce, Warr, & Cochrane, 1993; West, Murphy, Armilio, Craik, & Stuss, 2002). Increased RT variability has been shown to occur with ageing (Hultsch, MacDonald, & Dixon, 2002; West et al., 2002), along with a number of other conditions such as mild cognitive impairment or dementia (Bielak, Hultsch, Strauss, MacDonald, & Hunter, 2010; Dixon et al., 2007; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000; Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007; Tse, Balota, Yap, Duchek, & McCabe, 2010), traumatic brain injury (Stuss, Pogue, Buckle, & Bondar, 1994) and Parkinson’s disease (de Frias, Dixon, Fisher, & Camicioli, 2007). This measure has been suggested as a behavioural marker for CNS integrity (Hultsch, Strauss, Hunter, & MacDonald, 2008), a proposal supported by imaging studies where within person variability has been associated with white matter structural integrity (Bunce et al., 2010; Bunce et al., 2007; Fjell, Westlye, Amlien, & Walhovd, 2011; Jackson, Balota, Duchek, & Head, 2012; Lovden et al., 2013; Moy et al., 2011).

There are a number of methods that have been used to assess RT variability. One method was developed by Hultsch and colleagues (Hultsch et al., 2000; Hultsch et al., 2008) and involves using a regression procedure to partial out extraneous effects on RTs on a trial by trial basis. This can include factors such as time-on-task, condition and participant age. The residuals from the regression model are then used to generate the intraindividual standard deviation (ISD) as a measure of variability. By contrast, other studies have looked at the distribution of RTs. One method is to fit an ex-Gaussian curve to the data. This assumes that the distribution of RTs can be modelled as having both a Gaussian component and an exponential component, showing a longer right tail. The shape of the distribution can then be described by three parameters; mu and sigma, the mean and standard
deviation of the normal component respectively, and tau, representing the exponential component. Researchers have proposed cognitive interpretations of ex-Gaussian parameters, particularly mu and tau. Although these vary, higher order processes such as decision making are typically ascribed to tau, while lower order processes such as sensory influences are ascribed to mu (for a description of psychological interpretations see Matzke & Wagenmakers, 2009). For example, within the context of ageing, West et al. (2002) propose lapses of intention manifest as increases in tau as these exceptional slow RTs would fall in the tail of the distribution.

RT variability has not previously been assessed in individuals with SLE. In the present study, a group of NPSLE participants were compared with non-NPSLE participants and healthy adults on measures of variability taken from trial by trial RTs on a computerised Stroop task (Golden, 1978). In previous research, variability has been shown to be a more sensitive predictor of group membership than mean RT in Alzheimer’s disease (Hultsch, et al., 2000) and mild cognitive impairment (Dixon, et al., 2007). However, slower mean RTs have been found in participants with SLE compared to healthy adults (e.g., Hanly, Omisade, Su, Farewell, & Fisk, 2010; Shucard, Lee, Safford, & Shucard, 2011) and poorer Stroop performance has been shown in individuals with NPSLE compared to those with non-NPSLE and healthy adults (Kozora, Ellison, & West, 2004; Loukkola et al., 2003). Although we might therefore expect to see increased mean RT in NPSLE, distribution measures may give a fuller picture of the source of the differential performance. Deficits in SLE have commonly been identified in processing speed and attention, with greater impairment in those with NPSLE. Using variability measures as well as mean RT may allow us to draw conclusions as to which of these deficits account for differences in Stroop performance. For example, whether RTs are increased on a few intermittently slow trials (suggesting attentional deficits) or whether there is a more general slowing of responses.
Imaging studies typically indicate white matter damage in NPSLE and comparisons between persons with NPSLE and non-NPSLE suggest there is greater damage in NPSLE (for review, see Kozora & Filley, 2011). However, studies have also indicated subtle differences between individuals with non-NPSLE and healthy adults (e.g., Filley et al., 2009). Following the assumption that variability is a marker for neurobiological integrity, we expected that the NPSLE group would show increased variability compared to the non-NPSLE participants and the healthy adults. Performance in the non-NPSLE group was expected to fall between the two other groups.

Additionally, our interest was whether the same conclusions were reached using several methods that have been developed to assess variability. The calculation of ISDs allows the removal of potential confounds, such as practice effects or fatigue, as the variance due to trial and block order effects is partialled out. By controlling for these potential confounds the resulting measure may be more sensitive to group differences. Fitting distribution parameters does not control for these factors, but does provide information on whether increased RT is due to infrequent slow responses, as shown by an increase in tau, or a shift in the whole distribution. The coefficient of variation (CoV; intraindividual standard deviation divided by intraindividual mean RT) is a simpler method for measuring IIV and this adjusts for individual differences in mean level of performance. The various measures may provide different estimates of IIV, and therefore may have different implications in interpreting cognitive performance in NPSLE. Although many studies have compared results from multiple variability metrics, to our knowledge only Bunce et al. (2013) statistically contrasted different variability measures (ISD and CoV). Associations between the ex-Gaussian parameters have been assessed (e.g., Schmiedek, Oberauer, Wilhelm, Suss, & Wittmann, 2007), but to our knowledge the relationship between ISDs and ex-Gaussian parameters has not previously been investigated. If these different metrics do measure the same process, we would expect to see a high correlation between them.
Methods

Participants

Participants with SLE were recruited from a rheumatology clinic at the Royal Sussex County Hospital, Brighton, UK. They included 14 persons with SLE with either current or a history of neuropsychiatric disorders (NPSLE) and 22 persons with non-NPSLE. Twenty-eight healthy adults were recruited from the local community to form a non-SLE comparison group. All individuals with SLE met the American College of Rheumatology (ARC) classification for SLE. Participants were categorised into NPSLE and non-NPSLE groups by a Consultant Rheumatologist (KD) who used the ACR criteria for NPSLE (ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature, 1999). The following neuropsychiatric manifestations were identified in the NPSLE group, cognitive dysfunction (40%), headache (27%), mononeuropathy (27%), seizure disorder (27%), mood disorder (20%), myelopathy (20%), anxiety disorder (7%), cerebrovascular disease (7%), demyelinating syndrome (7%), and movement disorder (7%).

This study was approved by the East Kent Local Research Ethics Committee (REC reference 08/H1103/29).

Procedure

A 160 trial Stoop word task was used. Participants were presented with colour words (red, yellow, green or blue) that were displayed in either the corresponding colour (congruent trials) or a non-matching colour (incongruent trials). Participants were instructed to respond to the colour of the ink whilst ignoring the written word. Items were presented using PsyScope X (available at http://psy.ck.sissa.it) running on an Apple Macbook Pro laptop. Responses were recorded by
pressing keys labelled with coloured stickers. There were 80 congruent and 80 incongruent trials, divided into alternating blocks of 20 trials each.

**Data processing**

Prior to calculation of variability measures, outlier RTs were excluded from the data set: RTs that were less than 500ms or more than three standard deviations above the individual’s mean RT were removed. This resulted in removal of less than 1.5% of the data. One healthy adult and two non-NPSLE participants were excluded from analysis for failure to follow task instructions.

The intraindividual standard deviations (ISD) were calculated using a regression procedure that partialedled the effects of variables that could influence RT. Trial number, block and age were added to the regression model with the RT for each individual trial as the dependent variable. This removed the effect of these variables from the RTs along with higher order interactions between them. The ISDs were calculated as the standard deviation of the normalised residuals for each participant. Prior to these calculations the normalised residuals were converted to t-scores (Mean=50, SD=10) to ease interpretation. Ex-Gaussian parameters were generated using QMPE software (Cousineau, Brown, & Heathcote, 2004; Heathcote, Brown, & Mewhort, 2002) which fits the distribution to the data using maximum likelihood fitting. Finally a coefficient of variation (CoV) was generated for each individual by dividing their raw standard deviation of RTs by the raw mean RT.

**Analysis**

There were high congruent-incongruent correlations for all parameters ($r$-values ranging from .61 to .93. In a preliminary analysis using mean RT, there was a main effect of congruency, ($F(1,58)=31.15, p<.01, \eta^2_p = .35$) with slower mean RTs in the incongruent compared to congruent condition. However, there was no group x condition interaction ($F(2,58)=1.73, p=.19, \eta^2_p = .06$)
indicating the response congruency effect (i.e., incongruent RT – congruent RT) did not differ across groups. The same pattern was evident on all variability metrics, with significant main effects for congruency ($F(1,58)>9.41, p<.01, \eta^2_p>.14$) and no group x condition interactions ($F(2,56)<1.57, p>.22, \eta^2_p<.05$). This analysis indicates that cognitive load did not influence the expression of IIV. Given the above and precedents elsewhere (e.g., Tse et al., 2010), we therefore combined the congruent and incongruent trials to reduce the number of comparisons. For each participant, the different parameters (mean RT, ISD, mu, sigma and tau) were generated separately for the congruent and incongruent trials and these were then averaged. The distributions of these variables within each group were assessed using Shapiro-Wilk tests. Significant deviations from a normal distribution were identified for mean RT, ISD and tau on both congruent and incongruent trials. These variables were therefore log transformed prior to averaging. This was done before rather than after averaging to account for differences in the group distributions on the congruent and incongruent trials.

Group comparisons were made using Analysis of Covariance (ANCOVA) with age and errors on the National Adult Reading Test (NART) as covariates. Age and premorbid IQ (quantified by NART scores) are both factors that can affect performance on cognitive tasks, and both showed significant relationships with the outcome variables. Where the ANCOVAs were significant the groups were compared using Bonferroni post-hoc tests with the pairwise $p$-value set at .05. Effect sizes were calculated on the post-hoc comparisons and have been reported as Cohen’s $d_s$ (Lakens, 2013) where 0.2=small, 0.5=medium and 0.80=large effect (Cohen, 1992). Due to low error rates in all groups, these were analysed using Kruskal-Wallis tests. The relationship between different variability parameters was assessed across the whole group using partial correlations with age and NART added as covariates.
Results

Participant demographic and clinical data can be found in Table 1. The groups did not differ on age, gender distribution or number of years in education. There was, however, a significant group difference in NART error rates ($F(2,60)=6.61, p<.01$). The non-NPSLE group produced more errors ($M=20.7$) than the healthy adults ($M=12.8$) and this difference was significant on post-hoc tests ($p<.01, d_s=0.99$). Other post-hoc comparisons (NPSLE versus non-NPSLE and NPSLE versus healthy adults) were not significant. The NPSLE and non-NPSLE participants did not differ on clinical characteristics of disease duration or disease activity measured by the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K).

Stroop test error rates and mean reaction time

Overall, error rates were low (see Table 2) and did not differ between the groups for either congruent ($H(2)=4.35, p=.11$), or incongruent trials, ($H(2)=0.48, p=.79$). There were significant group differences on mean RT ($F(2,56)=3.95, p=.03, \eta_p^2=.12$) and post-hoc tests showed the NPSLE group had higher RTs than the non-NPSLE group ($p=.02, d_s=0.97$), while the healthy adults did not differ from either group ($p=.25, d_s=0.58$, comparison with NPSLE group; $p=.71, d_s=0.35$, comparison with non-NPSLE group).

Variability and distribution measures

There were significant group differences for ISD, ($F(2,56)=3.35, p=.04, \eta_p^2=.11$), CoV ($F(2,56)=4.16, p=.02, \eta_p^2=.13$) and the ex-Gaussian parameters tau ($F(2,56)=3.12, p=.05, \eta_p^2=.10$) and sigma ($F(2,56)=6.27, p<.01, \eta_p^2=.18$) but not for mu ($F(2,56)=2.31, p=.11, \eta_p^2=.08$). Post-hoc tests showed the NPSLE group had significantly greater variability indices than the non-NPSLE group for ISD ($p=.04, d_s=0.90$), CoV ($p=.02, d_s=0.98$), and sigma ($p<.01, d_s=1.19$), and the difference approached
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significance for tau ($p=.06, d_s=0.84$). The NPSLE group also had higher values for sigma compared to healthy adults ($p=.03, d_s=0.88$), but these groups did not differ on the other parameters, ($p>.13, d_s<0.58$). The non-NPSLE participants and healthy adults did not differ on any measure.

The relationship between different measures

The relationships between the different parameters were assessed in the whole sample together. The partial correlation coefficients are presented in Table 3. There was a strong positive correlation between ISD and tau ($r_p=.89$), indicating there was at least 79% shared variance between these measures. Both parameters also showed correlations of a similar magnitude with CoV ($r_p = .94$ and .86, respectively). Sigma was also related to the other variability measures, but to a lesser degree with correlation coefficients between .37 and .59. Mean RT was significantly associated with all the other parameters. For ISD, CoV, mu and tau the correlation coefficients were greater than .74, indicating greater than 53% shared variance. Sigma also showed a smaller, but significant association with mean RT, ($r_p(57)=.57, p<.001$). Further to the above, we also looked at the correlations in the separate sub-groups. The relationships did not vary across the groups (data not shown).

Discussion

The present study investigated IIV in individuals with NPSLE compared to those with non-NPSLE and healthy adults. Variability was measured by calculating the standard deviation of trial by trial RT residuals (ISDs) and by fitting the ex-Gaussian distribution to each individual’s RTs to generate mu (the mean of the normal component), sigma (the standard deviation on the normal component) and tau (the tail of the distribution). The main finding was that there were group differences on variability measures of ISD, CoV and the ex-Gaussian parameters sigma and tau, whilst there were no differences on the mu parameter. On post-hoc tests, the NPSLE group had higher scores than non-NPSLE participants on ISD, CoV and sigma, and the difference approached significance for tau.
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(p=.06). In contrast, sigma was the only measure that separated the NPSLE group from the non-SLE comparison group, and these healthy volunteers did not differentiate on any measure from the non-NPSLE sample.

The results support the hypothesis that RT variability is increased in NPSLE. Interestingly, the results are not consistent with the notion of a selective increase in extreme RT values in NPSLE. Increased tau compared to age matched comparison participants, in the absence of increases in sigma, has been seen in other diseases. For example, individuals with Schizophrenia (Rentrop et al., 2010), and in the early stages of dementia of the Alzheimer’s type (Tse et al., 2010). This has been interpreted as reflecting differences in attentional control. By contrast, in NPSLE there were group differences in both sigma and tau, and sigma was the only variable that separated the NPSLE group from both other groups. This suggests that in NPSLE, there is an increase in variability throughout the distribution rather than in extreme RTs on a few trials. Mu and sigma represent the mean and standard deviation of faster responses, while tau encompasses infrequent long responses. Lapses in attention are typically thought to affect the slowest RTs and therefore are quantified by tau. One interpretation of the current result is that less marked fluctuations in attention also influence the variability of the main component of the RT distribution, and therefore may be reflected as differences in sigma along with tau. Although there is conflicting evidence for the effect of ageing on ex-Gaussian parameters, an increase in both sigma and tau has been shown in older compared to younger participants (McAuley, Yap, Christ, & White, 2006; Myerson, Robertson, & Hale, 2007; Tse et al., 2010). These studies also all found increases in mu, suggesting shifts in the whole distribution with increasing age. It is important to note that differences in mu were not evident in NPSLE, indicating the distribution had broadened without a shift in the fastest RTs.

In the present study, there were also group differences for mean RT, with an increased group mean for the NPSLE participants compared to the non-NPSLE group. Mean RT also correlated with the
measures of variability. Linear relationships have been observed between mean RT and standard deviation (e.g. Wagenmakers & Brown, 2007) suggesting increased variability occurs together with increases in mean RT. Notably, in the present study, there were significant group differences on the CoV measure, which controls for shifts in mean values and there were no group differences on the mu parameter. Together, these findings clearly suggest that the results were not purely due to general slowing. In previous research, variability has been shown to be a more sensitive predictor of group membership in Alzheimer’s disease (Hultsch, et al., 2000) and mild cognitive impairment (Dixon, et al., 2007). Additionally, group differences in variability have been shown in the absence of group differences on mean RT (e.g. Rentrop, et al., 2010). In the present study we did not find a dissociation between variability and mean RT. Further research is needed to investigate whether this is fundamental to NPSLE, or whether IIV metrics may be more informative in other situations. For example in Multiple Sclerosis (a disease that shows a similar profile of cognitive impairment to SLE (Benedict et al., 2008)) IIV was a more sensitive indicator of white matter integrity in more regions than mean-level performance (Mazerolle, Wojtowicz, Omisade, & Fisk, 2013).

Imaging studies of IIV typically show a relationship with white matter integrity, with correlations with white matter hyperintensities (WMH) (Bunce et al., 2010; Bunce et al., 2007), diffusion tensor imaging (DTI) metrics (Fjell et al., 2011; Moy et al., 2011) and white matter volume (Jackson et al., 2012). Imaging studies of SLE also show white matter changes (for review, see Kozora & Filley, 2011). Comparisons between persons with NPSLE and non-NPSLE suggest there is greater damage in NPSLE, including an increased burden of WMH (e.g. Appenzeller, Faria, Li, Costallat, & Cendes, 2008), differences on imaging modalities including magnetic resonance spectroscopy (e.g. Handa et al., 2003; Lim et al., 2000) and DTI (Jung et al., 2010). In the present study, IIV was increased in the NPSLE group, but not the non-NPSLE group. It has been proposed that RT variability is a behavioural marker for CNS integrity (Hultsch et al., 2008) and this may explain the greater variability in the NPSLE participants. The effects in the present study were seen outside of an active lupus flare, and
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SLEDAI-2K scores were low, indicating low current disease activity. If variability does indeed reflect differences in brain structural integrity, the present results suggest there is ongoing disruption to cognitive processing, either due to a low level inflammatory response, or as a consequence of previous damage to brain. Although this study did not to look at IIV in relation to brain imaging, an obvious extension would be to compare these measures in NPSLE, non-NPSLE and healthy adults. This would allow firmer conclusions about the link between white matter structural integrity and IIV in NPSLE.

The second focus of the research was to see whether there was a relationship between the different measures of variability. The correlation analysis showed a strong significant association between ISD and tau. There was approximately 79% shared variance between these measures, which suggests that these measures are tapping similar processes. These two measures also showed similar effects in the between-group comparisons, although the ISD metric was slightly better at distinguishing the groups. This may be because it takes into account block and trial effects, which tau does not. Both ISD and tau also correlated with sigma, but to a lesser degree suggesting that they are measuring processes that are somewhat dissociable. Using structural equation modelling, Schmiedek et al. (2007) established that the ex-Gaussian parameters were differentially related to cognitive ability factors. Tau emerged as a unique predictor of working memory and reasoning, whilst sigma was a unique predictor of psychometric speed. Similarly, in older adults, tau was related to working memory capacity whilst mu and sigma were not (Tse et al., 2010). However, in correlational analysis, processing speed has been associated with all three ex-Gaussian parameters (Tse et al., 2010). Also using correlational analysis, Unsworth et al. (2010) found that both tau and sigma were related to working memory capacity, though tau further correlated with response inhibition and general fluid intelligence whilst sigma did not. Together these results suggest that tau is consistently related to working memory capacity and other higher order cognitive functions. However, both sigma and tau may be influenced by differences in working memory and processing speed, but to differing degrees.
The present study possessed several strengths: It is the first investigation of IIV in SLE and has identified differences between individuals with neuropsychiatric and non-neuropsychiatric manifestations. We used multiple measures of variability to gain a fuller picture of these effects and also the relationship between the different measures. Limitations include the small number in the NPSLE group. This reduced the power we had to detect post-hoc group differences, and may explain the non-significant differences between the NPSLE group and healthy adults on many of the parameters. Nevertheless, we were able to detect some differences between persons with NPSLE and non-NPSLE, and to detect differences with the healthy adults on the sigma parameter. The sample size does however restrict the extent to which we can generalise from the present results to the wider population. Counter to expectation, performance in the non-NPSLE group did not fall between the NPSLE and healthy comparison groups. As previous research suggests a significant number of individuals with non-NPSLE experience cognitive deficits, it is possible that our non-NPSLE group was therefore not representative, and in a larger sample the expected pattern of performance would emerge. Equally, it may be that our non-SLE comparison group was not representative of a healthy population. Although the NART error scores suggest they were of above average IQ, and had a higher IQ than both SLE groups, there may be other factors that influenced their performance on the task. These include current mood and fatigue.

A further limitation, linked to the small sample, was that it was not possible to subdivide the NPSLE group into those with current or past neuropsychiatric symptoms. Imaging studies of NPSLE indicate that differences from healthy adults persist outside of an active flare (e.g., Bosma et al., 2000). We therefore would not necessarily expect to see different levels of IIV among those with ongoing relative to a past history of neuropsychiatric manifestations. Heterogeneity in the NPSLE group may have impacted on our ability to detect group differences. Neuropsychological manifestations can be focal or diffuse, affect the central or peripheral nervous system, occur individually or in cohort with other manifestations, and can be directly attributable to SLE or be a secondary consequence of
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disease that is indirectly related to SLE. It is therefore possible that there are a number of separate mechanisms that can lead to increased variability in NSPLE. Clearly, a larger cohort is needed to untangle these potential effects.

Additionally, cognitive assessment in the present study was limited to IIV in a single task, and it is therefore possible that the effects seen were the result of task related factors rather than NPSLE. It would be beneficial to show whether there are similar effects across multiple tasks. This would indicate that IIV in NPSLE is a stable participant dependent factor and if it is related to brain integrity we would expect to see similar results on different cognitive tasks. An interesting extension of the study would be to investigate IIV at different disease stages. Here we studied individuals who were otherwise healthy, with low levels of disease activity. It is possible that variability within a single task would fluctuate with changes in disease activity. It would also be interesting to link these measures to non-specific illness related factors such as fatigue and pain and to psychiatric measures such as depression and anxiety.

To conclude, we found greater IIV in participants with NPSLE. The results suggest variability was higher throughout the distribution rather than being restricted to extreme RTs. Given that IIV has previously been linked to brain structural integrity, it is notable that this measure separated the NPSLE and non-NPSLE groups, even outside of an overt lupus flare and suggests that there is ongoing disruption to cognitive processing in NPSLE. Finally, we found a strong association between different IIV metrics (ISD, CoV and ex-Gaussian tau measures $r_s>.86$). To our knowledge, this is one of the first studies to demonstrate convergent evidence that IIV measures derived from the intraindividual standard deviation and those obtained from the ex-Gaussian distribution are tapping similar processes.
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Table 1: Demographic and disease characteristics for the healthy adult, non-NPSLE and NPSLE groups.

<table>
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<th>Non-NPSLE (n=20)</th>
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<tr>
<td>NART errors&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.78 (5.56)</td>
<td>20.60 (8.76)</td>
<td>16.50 (8.00)</td>
<td>&lt;.01</td>
<td>2&gt;1</td>
</tr>
<tr>
<td>Disease duration&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 (1-28)</td>
<td>4.5 (1-20)</td>
<td>4.5 (1-28)</td>
<td>.64</td>
<td></td>
</tr>
<tr>
<td>SLEDAI 2K&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (0-11)</td>
<td>2 (0-8)</td>
<td>2 (0-8)</td>
<td>.38</td>
<td></td>
</tr>
</tbody>
</table>

Note. SLEDAI-2K=Systemic Lupus Erythematosus Disease Activity Index 2000

<sup>a</sup>Mean (standard deviation).<sup>b</sup>Median (range).

<sup>c</sup>1=healthy adults, 2=non-NPSLE, 3=NPSLE.
Table 2: Mean RT, variability and distribution parameters and error rates for healthy adult, non-NPSLE and NPSLE groups.

<table>
<thead>
<tr>
<th></th>
<th>Healthy adult (n=27)</th>
<th>Non-NPSLE (n=20)</th>
<th>NPSLE (n=14)</th>
<th>P</th>
<th>Bonferroni post-hoc tests</th>
<th>Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RT log(^a)</td>
<td>3.13 (0.07)</td>
<td>3.12 (0.07)</td>
<td>3.17 (0.07)</td>
<td>.03</td>
<td>3&gt;2</td>
<td></td>
</tr>
<tr>
<td>Mu(^a)</td>
<td>1176.81 (138.86)</td>
<td>1147.22 (139.58)</td>
<td>1245.25 (131.44)</td>
<td>.11</td>
<td>3&gt;1,2</td>
<td></td>
</tr>
<tr>
<td>Sigma(^a)</td>
<td>83.24 (37.82)</td>
<td>72.57 (38.02)</td>
<td>115.79 (35.80)</td>
<td>&lt;.01</td>
<td>3&gt;1,2</td>
<td></td>
</tr>
<tr>
<td>Tau log(^a)</td>
<td>2.21 (0.29)</td>
<td>2.05 (0.29)</td>
<td>2.28 (0.27)</td>
<td>.05</td>
<td>3&gt;2*</td>
<td></td>
</tr>
<tr>
<td>ISD log(^a)</td>
<td>0.65 (0.21)</td>
<td>0.58 (0.19)</td>
<td>0.75 (0.18)</td>
<td>.04</td>
<td>3&gt;2</td>
<td></td>
</tr>
<tr>
<td>CoV(^a)</td>
<td>0.15 (0.01)</td>
<td>0.13 (0.02)</td>
<td>0.20 (0.02)</td>
<td>.02</td>
<td>3&gt;2</td>
<td></td>
</tr>
<tr>
<td>Congruent(^b)</td>
<td>0 (0-5)</td>
<td>0 (0-2)</td>
<td>0 (0-1)</td>
<td>.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incongruent(^b)</td>
<td>0 (0-4)</td>
<td>0 (0-6)</td>
<td>1 (0-8)</td>
<td>.79</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note.* ISD = Intraindividual standard deviation. CoV = coefficient of variation

\(^a\) Estimated marginal means (standard deviation). \(^b\) Median (range).

\(^c\) 1=healthy adults, 2=non-NPSLE, 3=NPSLE. \(*p=.059\)
Table 3: Partial correlation coefficients for the relationship between parameters controlling for age and NART error score.

<table>
<thead>
<tr>
<th></th>
<th>Mu</th>
<th>sigma</th>
<th>tau</th>
<th>ISD</th>
<th>CoV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RT</td>
<td>.91</td>
<td>.57</td>
<td>.73</td>
<td>.82</td>
<td>.75</td>
</tr>
<tr>
<td>Mu</td>
<td></td>
<td>.56</td>
<td>.45</td>
<td>.56</td>
<td>.45</td>
</tr>
<tr>
<td>Sigma</td>
<td></td>
<td></td>
<td>.37</td>
<td>.59</td>
<td>.58</td>
</tr>
<tr>
<td>Tau</td>
<td></td>
<td></td>
<td></td>
<td>.89</td>
<td>.86</td>
</tr>
<tr>
<td>ISD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.95</td>
</tr>
</tbody>
</table>

Note. ISD = Intraindividual standard deviation. CoV = coefficient of variation

For all correlations $p<.01$. 