A Longitudinal Investigation of Cognitive Function in Systemic Lupus Erythematosus: A Single-Case Observational Design

Hayley D. Shasteen
Kent State University at Salem

Rachael N. Blasiman
Kent State University at Salem

Systemic lupus erythematosus (SLE) is a multisystem inflammatory autoimmune disease that manifests in physical symptoms and central nervous system impairment. Cognitive impairment in SLE is difficult to define and can be affected by several variables, such as stress and anxiety. In this study, we investigate daily fluctuations in physical symptoms, cognitive symptoms, and cognitive performance in SLE using a single-case observational method. We surveyed three participants diagnosed with SLE over a period of seventy days, measuring variation in cognitive and physical symptoms via inventories; multiple environmental variables, such as temperature and sunlight exposure; and cognitive ability on tasks of working memory, short term memory, and inhibition. Self-reported cognitive symptoms did not correlate with cognitive performance on several memory tasks; however, cognitive symptoms were strongly correlated with physical symptoms, negative affect, diet, stress, sunlight exposure, and anxiety. Tasks of inhibition were influenced by sunlight exposure. Daily fluctuations in physical and cognitive symptoms in patients with SLE are influenced by a variety of environmental factors, including sunlight, but were not associated with cognitive performance.

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that can affect any system in the body, including the central nervous system (Heinlen et al., 2007; Kutner, Busch, Mahmood, Racis, & Krey, 1988; Monastero et al., 2001). Patients diagnosed with SLE present prevalent neuropsychiatric symptoms, including cognitive dysfunction (Ainiala, Loukkola, Korplea, & Hiteaharju, 2001; Sanna et al., 2003). Cleanthous et al. (2018) report that one of the chief complaints of patients with SLE is mental fatigue, also referred to as 'brain fog.' Similarly, Wang, Hanger, Woyczynski, Vaughn, and Wicks (2015) report that within an online community, most members with SLE report brain fog ranging from mild to severe.

In addition to brain fog, patients diagnosed with SLE may experience a variety of other cognitive symptoms (Ho, Husain, & Ho, 2018). These symptoms may vary greatly between individuals; it is possible that two people with SLE can present with few overlapping symptoms (Tunnicliffe et al., 2015). As a further complication, researchers investigating cognitive impairment in patients with SLE often use varying definitions of impairment. This creates confusion about which symptoms to measure in a study of SLE. For instance, Coín-Mejías et al. (2008) report that SLE patients suffer deficits in episodic visual memory, Monastero et al. (2001) report deficits in verbal and non-verbal long-term memory and visuo-constructional abilities, and Shucard, Lee, Safford, and Shucard (2011) report significant deficits in working memory (WM). Both Emori et al. (2005) and Mani, Shenavandeh, Sepehrtaj, and Javadpour (2015) found cognitive impairment in areas of attention and verbal memory. Table 1 provides a summary of various researcher's conceptualization of the cognitive symptoms of SLE and how these conceptualizations vary widely from study to study.

Table 1. Range of cognitive impairment observed in SLE

Reference	Type of cognitive impairment
Coín-Mejías et al., 2008	Episodic visual memory
Denburg, Carbotte, & Denburg, 1987	Verbal and nonverbal memory, reaction time, processing speed
Emori et al., 2005	Verbal memory, reaction time
Kozora, Thompson, West, & Kotzin, 1996	Attention, fluency
Monastero et al., 2001	Verbal and nonverbal long term memory, visuo-constructional abilities
Shucard et al., 2004	Working memory, processing speed
Shucard, Lee, Safford, & Shucard, 2011	Reaction time

Inconsistency in the conceptualization of the cognitive symptoms of SLE may be partially explained by contrasting SLE with neuropsychiatric SLE. Neuropsychiatric SLE is sometimes, but not always, differentiated from SLE in the literature, creating additional challenges in defining symptoms and diagnostic criteria. In a meta-analysis, Leslie and Crowe (2018) report that studies comparing SLE patients to control groups identify deficits in visual attention, cognitive fluency, immediate visual memory, and visual reasoning regardless of neuropsychiatric involvement. However, neuropsychiatric SLE patients experience deficits in complex attention, delayed verbal memory, language, and verbal reasoning compared to healthy controls (Leslie & Crowe, 2018). Similarly, Zabala et al. (2018) found that patients with neuropsychiatric SLE differ greatly in cognitive impairment than those without overt neuropsychiatric SLE.

Along with cognitive symptoms of SLE, researchers have identified numerous physical symptoms. The Systemic Lupus Activity Measure (SLAM) lists fatigue, rashes, pleurisy, abdominal pain, headache, and joint paint as some of the hallmark symptoms of SLE (Liang, Socher, Larson, & Schur, 1989). Patients report fatigue, overall pain, and musculoskeletal distress as the most difficult symptoms to deal with (Pettersson et al., 2012). Similarly, Grootscholten et al. (2003) list painful joints, painful muscles, and fatigue as the chief complaints of SLE patients. Notably, SLE operates in a series of flares and variations in physical health status as symptoms fluctuate over time (Dobkin et al., 2001).

In patients with neuropsychiatric SLE, researchers have found a significant relationship between greater pain and scores on the American College of Rheumatology neuropsychology battery of tests for SLE patients (Kozora, Ellison, & West, 2006). In other chronic inflammatory diseases, such as rheumatoid arthritis, greater reported pain negatively affects cognitive functioning on a number of tasks (Brown, Glass, & Park, 2002). Additionally, lower cognitive scores on several tasks testing visual attention and task switching can be used to predict pain intensity in chronic pain patients (Attal et al., 2014). Somatic awareness of the experience of pain interrupts attention functioning and is related to the threat value of pain and other environmental variables, such as emotional arousal (Eccleston & Crombez, 1999).

Variables Influencing Cognitive Impairment

Multiple variables may influence the appearance of cognitive dysfunction in patients with SLE, ranging from stress and anxiety to weather and diet. Daily stress is a predictor of cognitive functioning in tasks of delayed recall visual memory, visual fluency, and attention speed (Peralata-Ramírez et al., 2006). Perceived stress also shows a higher prevalence of subjective cognitive symptom reports (Plantinga, Lim, Bowling, & Drenkard, 2017). Anxiety and mood disorders appear to be common in patients with SLE, with researchers in one study concluding that 65% of patients are diagnosed with either a mood or anxiety disorder (Bachen, Chesney, & Criswell, 2009). However, the effect of anxiety on cognition in SLE patients has little consensus, with some studies reporting an impact on some aspects of function while others report no relationship (Hay et al., 1992; Peralata-Ramírez et al., 2006). The link between anxiety and cognitive impairment is not limited to patients with SLE; diagnosed anxiety disorders contribute to cognitive impairment in the general population as well (Ferreri et al., 2011; Gualtieri & Morgan, 2008).

Mood and affect also play a role in cognitive functioning. Affect can influence information processing, which can then have an impact on certain aspects of cognitive performance (Bless, Fiedler, & Forgas, 2006). Negative mood is associated with mind wandering, leading to changes in performance on attentional tasks (Smallwood, Fitzgerald, Miles, & Phillips, 2009). Furthermore, participants who experience positive moods during testing demonstrate better cognitive performance than those with negative or neutral moods (Nadler, Rabi, & Minda, 2010).

Hours and quality of sleep impact cognition as well. In chronic inflammatory conditions like SLE, sleep disturbances can worsen physical symptoms, including fatigue, and increase disease activity (Chandrasekhara, Jayachandran, Rajesekhar, Thomas, & Narsimulu, 2009; Ranjbaran, Keefer, Stepanski, Farhadi, & Keshavarzian, 2007). In addition, the effect of pain on cognitive dysfunction of SLE is mediated by sleep disturbances (Lillis et al., 2018). Broadly, older adults who self-report poor sleep quality differ significantly in several cognitive domains compared to good sleepers (Nebes, Buysse, Halligan, Houck, & Monk, 2009).

Weather-related variables affect cognitive functioning in general and specifically in people with SLE. For instance, heat stress and reduction in thermal comfort can affect performance in complex cognitive tasks (Taylor, Watkins, Marshall, Dascombe, & Foster, 2016), while barometric pressures at high altitudes can impact performance in tasks of WM and executive functioning (de Aquino Lemos et al., 2012). In the SLE population, there is some evidence that exposure to sunlight increases flares of disease activity and contributes to overall expression of physical symptoms (Chiche et al., 2012; Haga, Brun, Rekvig, & Wetterberg, 1999).

Some components of diet influence cognitive functioning in both healthy controls and patients with SLE. People who self-report diets high in saturated fat and refined sugars show impairment on several memory tasks (Francis & Stevenson, 2011). The impact of eating carbohydrates on cognition is a complex mechanism, but even eating one meal high on the glycemic index may be enough to induce some impairment in cognition (Micha, Rogers, & Nelson, 2011). The effects of caffeine on cognition vary, with some studies reporting an increase in cognitive functioning while others report an effect on attentional capacities (Brunyé, Mahoney, Lieberman, & Taylor, 2010; Lorist & Tops, 2003). Diet can also influence the presence and severity of inflammation, which consequently may cause alterations in cognitive function (Thaler et al., 2012).

Overall, cognitive impairments have a negative impact on psychological health and social well-being in patients with SLE. Patients with SLE are more likely to use negative, disengaging coping mechanisms and experience more negative life events when compared to healthy controls (Kozora, Ellison, & West, 2009). In a survey of 832 SLE patients, 56.3% reported being unable to work due to severe cognitive impairment (Panopalis et al., 2007). Executive dysfunction in patients with SLE can influence quality of life, particularly resulting in lower scores on role limitation due to physical health and emotional problems (Calderón et al., 2016). However, Vogel, Bhattacharya, Larsen, and Jacobsen (2011) suggest that patients with SLE may not be fully aware of their cognitive deficits, which makes psychosocial aspects difficult to fully measure.

Relationship Between Cognitive Symptoms and Cognitive Performance Over Time

While cognitive dysfunction and cognitive complaints have been documented in patients with SLE, few researchers have compared self-reported cognitive symptoms to actual cognitive performance. Kozora et al. (2008) report that SLE patients had greater self-reported cognitive problems than control participants, but this measure was not compared to their performances on several cognitive tasks. Mikdashi (2007) suggests that both a neuropsychological battery and a cognitive symptoms inventory be employed to quantitate cognitive functioning in patients with SLE. Although researchers report that global psychological distress in patients with SLE fluctuates over time (Dobkin et al., 2001), there remains a lack of longitudinal studies investigating how cognition changes over time in patients with SLE. In a 12-month longitudinal study in which participants completed a baseline and post assessment, patients with SLE improved on several cognitive tasks while those with neuropsychiatric SLE did not improve over time on the same tasks (Gao, Lau, Wan, Lau, & Mok, 2016). However, this study did not account for environmental variables and only relied on two assessments. Over a three-year period, Appenzeller, Cendes, and Costallat (2009) found that the likelihood of patients with SLE becoming unemployed was predicted by the number of cognitive domains impaired and that these domains change over time. In a two-year studying utilizing a baseline and post assessment, Hay et al. (1994) noted considerable change in SLE patients' cognitive functioning; only 1 out of 9 participants were still considered cognitively impaired at the time of the second assessment. Previous longitudinal studies indicate fluctuations in cognitive functioning over time in patients with SLE; however, these variations have not been connected to changes in physiological disease manifestation or emotional and environmental variables.

Aims

In this study, we aim to address deficits in the SLE research to better understand the relationship over time between cognitive symptoms, cognitive performance, physical symptoms, and environmental factors. We hypothesize that performance on tasks of short-term memory (STM), WM, reaction time (RT), attention, and inhibition will fluctuate over time in patients with SLE and also be related to subjective cognitive symptoms. We hypothesize that both cognitive performance and cognitive complaints will be negatively affected by high levels of anxiety and stress, low reported hours and quality of sleep, high temperatures, negative affect, the total number and severity of physical symptoms reported, exposure to sunlight, and several dietary factors. We also hypothesize that over time, the total number and severity of self-reported physical symptoms will be negatively affected by UV index, exposure to sunlight, hours and quality of sleep, negative affect and negative mood, dietary measures, high temperatures, and high levels of anxiety and stress.

Method

This study was approved by the Kent State University Institutional Review Board (#18-207).

Design

In this study, we utilized a single-case observational design to allow us to investigate fluctuations that may have been otherwise lost in aggregate data. A total of three participants diagnosed with SLE were recruited for this study via personal contact and tested using multiple baselines. After obtaining informed consent, one participant was tested daily over the course of ten weeks, the second participant was tested once per week, and the final participant was tested once at the beginning of the ten weeks and again at the end of the ten weeks. Different timepoints were utilized to control for and monitor practice effects and were determined *a priori*.

Surveys and Questionnaires

Physical symptoms. A 17-item inventory was adapted from the Grootscholten et al. (2003) lupus specific symptom checklist that included symptoms from the Lupus Symptom Inventory (Peralata-Ramírez et al., 2007). Symptoms that appear on the checklist include painful joints, painful muscles, headache, hair loss, red and/or painful eyes, skin rash, pain while breathing, shortness of breath, muscle weakness, nausea and/or vomiting, abdominal pain, malaise, sensitivity to sunlight, sensitivity to artificial light, dizziness, overall pain, and fatigue. Participants were asked to rate the intensity of items on the inventory on an eleven-point Likert scale with “0” being not at all intense and “10” being most intense. Increased number of symptoms reported with higher severity indicate poorer physiological function in SLE patients.

Subjective cognitive symptoms. To assess subjective cognitive symptoms, the 21-item Cognitive Symptoms Checklist-Work (Ottati & Feuerstein, 2013) was employed. Participants were asked to select all items that were applicable to how they felt cognitively in the past day. A higher number of selected items suggest that participants are experiencing poorer subjective cognition.

Stress. The Perceived Stress Scale (Cohen, Kamarck, & Mermelstein, 1983) was modified to assess for daily stress. Participants were asked to quantify how often in the past day they had felt the items applied to them using a five-point Likert scale with "0" being never and "4" being very often. Participants that score high on the Perceived Stress Scale experience higher perceived stress.

Anxiety. Anxiety was measured utilizing the six-item short-form Spielberger State-Trait Anxiety Inventory (Marteau & Bekker, 1992). Participants were asked to use a four-point Likert scale to indicate how much an item related to them on that day with "1" being not at all and "4" being very much. Higher scores indicate a participant experiences higher perceived anxiety.

Mood. Daily mood was measured utilizing the Quick Mood Scale (Woodruffe-Peacock, Turnbull, Johnson, Elahi, & Preston, 1998) which measured positive and negative affect using a 12-item inventory. Participants were asked to rate the given mood word in relation to how they felt on that day using a five-point Likert scale with "1" being not at all and "5" being extremely. Participants were also asked to rate their demeanor using a 10-point Likert scale where "1" is unhappy and "10" is happy. Participants were then asked to rate the intensity of their demeanor with "1" being least intense and "10" being most intense.

Other measures. Participants were asked to self-report how much time in minutes they had been exposed to sunlight on the day they were taking the survey. One participant self-reported daily diet measures including grams of sugar, saturated fat, unsaturated fat, carbohydrates, sodium, and caffeine. The survey administrator recorded weather variables including temperature, humidity, barometric pressure, UV index, and pollen using the Weather Channel application for phones according to the location in which the survey was being administered. Participants were also asked to self-report how many hours they slept the previous night and were asked to rate the quality of their sleep using a ten-point Likert scale where "1" was worst and "10" was best.

Short term memory. STM was measured using the forward digit span task (Wechsler, 2003) and the auditory forward digit span task using a website. In the forward digit span task, participants were shown a series of flashing numbers and were asked to type the numbers in the order in which they appeared. In the auditory forward digit span task, participants were asked to listen to a series of numbers and then type them in the order in which they were heard. STM in both tasks is measured by observing the highest sequence of digits that can be accurately remembered and the number of errors made.

Working memory. WM was tested utilizing the reverse Corsi block task and the *n*-back task using a website. In the reverse Corsi block task (Corsi, 1972), participants were shown a collection of boxes on the screen. A black dot appeared in several of the boxes in a randomized order. Participants were asked to select the boxes in which the black dot appeared in the reverse order of which it occurred. In the *n*-back task, participants were shown a series of pictures and asked to select the images they saw two images ago. The *n*-back task was a modified version of that presented by Kirchner (1958). WM in both tasks is measured by assessing how many patterns participants can accurately repeat.

Inhibition. Inhibition was measured utilizing the Stroop task (Stroop, 1935) and the go/no go task using a website. During the Stroop task, participants were shown a series of color words. Some of these words were typed in the same color as their definition, while others were typed in a different color. Participants were asked to type the first letter of the color of the word. In the go/no go task (Constantini & Hoving, 1973), participants were shown either a solid green dot on the screen or a patterned green dot. Participants were asked to click as quickly as they could on the solid green dot but not the patterned green dot. This task was also utilized to measure RT and attention. Inhibition is scored by assessing a participant's ability to react to the correct stimulus when presented with both correct and incorrect stimuli.

Results

The three participants in this study self-identified as female, were between the ages of 20 and 51, and self-reported being diagnosed with SLE and experiencing daily symptoms of the disease. Participants completed their surveys via an online platform. Daily surveys and tests were completed during morning hours (27.7%), afternoon hours (41.0%), and evening hours (31.3%). We designated morning as 5:00 a.m. to noon, afternoon as noon to 5:00 p.m., and evening as after 5:00 p.m. Time of day did not have an effect on any cognitive performance measures (all *p*s > .08) but did influence the number of cognitive symptoms reported (see Figure 1); more symptoms were reported during the evening hours ($F = 15.22$, $p < .001$). In addition, some cognitive symptoms were reported more frequently than others over the 70-day study. See Table 2 for a summary of cognitive symptom frequency. Severity of physical symptoms of lupus also varied over the course of 70 days. Table 3 summarizes the range, mean, and standard deviation for physical symptoms.

Figure 1. Number of cognitive symptoms varies by time of day

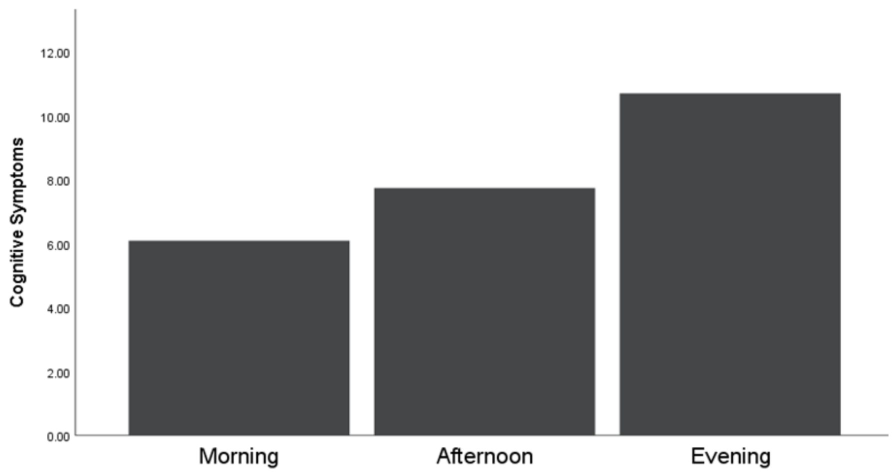


Table 2. Frequency of cognitive symptoms over seventy days

% of days	I have difficulty…
85.4	…remembering the content of conversations and/or meetings.
61.0	…concentrating.
57.3	…remembering information that is 'on the tip of my tongue'.
51.2	…remembering a word I wish to say.
50.0	…remembering things someone has asked me to do.
48.8	…remembering my train of thought as I am speaking.
48.8	…considering all aspects of what I hear or see instead of focusing on only one part.
48.8	…keeping track of things to do without a list.
47.6	…remembering what I intended to write.
47.6	…remembering past experiences.
32.9	…knowing where to look for information to solve a problem.
30.5	…remembering the name of a familiar object or person.
29.3	…following the flow of events.
28.0	…staying with a task until completion.
26.8	…to understand the specific tasks to a larger whole.
25.6	…putting steps in order such that the most important steps are done first.
23.2	…remembering the content of telephone conversations.
23.2	…using new information to re-evaluate what I know.
23.2	…completing all steps of a task or activity.
11.0	…understanding how a task fits into a plan or system.
11.0	…understanding what a problem is when it occurs and clearly stating what the problem is.
3.7	…figuring out how a decision was reached.
3.7	…understanding graphs or flowcharts.

Table 3. Summary of physical symptoms of SLE ratings over seventy days

	Minimum	Maximum	Mean	Std. Deviation
Fatigue	0.00	10.00	6.73	1.80
Appetite	1.00	10.00	6.04	2.02
Overall pain	0.00	9.00	5.78	1.75
Painful joints	2.00	8.00	5.60	1.56
Painful muscles	0.00	9.00	5.59	1.80
Energy levels	1.00	9.00	5.33	1.64
Malaise	0.00	9.00	4.30	2.04
Muscle weakness	0.00	9.00	4.28	2.19
Abdominal pain	0.00	10.00	3.08	2.59
Sensitivity to sunlight	0.00	10.00	3.06	3.09
Skin rash	0.00	9.00	2.76	1.95
Red and/or painful eyes	0.00	7.00	2.45	2.14
Hair loss	0.00	5.00	2.09	1.73
Headache	0.00	6.00	1.34	1.90
Nausea and/or vomiting	0.00	8.00	1.19	1.87
Sensitivity to artificial light	0.00	6.00	1.07	1.53
Shortness of breath	0.00	6.00	0.87	1.64
Dizziness	0.00	6.00	0.31	1.06
Pain while breathing	0.00	3.00	0.06	0.39

Hypothesis testing

Our first hypothesis was that performance on the measures of STM, WM, RT, attention, and inhibition would fluctuate over time, and performance on these cognitive measures would be related to reported cognitive symptoms. That is, we predicted that there would be a direct link between the experience of cognitive symptoms associated with lupus and cognitive performance over time so that an increase in cognitive symptoms would correspond with a decrease in cognitive performance. Because we were examining a potential relationship between variables over time, we used correlation to analyze our results. Specifically, we used participants' scores over time as multiple points of data and were then able to examine fluctuations in variables over time. Table 4 is a summary of the correlations between cognitive symptoms and each of the five measures of cognitive function. Although there were no significant correlations between cognitive symptoms and cognitive performance, we found a positive correlation between cognitive symptoms and physical symptoms ($r = .63$, $p < .001$), meaning that participants were likely to experience greater cognitive symptoms on days they had more physical symptoms.

Table 4. Relationship between cognitive symptoms and cognitive function

	Cognitive Symp-toms	Reaction Time	WM	STM	Problem Solving	Attention
Cognitive Symptoms	-	.121	-.195	.293	-.030	.005
Reaction Time		-	.560**	.093	.365	.608**
WM			-	.030	.787**	.591**
STM				-	.203	-.006
Problem Solving					-	.491**
Attention						-

*$p < .05$, **$p < .01$

Surprisingly, there were no significant relationships between cognitive symptoms and any of the cognitive performance measures. In fact, multiple correlations were positive, so that performance increased when cognitive symptoms were worst, as in the case of STM ($r = .293$, $p > .05$). While there were multiple significant relationships between the measures of cognitive performance, cognitive symptoms appear unrelated. Although this hypothesis was not supported, it opens an intriguing possibility that the cognitive symptoms associated with SLE and the subjective experiences of brain fog are either unrelated to actual cognitive function or that SLE impairs accurate judgements of cognitive function.

Our second hypothesis was that cognitive symptoms, cognitive performance, and physical symptoms would vary from day to day, influenced by a variety of environmental factors, including stress, anxiety, hours and quality of sleep, temperature, sunlight exposure, negative affect, negative mood, and diet. See Table 5 for a summary of the correlations between these variables.

Table 5. Variables influencing cognitive and physical symptoms

	Cognitive Symptoms			Physical Symptoms		
Variables	r	*p*	R^2	r	*p*	R^2
Stress	.17	.14	.03	**.39**	.001	.15
Anxiety	.01	.93	.0001	-.06	.57	.004
Negative affect	**.61**	.001	.37	**.38**	.001	.14
Hours of sleep	-.20	.07	.04	-.13	.24	.02
Quality of sleep	-.12	.28	.01	-.21	.06	.04
Weather						
Humidity	**-.26**	.02	.07	**-.48**	.001	.23
Temperature	**.23**	.04	.05	**.48**	.001	.23
Barometric pres.	-.09	.43	.008	.02	.89	
UV index	-.15	.19	.02	**.23**	.04	.05
Pollen count	-.06	.58	.004	-.04	.73	
Appetite	**-.26**	.02	.07	-.06	.59	.004
Diet						
Sugar	**.27**	.02	.07	**.31**	.01	.10
Caffeine	**.31**	.01	.10	**.49**	.001	.24
Saturated fat	**.48**	.001	.23	**.46**	.001	.21
Unsaturated fat	**.43**	.001	.18	**.37**	.002	.14
Carbohydrates	**.37**	.01	.14	**.34**	.005	.12
Sodium	**.36**	.01	.13	**.27**	.03	.07
Sunlight exposure	.15	.19	.02	**.42**	.001	.18

Note: Significant correlations are in bold.

As this was a small-N design study of three participants, we created multiple longitudinal graphs for visual inspection of the data. We present three of these graphs as Figures 2, 3, and 4. Each figure includes cognitive and physical symptoms along with a third variable; we selected sugar as an example of a dietary variable, anxiety as an example of a cognitive variable, and sunlight as an example of an environmental variable. Each figure visually demonstrates the results of the correlational analyses, in that there is a significant relationship between the cognitive symptoms of lupus, the physical symptoms of lupus, and a variety of variables.

Figure 2. Cognitive and physical symptoms of SLE vary with sugar consumption

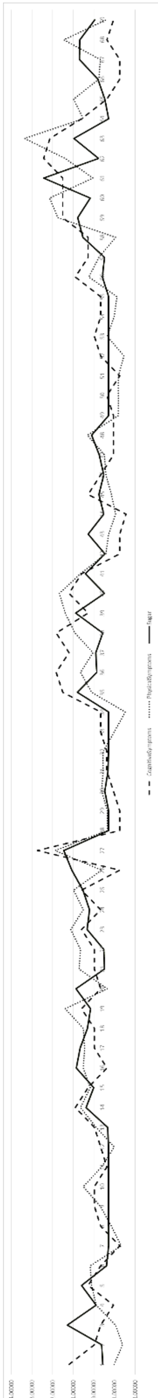


Figure 3. Cognitive and physical symptoms of SLE vary with anxiety

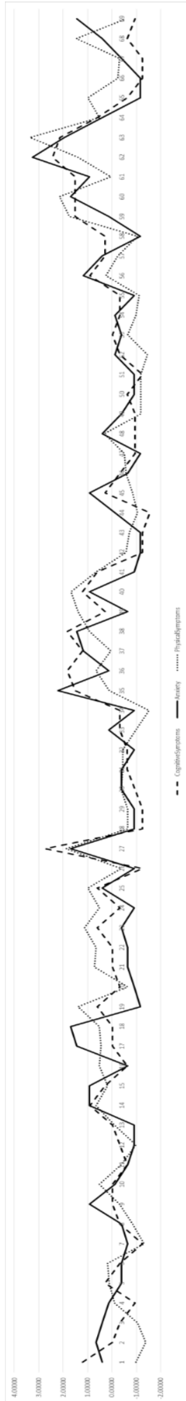
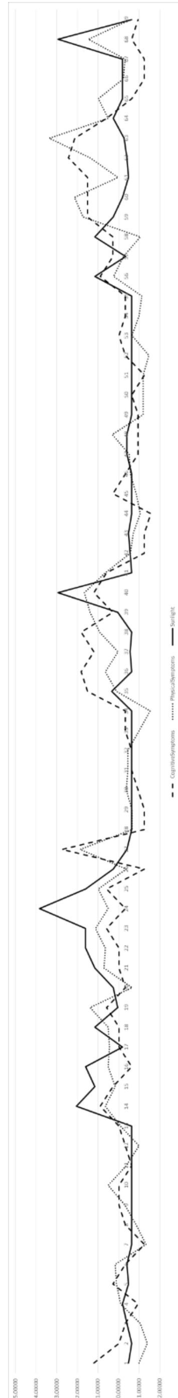


Figure 4. Cognitive and physical symptoms of SLE vary with sunlight exposure



Exploratory Analyses

During our analysis, we were intrigued by some of the results involving exposure to sunlight. Little research has been conducted on the relationship between sunlight exposure and SLE symptoms (Chiche et al., 2012; Haga, Brun, Rekvig, & Wetterberg, 1999), however, there are frequent anecdotal reports in the SLE community regarding this relationship. In this study, minutes of exposure to sunlight ranged from 0-300 minutes per day, with an average of 39.96 and standard deviation of 62.05 minutes. In this study, we defined sunlight exposure as total amount of time spent outdoors during the day. Sunlight exposure was positively correlated to physical symptoms, including painful muscles (r = .30, $p < .05$), painful joints (r = .38, $p < .05$), muscle weakness (r = .23, $p < .05$), shortness of breath (r = .23, $p < .05$), abdominal pain (r = .23, $p < .05$), and overall pain (r = .37, $p < .05$). Sunlight exposure was also positively correlated to multiple cognitive symptoms, including difficulty keeping a train of thought (r = .42, $p < .01$), inability to name an object or person (r = .29, $p < .05$), difficulty seeing how a task fits in a plan (r = .29), difficulty seeing how a decision was reached (r = .27, $p < .05$), and difficulty following the flow of events (r = .26, $p < .05$). In addition to physical and cognitive symptoms, sunlight exposure impaired performance in the go/no-go paradigm, one of the inhibition tasks. Both accuracy (r = -.58, $p < .01$) and time (r = -.66, $p < .01$) were significantly affected by minutes of sunlight exposure per day. Figure 4 shows the relationship between cognitive symptoms, physical symptoms, and sunlight exposure over the 70-day period of the study.

Discussion

This study was designed to investigate the fluctuations of objective and subjective cognition in patients with SLE over time in relation to various environmental variables. Although performance on tasks of STM, WM, RT, attention, and inhibition fluctuated over the course of the study, they were not related to fluctuations in subjective cognitive symptoms. Cognitive performance and cognitive complaints, however, were related to several external variables over time including negative affect, humidity, temperature, appetite, and the consumption of sugar, caffeine, saturated fat, unsaturated fat, carbohydrates, and sodium. Physical symptom fluctuations were also related to external variables including sunlight exposure, stress, negative affect, humidity, temperature, UV index, and the consumption of sugar, caffeine, saturated fat, unsaturated fat, carbohydrates, and sodium. Of note, sunlight exposure was associated with increased cognitive and physical symptoms and decreased performance on the inhibition task.

One unexpected result is the large disconnect between cognitive symptoms and cognitive performance. Based on the results of this study, we now hypothesize that the experience of 'brain fog' in patients with SLE is unrelated to actual cognitive performance. However, the mechanism of this experience requires additional research. Specifically, we must determine if SLE simply impairs accurate judgements of cognitive ability or if it truly has no relationship to cognitive performance. In studies of clinical depression, objective and subjective cognition are not related (Srisurapanont, Suttajit, Eurviriyanukul, & Varnado, 2017) which may be due to the inability to properly assess cognitive functioning. It is possible that this may be true for patients with SLE as well. There are also some intriguing possibilities in neuropsychiatric research that may be related to this disconnect; for instance, the immune system may play a role in attacking key components of biological processes such as synaptic plasticity, neurogenesis, and long-term potentiation, as discussed by Mackay (2015).

Our study addresses the day-to-day fluctuating nature of SLE in both physical and cognitive symptoms as well as cognitive performance over a 70-day period. Many cognitive studies of SLE currently focus on one time point to assess cognition. In this study, however, we show that cognition fluctuates similarly to physical symptoms over time. It is therefore imperative to assess cognition across several time points in order to accurately measure cognition in an SLE population. Additionally, SLE disease activity and physical manifestations can fluctuate differently according to several variables such as seasonal weather conditions, consumption of carbohydrates and fatty acids, abnormal illness-related behaviors, and stress (Alarcón et al., 2006; Elkan et al., 2012; Greco, Rudy, & Manzi, 2004; Schlesinger & Schlesinger, 2009). These variables themselves also fluctuate on a day-to-day basis, which can cause changes in diseases manifestations which in turn can affect cognition in patients with SLE. It is critical for future studies to be conducted in a longitudinal manner to account for these fluctuations in order to understand the pattern of cognitive impairment in SLE patients.

Our results also indicate that sunlight exposure plays a large role in affecting different components of SLE, namely physical symptom presentation and the executive function of inhibition. Previous researchers have reported that sunlight and sunlight prevalent seasons negatively impact patients with SLE and exacerbate physical symptoms and disease progression (Duarte-García, Fang, Hung To, Madger, & Petri, 2012; Krause, Shraga, Molad, Guedj, & Weinberger, 1997). However, few studies have been conducted that look at how sunlight exposure affects cognition in SLE, despite anecdotal evidence within the SLE community. Pace, Erb, and Kitas (2001) reported a case study in which a patient with SLE presented with acute confusion, disorientation to time and place, and short-term amnesia after heavy amounts of sunlight exposure. In this study, we found evidence that prolonged sunlight exposure has a negative effect on tasks of inhibition. We suggest that this impairment is explained at the neural level; specifically, that GABA, the neurotransmitter involved in inhibitory processes, may play a role in this dysfunction. Additionally, melatonin may be involved in this process as increased production melatonin leads to increased GABA inhibitory activity (Cheng, Sun, Ye, & Zhou, 2012). Additional research is needed to understand the role of sunlight in neuropsychiatric processes in SLE.

Limitations

The sample size for this study was small but ameliorated by repeated subjects and a longitudinal design, which offered the opportunity to closely examine fluctuations that might have been hidden in aggregate data. dditionally, this study was conducted during the summer months when days are longer, in a location where weather variables (such as temperature and humidity) are consistently higher than at other times during the year, and at a latitude of 40° above the equator.

Future Directions

Future SLE studies should further investigate the role of sunlight in cognitive and physical symptoms. In addition, studies of SLE should be longitudinal to account for the daily fluctuations of symptoms and their sensitivity to multiple environmental factors, including diet, and longitudinal designs should be conducted during other seasons. Additional research is required to investigate the true nature of the relationship between brain fog and cognitive dysfunction in patients. Specifically, researchers should examine the accuracy of judgments of learning in patients with SLE and compare these judgments to both cognitive symptoms and cognitive performance. Finally, researchers must clarify the differences between SLE and neuropsychiatric SLE both in terms of symptoms and diagnostic criteria.

SLE is a complex disease with many unanswered questions, particularly about the exact mechanism of the autoimmune attack on multiple systems of the mind and body. This results in many and varied cognitive and physical symptoms. Further complicating research on this topic is that these symptoms fluctuate daily and in response to multiple environmental variables. Large scale longitudinal studies are necessary to elucidate the relationships between these variables and disease response so that patients with SLE can make dietary or lifestyle changes to improve their subjective well-being and overall quality of life.

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