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Evaluating the Relationship Between Depression, Perceived Stress, Sleep Quality, and Lure Discrimination

Jessica Rothberg
Montclair State University

Abstract

Depression, Stress and disordered sleep have been found to negatively affect cognition. However, the specific mechanisms affected are still unclear. These clinical symptoms are all independently associated with the hippocampus, where a memory process called pattern separation is assumed to occur. The current study aimed to further investigate the association between depression and pattern separation by further examining the role that sleep and stress play in this relationship. This study is an expansion from Shelton and Kirwan (2013) where they used the Mnemonic Similarities Task to evaluate lure discrimination and depression. I expanded on this by also evaluating sleep quality and perceived stress. These data were assessed using depression, sleep, and stress as predictors in a regression model to predict lure discrimination. The overall model was not significant. Depression and sleep were both significant main effects and the results in regards to anti-depressant use warrant further investigation. Limitations and future directions are discussed.

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by

Jessica Rothberg

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[redacted]

Joshua Sandry, PhD

[redacted]

Sarah Lowe, PhD

[redacted]

Daniel Simonet, PhD

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JESSICA ROTHBERG

Montclair State University

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Introduction

Major Depressive Disorder is the leading cause of disability in the U.S. for people between the ages of 15 and 44.3. Approximately 6.7% of the population is diagnosed with Major Depression. This rises to 10.3 % in people between the ages of 18-25, and over half of these individuals are assessed as having a severe impairment (National Institute of Mental Health, 2016). There is ample evidence that depression correlates with cognitive dysfunction, especially memory (Rogers, Yamasue & Kasai, 2016; Mannie, Filippini, Williams, Near, Mackay & Cowen, 2014, Hickie et al., 2015, Rock et al., 2014). Stress and disordered sleep, which can be common symptoms in depressive disorders, have also been found to negatively affect cognition. However, the specific mechanisms affected are still unclear. These clinical symptoms are all independently associated with the hippocampus, where a memory process called pattern separation is assumed to occur. There is preliminary evidence correlating depressive symptoms to behavioral pattern separation performance, but whether or not stress and sleep quality may moderate this relationship is still unclear. The current study aims to further investigate the association between depression and pattern separation by further examining the role that sleep and stress play in this relationship.

The Hippocampus

The hippocampus is the biological connection to the clinical and cognitive symptoms being investigated in this study. The hippocampus consists of two major structures, the Cornu Ammonis (CA1-CA4) and the Dentate Gyrus (DG) (Yassa, Stark, Bakker, Albert, Gallagher, Stark, 2010). The dentate gyrus is where both neurogenesis and pattern separation are assumed to occur. Pattern separation is a memory process that has been shown to be impaired in those with both hippocampal damage and depressive symptoms. Neurogenesis is the process of creating

new neurons and occurs in only two areas of the brain, one of which is the dentate gyrus. Reduction of neurogenesis has been linked to hippocampal volume, where a decrease in neurogenesis results in a smaller overall hippocampal volume. Reduced hippocampal volume has been linked to depression, stress, and sleep disturbance, as well as memory impairment. Despite these strong theoretical links, in practice it is impractical to measure hippocampal volume clinically. Understanding the specific nature of hippocampal relationships to these variables could eventually lead to more detailed and sensitive evaluations of cognitive impairments in depressed individuals (Yassa, 2010).

Depression

Common depressive symptoms include, hopelessness, fatigue, weight changes, and frequently difficulties with cognitive function (American Psychiatric Association, 2013). Depressive disorders may manifest as common negative or sad mood, the difference is that these symptoms may have no environmental stimulus, and are prolonged over the course of months. Major Depression and other depressive disorders are considered extremely heterogeneous and may look considerably different from person to person. As such, it is important to find both core symptoms, and individual difference that may diminish or exaggerate these core criterion (Hammenn, 2005; Spaner, Bland & Newman, 1994).

There is a large body of evidence linking depression to both cognitive impairment and hippocampal functioning (Rogers, Yamasue & Kasai, 2016; Mannie, Filippini, Williams, Near, Mackay & Cowen, 2014, Jayaweera et al., 2015, Rock et al., 2014). Depression is commonly associated with cognitive deficits and up to two thirds of patients with depression show impaired cognition (Rock et al., 2014). Patients who are actively depressed show deficits in executive function, memory, and attention (Rock et al., 2014). More specifically, un-medicated patients

exhibit deficits in their visual, and spatial recognition memory, compared to healthy controls. Depression has also been associated with decreased hippocampal volume (Rogers, Yamasue & Kasai, 2016; Mannie et al., 2014).

There is evidence to equate hippocampal volume to depressive symptoms; although results are mixed, presumably due to differences in disease onset, treatment duration, and medication use across different participant samples. An association was found between hippocampal volume and poorer memory in depressed participants, whereas, no association was found in control participants (Jayaweera et al., 2005). This along with the evidence of visual and spatial deficits (Rock et al., 2014) suggest that memory impairment found in depressed patients is at least partially, hippocampally dependent.

Hippocampal volume is reduced in participants with major depression on antidepressant medication compared to healthy controls. Imaging evidence found that compared to healthy controls, depressed individuals had significantly smaller left hippocampi. Further, correlations (trending toward significance) support the finding that antidepressant use reduced the negative correlation between disease length and hippocampal volume (Rogers et al., 2016). The ability to accurately measure hippocampal volume in relationship to antidepressants is challenging due to variability in antidepressant, depressive symptom severity and manifestation, as well as possible premorbid individual differences in hippocampal functioning and volume. Because of this, hippocampal volume can only give us partial clarity of hippocampal functioning in depressed individuals.

Recent studies have found a negative correlation between depressive symptoms and pattern separation performance (Shelton & Kirwan, 2013). In this investigation, the authors also measured relationships between pattern separation and anxiety, exercise, and sleep quality but no

significant results were found with these measures. Paradoxically, there have been hippocampal and cognitive links to all three of these constructs. Although, sleep quality is the only one that is a clinical criterion of depressive disorders. Preliminary evidence from this study showed that participants with more depressive symptoms lean toward overgeneralization and struggle recognizing highly similar yet distinct representations. In other words, participants with more depressive symptoms failed to pattern separate as accurately as those with fewer or no depressive symptoms. According to the DSM-V, "diminished ability to think or concentrate, or indecisiveness, nearly every day…" is a diagnostic criterion in Major Depressive Disorder, as well as Dysthymia, and other depressive disorders. Specifically, overgeneralization is a recognized deficit amongst people with depression, the specific mechanisms behind this deficit however, remain unclear (Blake, Dobson, Sheptycki & Drapeau, 2016). This study provided an important introduction to the relationships between pattern separation, and depression (Shelton & Kirwan, 2013) and this study also provides rational for the current research.

Neurologically, the exact theories of depression remain up for debate. The importance of the neurochemical serotonin is widely accepted, in large part due to the success rate of SSRIs in treating depression as well as the large number and variety of serotonin receptors within the hippocampus, which as mentioned has strong links to depression in the literature. These drugs over time, have been shown to inhibit further hippocampal damage, and allow it to regain volume. Interestingly, this occurs because of the reduction of stress hormones that can keep the body in a damaging state of hyperarousal (Spaner et al., 1994). It is therefore unsurprising, that stress plays a key role in both depression, and hippocampal integrity.

Stress

There is an established link between depression and stress (Hammen, 2005). Stressful events such as sudden unemployment, or trauma can overtime create chronic stress. Between 50 and 80 percent of individuals with depression have experienced some kind of stressor 3-6 months before the onset of disease (Cohen, Janicki-Deverts and Miller, 2007). There is a large body of evidence focused on early life stressors as precursors to depression (Hammen, 2005; Saleh et al., 2017). Early life stress is an extreme type of stressor that occurs during childhood or adolescence. Early life stress is associated with many adulthood psychopathologies, in particular Major Depressive Disorder. Early life stress is also associated with poor cognitive functioning, warranting further investigation by Saleh et al., (2017). They found that three types of early life stress variables significantly predicted patients being diagnosed with MDD, 1) emotional trauma, 2) sexual abuse, 3) severe family conflict. Further, they found that the depressed population has more early life stress than the control population. They also found that the depressed individuals performed worse on episodic memory, executive functioning, and processing speed composites.

Chronic stress, may interact with depression prior to onset, but also during active depression (Hammen, 2005). Over time, chronic stress may be exaggerated because of depressive symptoms (i.e. missing work too much and losing your job), or the opposite may be true (being too stressed to enjoy life and developing feelings of hopelessness). There is no clear way to distinguish a directionality when it comes to chronic stress and ongoing depression in humans. Chronic stress reduces hippocampal neurogenesis (creation of new neurons), thus reducing overall hippocampal volume. As mentioned earlier, reduced hippocampal volume is also associated with depressive disorders, and the cognitive disparities associated with these

disorders. These similarities make it apparent that to study depression in terms of hippocampal-dependent memory processes, stress should also be evaluated (Hammen, 2005).

Biologically, chronic stress impacts the hippocampus by creating strong stress hormones (Lucassen & Oomen, 2016). When cortisol levels increase too much, the hippocampus becomes oversaturated which has been shown to impair retrieval performance of long term memories (Newcomer et al., 1999). There is preliminary evidence that stress can specifically impact hippocampal-dependent memory processes in the animal literature. Rats under chronic stress conditions show more severe impairment in hippocampal-dependent memory processes than hippocampal-independent memory processes (Conrad, Mauldi-Jourdan & Hobbs, 2001). Rats also showed impaired spatial memory (hippocampal-dependent) when navigating either a cued or traditional maze environment, under chronic stress conditions (Wright & Conrad, 2005). In the cued version of the maze rats were more likely to explore the novel arm of the maze, which is to be expected as rats are novelty seeking. This behavior implies that the rats recognized that the environments were not the same. In the traditional maze, chronically stressed rats explored the novel arm as frequently as the learned arms, which suggests they could not distinguish the novelty or difference between environments. This performance contrast suggests that chronic stress impaired spatial memory (Wright & Conrad, 2005). Spatial memory is associated with the hippocampus and overlaps with pattern separation frequently in the animal literature. A visual stimulus based object task would not be possible to study in rodent research, thus spatial pattern separation provides the animal basis of pattern separation knowledge.

Sleep Disturbance

Sleep disturbance is a diagnostic criterion of Major Depressive Disorder according to previous and current editions of the Diagnostic Statistical Manual for Mental Disorders. The

Pittsburgh Sleep Quality Index was designed to measure sleep in clinical populations with depressed individuals in mind (Buysse, Reynolds, Monk, Berman & Kupfer, 1989). More recently, a longitudinal study found that in older adults, sleep disturbance for one year, led to an increased risk of depression onset the following year, or persistent depression in those already diagnosed (Eun Lee et al., 2013). Over the course of four years, younger adults (21-30) with reported sleep disturbance were also more likely to develop major depression than their peers with healthy sleep patterns.

Sleep, and therefore sleep disturbance have a well-documented relationship to the hippocampus, and by extension certain memory processes. Memory consolidation occurring during sleep is perhaps one of the most traditional hippocampal associations. Consolidation is the process a new memory goes through to be stabilized and maintained in long term memory (Ricker, 2015). Although the specific mechanisms behind this consolidation process are still being investigated, most scientists agree that a critical memory process (consolidation) takes place in the hippocampus during sleep (Chambers, 2017). Even a single night of sleep deprivation has been shown to reduce hippocampal activity and impair long term memory (Yoo et al., 2007; Marshall & Born, 2007). Spatial memory in particular, is consolidated and learned during sleep in the hippocampus (Nguyen et al., 2013). This study found that participants who slept after learning a maze were more accurate when navigating it the next day compared to those who learned the maze then spent the day awake after learning it. Recall, that spatial memory has links to pattern separation in the animal literature.

Chronic sleep deprivation is associated with learning and long-term memory impairments, and decreased hippocampal volume (Kreutzmann, Havekes, Abel & Meerlo, 2015). Long term memory (hippocampally dependent) is frequently evaluated using this maze model.

Sleep deprivation in animal and human models has been shown to result in worse performance. Chronically, sleep deprivation results in decreased neurogenesis, which may contribute to decreased overall hippocampal volume (Kreutzmann et al., 2015). Decreased hippocampal volume may contribute to poor consolidation performance consistently, and not just on single nights where sleep is disturbed (Rasch & Born, 2013). Sleep has strong ties to the hippocampus and being a precursor to depressive disorders, thus understanding a participant's sleep health is important when evaluating the primary relationship between pattern separation performance and depressive symptoms.

Pattern Separation

Pattern separation is the ability to store similar information as distinct representations. This process takes place within the hippocampus, and can be directly evaluated in the rodent literature by lesioning rodent hippocampi (Hunsaker, Rosenberg & Kesner, 2008; Kesner, Kirk, Yu, Polansky & Musso, 2016; Van Hagen, Van Goethem, Lagatta & Prickaerts, 2015). The recognition of an environment as old or new relies on spatial pattern separation. One study evaluated pattern separation by placing rodents in different environments and evaluating their reactions (Hunsaker et al., 2008). Rodents are novelty seeking, and thus will inspect and react to something they deem new to them. Two groups of rodents (lesioned and non-lesioned) were placed in several different environments. Each environment was a small box with two shapes in it, and they were given three five-minute exploration sessions in this environment. Then, the shapes were made closer together (metric change) or a round box was replaced with a square box (environmental change). They were then reintroduced to the changed environment and their behavior was evaluated for novelty seeking. Rodents with lesions to the hippocampus were found to inspect environmental changes less than healthy rodents. Lesioned rodents, had less

object exploration, and rearing directed toward both changes in object distance, and environment shape than non-lesioned rodents. This suggests that lesioned rodents were unable to detect the changes made to their environment and thus failing to accurately pattern separate (Hunsaker et al., 2008). In humans, I attempt to evaluate this by asking people to determine if something is old, similar, or new, to a stimuli they were presented earlier (Stark et. al., 2013).

Shelton and Kirwan, 2013

The Shelton and Kirwan (2013) study has a large impact on the nature of the current study. Ninety-eight students completed questionnaires on exercise, anti-depressant use, stress, anxiety, sleep quality, and depression. Then, they completed an earlier version (2013) of the Mnemonic Similarities Task. Shelton and Kirwan found a negative correlation between depression and pattern separation. This result coincides with the literature and I expect to replicate this finding. They found no significant correlation between the MST and stress, or sleep. Despite these null findings, the literature supports the notion that there may be a primary relationship between stress and/or sleep and performance on a task like the MST. This study is the only one I am aware of that has looked at these relationships in this manner. The contradiction between results and the literature warrants further evaluation of these relationships.

Current Study

Preliminary evidence has correlated depressive symptoms with pattern separation performance (Shelton & Kirwan, 2013). In addition to depressive symptoms, there are several other clinically important symptoms that have hippocampal and memory links, mainly stress, and sleep. Stress and sleep have complex but salient interactions with depressive symptoms. Therefore, it is pertinent to investigate the relationship all three of these clinical symptoms have with the memory process of pattern separation. The specific interaction of these symptoms

together is unknown, leaving us with an incomplete understanding of how hippocampally mediated clinical symptoms interact with mnemonic similarity performance. Investigation of this sensitive measure of memory performance has both theoretical and applied potential in further understanding the relationship between cognition and clinical symptoms. Although these symptoms have unclear and perhaps in reality, flexible directionality, several hypotheses can be evaluated.

Hypotheses. I hypothesize a negative correlation between the Mnemonic Similarities Task and depressive symptoms on the Hospital Anxiety and Depression Scale. This finding would independently replicate the findings in Shelton and Kirwan (2013), while expanding the correlation into a different but widely used measure of depressive symptoms. Based on previous research, I also hypothesize a negative correlation between stress as measured by the Perceived Stress Scale, and performance on the Mnemonic Similarities Task as well as a negative correlation between sleep quality as measured by the Pittsburgh Sleep Quality Index, and performance on the Mnemonic Similarities Task.

Interaction Hypothesis. Depression is a very heterogeneous disorder. As such, sleep quality, and high perceived stress, may or may not be part of presenting symptoms. I expect to find that the correlation between depression and mnemonic similarity will increase as a function of perceived stress and sleep quality. Further, I expect a three-way interaction where those with high depression, high stress, and poor sleep will perform the worst on the Mnemonic Similarities Task (low LDI scores).

Method

Procedure

As part of a larger study, 164 undergraduate Introduction to Psychology students (age M=19.8, SD=3.35, 79% female) from Montclair State University participated in the study for

partial course credit. Participants signed up online through Sona Systems, and reported to the lab during their assigned time. Participants completed demographic information followed by a series of cognitive and neuropsychological assessments. Then, participants completed a number of surveys to assess clinical symptomology, and were debriefed. All of the clinical surveys were completed using Qualtrics to expedite, and ensure completion of participant responses.

Measures

Mnemonic Similarities Task. The Mnemonic Similarities Task is a visual object task administered on the computer that tests visual recognition memory, and infers pattern separation performance (Stark et al., 2013). The anatomy of the task is as follows step 1) participants go through an incidental encoding phase of a designated number of object visual stimuli. Here they are asked to decide if the item is an indoor or outdoor item using a key press. Step 2) They are shown another set of visual stimuli where 1/3 of the items are repetition (target) items, 1/3 are novel (foil) items and 1/3 are similar (lures) items. Again, the participant must decide which object goes into which category (old, similar, or new) by a designated key press. Stark et al., assess pattern separation here by calculating an MST ratio score. This is done by calculating the ratio of similar responses to lures (correct answers) minus similar responses to foils (incorrect). This MST score will be higher with better pattern separation performance. According to Stark, a low MST score will usually mean someone was more inclined to say old to lures, instead of similar, indicating a tendency to pattern complete instead of pattern separate (Stark et al., 2013).

Hospital Anxiety and Depression Scale. The Hospital Anxiety and Depression Scale is a self-assessment scale that measures psychological symptoms of anxiety and depressive related disorders (Zigmond & Snaith, 1983). This scale is designed with patients in mind, and therefore does not focus on vague symptoms that could be attributed to other diseases such as pain, or

headaches. This scale also focuses on differentiating between anxiety and depressive symptoms which is important considering the high rate of comorbidity between the two. The scale consists of seven questions related to depression and seven questions related to anxiety. Questions are scored on a 4 item Likert Type scale of 0-3, and based on the participant's symptoms within the last week. Scores of seven or less per scale are considered normal, scores of 8-10 are considered borderline, scores of 11-21 are considered abnormal. The present study's A priori analyses focus on depression, and I will consider a score of 8 or above symptomatic.

Pittsburgh Sleep Quality Index. The Pittsburgh Sleep Quality Index is a comprehensive self-assessment survey of overall sleep quality within the past month (Buysse, Reynolds, Monk, Berman & Kupfer, 1989). In addition to a total score, there are seven components that are also measured separately (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) to give a multifaceted evaluation of sleep quality. This scale was designed specifically with clinical populations in mind and was normed using healthy controls compared to depressed and sleep disordered patients. This specificity makes it exceptionally useful for clinical research as a whole, and for the current study. The Pittsburgh Sleep Quality Index is a seven question Likert Type scale from 0-3. Question 5 is compiled of 9 sub questions measured on the same scale.

Perceived Stress Scale. The Perceived Stress Scale is a 10-item questionnaire that assesses self-perceived stress levels within the past month. This scale aims to get away from traditional objective stress measurements such as event type or duration. Instead, it is individually focused and assesses personal perceptions. For example, question number three is "How often have you felt nervous and 'stressed'?" This type of question focuses on the feeling

of stress, as opposed to creating a numeric value to certain, traditionally accepted stressors such as job loss. The scale has an equal number of positively and negatively worded items.

Analysis

Statistical differences were evaluated using correlation and linear regression between LDI and centered HADS depression scores, PSS scores, and PSSQI scores. This model was computed twice once including antidepressant users, and once excluding them. The reason for this differentiation between two models is based on evidence that antidepressant usage can affect hippocampal processing (Rogers et al., 2016). There was no outright exclusion of antidepressant users for two reasons 1) the non-clinical nature of the sample and 2) the lack of available data on type of antidepressant, and length of use. All analyses including demographics were computed using R (R Core Team, 2016); the Pequod package (Mirisola & Seta, 2016) version 0.0-5 was used to compute the models. See Appendix A for complete code.

Results

Group Characteristics

The sample N=164 of undergraduate psychology students was reduced to 155 for analysis. Participants were excluded due to MST errors (N=9, computer and administrator errors) and one participant was excluded as an age outlier (+35) at 56 years old. The included sample had a mean age of 19.8, SD=3.35 and was predominately female at 79%. The second regression model, excluding anti-depressant users, left a sample size of N=147.

Analysis

A linear regression model accounting for HADS depression, PSS scores, and PSQI scores approached significance, F (7,145) = 1.99, p=.06. HADS depression scores were a significant predictor in LDI, beta =-.23, p=.03, as were PSQI scores, beta = .22, p = .03. PSS scores were

not significant when accounting for depression and sleep quality, beta = .01, *p* =.9. This model was run again excluding participants who reported using anti-depressant medication at the time of the evaluations. The model was again marginal but not significant in this reduced sample, F(7,139) = 1.84, *p* =.08. Importantly, HADS depression score was no longer a significant predictor, beta = -.18, *p* =.08, and PSQI played a slightly stronger role in prediction beta = .26, *p* =.01.

Table 1
Prediction Model of Lure Discrimination Index Scores: Anti-Depressant Use Included

Variable	Estimate	Std Err	t.value	Beta	p.value
(Intercept)	0.34805	0.01525	22.82403	NA	0
Depression	-0.01097	0.00509	-2.15606	-0.22712	0.03273*
Stress	0.00031	0.00255	0.12161	0.01269	0.90338
Sleep	0.01248	0.00566	2.20442	0.22272	0.02907*
Depression X Stress	-0.00034	0.00061	-0.55206	-0.06219	0.58175
Depression X Sleep	-0.00132	0.00198	-0.66446	-0.09797	0.50745
Stress X Sleep	0.00042	0.00081	0.52251	0.06011	0.60212
Depression X Stress X Sleep	0.00002	0.00015	0.10358	0.01555	0.91765

Note: R^2= .09 *p*= .06

Table 2
Prediction Model of Lure Discrimination Index Scores: Anti-Depressant Use Excluded

Variable	Estimate	Std Err	t.value	Beta	p.value
(Intercept)	0.34504	0.01552	22.23105	NA	0
Depression	-0.00922	0.00521	-1.76802	-0.18465	0.07925
Stress	-0.00029	0.00265	-0.10917	-0.01154	0.91323
Sleep	0.01493	0.00583	2.55842	0.26346	0.01159*
Depression X Stress	-0.00007	0.00073	-0.09954	-0.01217	0.92085
Depression X Sleep	-0.00132	0.00204	-0.64378	-0.09963	0.52078
Stress X Sleep	0.00055	0.00083	0.65574	0.07849	0.51308
Depression X Stress X Sleep	-0.00002	0.00016	-0.15839	-0.02523	0.87438

Note: R^2=.08 *p*=.08

Discussion

In the present study, I evaluated the potential relationship between depression symptoms, stress, sleep quality, and Lure Discrimination (pattern separation). This study aimed to replicate

the correlation between depression and LDI found by Shelton and Kirwan (2013) and expand on them. Depression symptoms negatively correlated with LDI, even using a different assessment of depression. Our further exploration found that sleep quality was also a significant predictor of LDI performance, stress however was not.

The relationship between sleep and LDI performance is unsurprising given the hippocampal nature of both tasks. PSQI scores were actually the strongest predictor. The relatively healthy nature of our population may help to explain this finding. Sleep deprivation or disturbance is quite common in college students (Hershner & Chervin, 2014) and as mentioned above can often be a precursor to major depressive disorder. Impaired performance on a task like the MST shows the measurable deficits of someone with poor sleep quality. The sleep sensitivity of long term memory performance combined with these results would indicate a need to further investigate. Perhaps the sleep disturbance people with depression often experience accounts for the cognitive problems obsereved in that population.

Although stress was hypothesized to be a predictor of LDI performance, it was not a significant predictor. Unlike depression, and poor sleep however, stress can also cause arousal in the brain. Anxiety, which also causes arousal, has a very unique relationship to pattern separation (Balderston, Mathur, Adu-Brimpong, Hale, Ernst, & Grillon, 2015). A healthy, or manageable amount of anxiety has actually shown an increase in pattern separation performance. This unique relationship would interfere with the model we used, since Anxiety was not investigated. Further, measuring stress linearly may not be the best method when applying it to pattern separation. It is also possible that perceived stress, which was the type evaluated, may not be the best indicator of biological stress that would impact a cognitive process.

One very notable result was that depression was no longer a significant predictor of LDI when the participants with anti-depressant use were excluded from the model (and the strength of this relationship was reduced). There are many reasons why this result exists but the population from which our sample was drawn seems the most likely. Our sample as mentioned was overall young and healthy. They were not a clinically depressed sample, therefore removing those with severe enough depression to be medicated may have reduced the overall depression of the sample too much for the relationship to exist. If this is the case, it suggests also that depression itself and not merely a few of its symptoms is what drives the model. There was no data collected on the type of medication and duration of use, so it is impossible to speculate as to the nature of pharmacological effects in the present study. However, it is important to note that past research has shown an improvement in memory performance in people with depression who use SSRI's (Porter, et al., 2003; Rogers et al., 2016).

Future Research

These data reinforce the results of Shelton and Kirwan (2013) and expand on them using different measures. The limitations of a healthy sample, and limited data on medication use would be more easily addressed in a second study. Further research should reevaluate this model using a clinical sample of people with Major Depressive Disorder. Using a specific, and by definition, ongoing subtype of depression would allow for more in depth investigation of the relationship between depression and pattern separation. For example, a limitation of the current study is that sleep disturbance is not necessarily found in those with depression. In fact, the results of the differing models suggest in our sample, these are different individuals at least concerning those with medication. Using a clinical sample would more accurately investigate sleep disturbance to evaluate whether or not the depression, or the sleep disturbance accounts for

more of the impaired performance on pattern separation tasks. With the current heterogeneous, healthy sample, that is not possible.

The connection has been made between LDI and depression, a clinical sample would allow for more specific questions. In the future, it would also be valuable to separate those with depression from those with depression and anxiety. The two disorders are frequently found to be comorbid. However, when it comes to arousal, and tentatively pattern separation, they are extremely different. Since anxiety can actually improve pattern separation (Balderston et al., 2015) at certain levels it could improve performance in someone with depression. I would hypothesize the performance of someone with depression would be significantly lower than someone with comorbid depression and anxiety. Therefore, to understand the relationship as it relates to depression, those with anxiety should be excluded. Beyond a questionnaire, a medical history remarkable of these two disorders would be required to accurately sort that type of sample.

If this study was repeated on a clinical sample I would expect some things to remain the same and some things to be different. In a non-anxious depressed sample, I would expect sleep disturbance and stress to have a compounding effect on MST performance. It would be reasonable to characterize the sample in terms of four groups 1) Depressed, non-sleep disturbed, non-stressed; 2) Depressed, sleep disturbed, non-stressed; 3) Depressed, non-sleep disturbed, stressed; and 4) Depressed sleep disturbed, stressed. I would expect group four to perform the worst, and group one to perform the best. I would hypothesize that this model would be stronger than the one in the current study. Further, I would predict the moderators would be significant, in particular sleep and depression, giving us a more complete look at how they relate.

Using a clinical sample would help control for levels of depression and I could with more certainty relate the stress and sleep performance with the depression. Prior to the current study, I would have assumed a compounding affect across the board. However, with these results, the effect of stress on depression has to be thought of from additional perspectives. Now, I would hypothesize the level of stress may impact the MST performance differently. For example, a participant with high depression, high sleep disturbance, and moderate stress may benefit from their stress when it comes to MST performance. Therefore, I would go beyond replicating the current study model, and evaluate stress more in depth, perhaps in groups of high, moderate, and low.

Conclusion

The aim of this study was to evaluate the potential relationship between depression, sleep quality, perceived stress, and ability to discriminate lures on the MST. I found that higher levels of depression, and lower levels of sleep quality independently help predict performance on the MST. The evidence did not support a relationship between perceived stress and MST performance, or any moderating effects of the three variables evaluated. There were considerable limitations when it came to the measures, including an overall healthy sample, shallow data in regards to medication, and potential comorbidity of anxiety within the sample. However, these results lay a foundation for further investigation within a clinical sample of cognitively impaired depressed individuals.

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Appendix A

```
##########################################
##########################################
###Thesis Analysis: Multiple Regression###
##########################################
##########################################
#219 10-27-16 8:01 AM is correct participant
#219 10-26 is not a participant RA ERROR#
#234 12-6-16 @11:00 was run on AW2 NOT Pattern Separation#

#################################################
#########Demographics#############################
#################################################
setwd("/Users/jessicarothberg/Dropbox/analysis")
thesis <- read.csv("thesis2.csv")
demog <- read.csv("demog.csv")
as.matrix (names(demog))
demog <- demog[c(11, 15, 16)]
demog.b <- demog[-c(36,128, 100),]
df <- merge(demog.b, thesis, by="sn", all=TRUE)
# 36 was an RA Error duplicate
# 100 was a test non subject
# 128 was am RA Error duplicate
write.csv(df,"demogthesis.csv", row.names=FALSE)
summary(demog.b$age)
sd(demog.b$age)
prop.table(table(demog.b$sex))


##########################################
#######Analysis###########################
##########################################

#Set your working directory#
setwd("/Users/jessicarothberg/Dropbox/analysis")

#import and name your data set#
thesis <- read.csv("demogthesis.csv")

###############################
##Summaries of variables used##
###############################
#A couple outliers (high depression)#
summary(thesis$depscoreHADS)
plot(thesis$depscoreHADS)
boxplot(thesis$depscoreHADS)


#one outlier .88#
summary(thesis$LDI)
plot(thesis$LDI)
boxplot(thesis$LDI)
#
summary(thesis$PSS_total)
plot(thesis$PSS_total)
boxplot(thesis$PSS_total)
```

```
#two outliers on high end#
summary(thesis$PSQITOT)
plot(thesis$PSQITOT)
boxplot(thesis$PSQITOT)

################################
#Edit sample for MST errors, age
#include antidepressants########
################################
thesis.mst <- thesis [-c(2, 8, 9, 89, 93, 126, 135, 141, 153), ]

################################
#centering variables#############
################################
thesis.mst$LDI_Z <- scale(thesis.mst$LDI)
thesis.mst$dep_Z <-scale(thesis.mst$depscoreHADS)
thesis.mst$PSS_Z <- scale(thesis.mst$PSS_total)
thesis.mst$PSQI_Z <- scale(thesis.mst$PSQITOT)


################################
#regression using pquod package#
################################
#pequod package#
library(pequod)


#regression for LDI dep, sleep, stress model1#
model1 <- lm(LDI_Z ~ dep_Z + PSS_Z + PSQI_Z, data=thesis.mst)
summary(model1)
plot(model1)

#################################
#Model 2 with moderator variables#
#################################

#Make moderator variables, can't use Pquod yet because it will do 3 way
automatically
thesis.mst$dep_pss <- scale(thesis.mst$dep_Z) * scale(thesis.mst$PSS_Z)
thesis.mst$dep_psqi <- scale(thesis.mst$dep_Z) * scale(thesis.mst$PSQI_Z)
thesis.mst$pss_psqi <- scale(thesis.mst$PSS_Z) * scale(thesis.mst$PSQI_Z)

model2 <- lm(LDI_Z ~ dep_Z + PSS_Z + PSQI_Z + dep_pss + dep_psqi + pss_psqi,
data=thesis.mst)
summary(model2)
plot(model2)

#####################################
#Model 3 with all moderator variables#
#Model used in paper#################
#####################################
model3 <- lmres(LDI ~ depscoreHADS*PSS_total*PSQITOT, centered =
c("depscoreHADS", "PSS_total", "PSQITOT"), data=thesis.mst)
summary(model3)
```

```
#########################################################
#########################################################
#########################################################
#########################################################
####same process but exlcluding anti-depressant use###
# 9 total participants using antidepressants sn:108, 206, 207
#241, 276, 280, 291, 319, 336#########################
#########################################################
thesis.antid <- thesis [-c(2, 8, 9, 89, 93, 126, 135, 141, 153, 23, 24, 58,
97, 108, 144), ]

################################
#centering variables############
################################
thesis.antid$LDI_Z <- scale(thesis.antid$LDI)
thesis.antid$dep_Z <-scale(thesis.antid$depscoreHADS)
thesis.antid$PSS_Z <- scale(thesis.antid$PSS_total)
thesis.antid$PSQI_Z <- scale(thesis.antid$PSQITOT)

################################
#regression using pquod package#
################################
#pequod package#
library(pequod)


#regression for LDI dep, sleep, stress model1#
model1.b <- lm(LDI_Z ~ dep_Z + PSS_Z + PSQI_Z, data=thesis.antid)
summary(model1.b)
plot(model1.b)



#####################################
#Model 3 with all moderator variables#
#model used in paper##################
#####################################
model3.b <- lmres(LDI ~ depscoreHADS*PSS_total*PSQITOT, centered =
c("depscoreHADS", "PSS_total", "PSQITOT"), data=thesis.antid)
summary(model3.b)


#########################
#TABLES#
#########################
write.csv(data.frame(summary(model3)$coefficients), file="table1.csv")

write.csv(data.frame(summary(model3.b)$coefficients), file="table12.csv")



##SIMPLE CORRELATIONS##
cor.test (thesis.mst$LDI, thesis.mst$depscoreHADS)
cor.test (thesis.mst$LDI, thesis.mst$PSS_total)
cor.test (thesis.mst$LDI, thesis.mst$PSQITOT)
```