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The Relationship between Circadian Dysfunction and Cognitive Impairment in Individuals with Parkinson's Disease

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Abstract

Parkinson's Disease (PD) is a brain disorder associated with a variety of motor (e.g., rigidity, tremor) and nonmotor (e.g., cognitive impairment, sleep dysfunction) symptoms. Recent evidence suggests that PD patients may also have dysfunctional circadian rhythms: oscillators responsible for many behavioral and physiological functions (e.g., sleep-wake cycle, cognitive performance). No study to date has measured both circadian rhythms and cognitive functioning in the same group of PD patients. This was the aim of the current project. The archival data set included 34 PD patients and 12 normal control participants (NC) matched by age and education. Cognition was measured through a series of neuropsychological tests measuring memory and executive functioning. Archival circadian rhythm data, collected through watch actigraphy, was analyzed using three nonparametric variables: relative amplitude (RA), interdaily stability (IS), and intradaily variability (IV). Higher RA and IS values indicate a more stable rhythm, while higher IV values indicate a less stable rhythm. Patients with PD had significantly higher RA values than NCs; however, there was no significant difference between PDs and NCs in IS or IV values. There was a significant positive correlation between executive functioning and RA and IS values in PDs. No significant correlations were found between executive functioning and IV values or between working memory and RA, IS, or IV values among PDs. This preliminary evidence suggests that disrupted circadian rhythm in PD patients may be related to cognitive impairment. Future research should investigate this potential link by using additional and more sophisticated circadian rhythm measures. This, in turn, could shed more light on the role circadian rhythm dysfunction plays in the cognitive impairment of PD patients and thus, highlight the potential need for new treatment and intervention strategies aimed at improving the quality of life of these individuals.

The Relationship Between Circadian Dysfunction and Cognitive Impairment in Individuals with Parkinson's Disease

Parkinson's disease (PD) is an incurable neurodegenerative brain disorder. Approximately one million Americans have PD; about 40% developed the disease between the ages of 50 and 60 (National Parkinson's Foundation, 2015; Parkinson's Disease Foundation, 2015). Although the cause of PD is unknown, the pathology of the disease is associated with the death of dopamine neurons (National Parkinson's Foundation, 2015). PD symptoms are characterized by both motor (e.g., tremor, rigidity, abnormalities of movement) and non-motor (e.g., cognitive impairment, sleep abnormalities) impairments (Rodriguez-Oroz et al., 2009); however, diagnosis is based on the presence of motor symptoms (National Parkinson's Foundation, 2015). Non-motor symptoms (NMS) are the biggest factor in determining a PD patient's quality of life (Martinez-Martin, 2011). Despite their significance, NMS are often overlooked by clinicians and researchers (Chaudhuri, Odin, Antonini, Martinez-Martin, 2011), making them an important area of focus for future research efforts.

Evidence suggests that PD patients may also have dysfunctional circadian rhythms (Willison, Kudo, Loh, Kuljis, & Colwell, 2013; Videnovic & Golombek, 2013). Circadian dysfunction

results in a variety of widespread symptoms in the general population, including cognitive impairments, metabolic abnormalities, and sleep/wake/arousal disturbances (McDonald, 2002), similar to many of the NMS observed in PD. One question, therefore, concerns whether the NMS seen in PD occur due to circadian dysfunction. Although a theoretical link exists between circadian dysfunction in PD and NMS (Willison et al. 2013; Videnovic & Golombek, 2013), few studies have explicitly examined this relationship. Because of the important role cognitive functioning plays in life's most basic functions, of interest to this study will be its potential relationship to circadian dysfunction in PD, specifically executive functioning and memory, two areas of cognitive impairment which have also been directly linked to the circadian system (Valdez, Reilly, & Waterhouse, 2008).

Cognitive impairments are seen in approximately 19%-38% of newly diagnosed, untreated PD patients (Dirnberger, & Jahanshahi, 2013). Some studies have shown executive functioning and memory to be the cognitive areas where PD patients show the most impairment (Verbaan et al., 2007). Executive dysfunction, in particular, may be the most documented cognitive impairment in PD (Dirnberger & Jahanshahi, 2013). It is imperative for functioning in daily life, particularly in non–routine tasks that require inhibitory control and conflict resolution. Working memory is considered part of executive functioning and is broken down into two components which consist of visuospatial (visual) and phonological (verbal) systems (Valdez et al., 2008). Working memory's functions are essential for many of life's daily tasks (e.g., speech, reading and writing, processing images; Valdez et al., 2008). PD patients also exhibit deficits in recognition and recall memory (Whittington, Podd, & Stewart-Williams, 2006). Recall memory is accessing memories previously stored in the brain, and recognition memory is associating an event or an object with a previous experience; impairment in either of these can lead to a significant decline in quality of life. While executive functioning and memory impairments have been well-documented in PD, they have also been directly linked to the circadian system.

The circadian system is made up of oscillators throughout the brain and body and is responsible for many behavioral and physiological functions (e.g., sleep-wake cycle, endocrine and autonomic systems, neurotransmitter activity, task performance) and processes (Hofstra & de Weerd, 2008). The central clock of the circadian system, found in the suprachiasmatic nucleus (SCN) of the hypothalamus, is responsible for regulating these independent oscillators of the circadian system (Shanahan & Czeisler, 2000). Disruption of this system is thought to have widespread implications, many of which overlap with the NMS seen in PD patients (e.g., sleep-wake disturbance, cognitive and psychiatric deficits, cardiovascular problems). Because of this overlap, coupled with the knowledge that NMS are present well before motor symptoms, it has been hypothesized that circadian dysfunction is not merely a byproduct of other PD symptoms, but instead a core component of PD pathology (Willison et al., 2013).

In normal functioning, the circadian system has been linked to specific cognitive functions such as recognition and recall memory (processed by the hippocampus), with evidence pointing to an important relationship between the SCN and the hippocampus (Smarr, Jennings, Driscoll, & Kriegsfeld, 2014), and executive functioning (processed by the prefrontal cortex). For instance, both types of working memory, verbal and visual, have been documented as having circadian rhythms, with the lowest level of performance occurring early in the morning (4:00-7:00 am), and highest performance seen in the early afternoon. (Valdez et al., 2008). The circadian system is thought to run on an approximately 24.3 hour cycle in humans (Waterhouse, 2010), with cognitive functioning levels paralleling other circadian processes such as arousal/alertness, rest/activity levels, and the sleep/wake cycle. In other words, a person with circadian dysfunction may exhibit lower levels and duration of peak activity and arousal than those with normally functioning circadian rhythms, and because levels of cognitive performance tend to run parallel to these parameters, that same individual is more likely to experience impairments in cognitive functioning. While there is research to suggest there are links between circadian disruptions and cognitive performance, there has yet to be a study that objectively measures circadian rhythm and cognitive performance in PD patients.

This is the aim of the present project.

In the present project, archival data in Boston University's Vision and Cognition Laboratory were used to examine the relationship between circadian disruptions and cognitive impairment in working memory and executive functioning in PD and control participants. Hypotheses for this project include the following: 1) PD patients, when compared to healthy control participants, will perform more poorly on a series of cognitive assessments; 2) PD patients, when compared to healthy control participants, will show less stable circadian rhythm patterns; and 3) less stable circadian rhythms among PD patients will be correlated with poorer performance on the cognitive assessments.

Method

Participants

This project examined archival data from a prior study of 34 non-demented individuals with PD (21 men and 13 women) and 12 normal control (NC) participants (6 men and 6 women). PD patients were recruited from the Movement Disorders Clinic at the Boston University School of Medicine and control participants from the local community. All participants gave informed consent and were matched for age (PD: M = 66.38, SD = 7.9; NC: M = 62.17, SD = 9.3), t(44) = -1.52, p = .14, and education (PD: M = 16.71, SD = 2.4; NC: M = 17.17, SD = 2.4) t(44) = .57, p = .57. This study was approved by the Boston University IRB.

Measures and Procedures

Participants wore Actiwatch AW-64 wrist actigraphs for a continuous period of one week in order to extract real-time rest-activity data. From this, circadian rhythm parameters were derived using MotionWare software (CamNtech, Cambridge, UK) and analyzed using SPSS (IBM Corp, 2013). Three non-parametric variables were used to measure circadian rhythm: relative amplitude (RA), interdaily stability (IS), and intradaily variability (IV). For executive functioning, the neuropsychological tests used included digit span backwards, Trail Making Test B, Stroop Color-Word Test,

verbal fluency (FAS and category-animals), and RUFF figural fluency. For recognition and recall memory, tests included the California Verbal Learning Test-II (CVLT-II) and the Brief-Visual Memory Test (BVMT). Each measure is described in more detail below.

Circadian rhythm measures actiwatch AW-64. An actigraph worn on the wrist was used to monitor activity levels in participants for sleep, circadian rhythms, pain, drug response, or many other applications. Participants wore the actigraph, continuously, for one week. The Actiware 5.3 (Mini-Mitter) software was used to organize and analyze data gathered from the Actiwatch AW-64. To extract and analyze circadian rhythm data from the actigraph data, three non-parametric measures were chosen based on their utilization and validation in previous studies: interdaily stability, intradaily variability, and relative amplitude (Whitehead, Davies, Playfer, & Turnbull, 2008; Goncalves, Cavalcanti, Tavares, Campos, & Araujo, 2014; Goncalves, Adamowicz, Louzada, Moreno & Araujo, 2015).

Interdaily Stability (IS) is used to measure how synchronous the rest/activity patterns are between individual days. To calculate IS, the variance of the average daily rest/activity profile of each participant is divided by the total rest/activity variance (Goncalves, Adamowicz, Louzada, Moreno & Araujo, 2015). A higher IS value indicates a more stable rhythm. Intradaily Variability (IV) is used to indicate the fragmentation of rest/activity rhythms through measurement of how frequent and to what extent the transitions from rest periods to activity periods are in each 24 hour period. IV is calculated by the ratio of the means squares of the first derivative and its population variance (Goncalves, Cavalcanti, Tavares, Campos, & Araujo, 2014). Higher IV values indicate more frequent and/or larger transitions and therefore a less stable rhythm. Relative Amplitude (RA) is the ratio of the most active 10 hours to the least active 5 hours in an average 24-hour period. A higher RA value indicates a more stable rhythm. RA is thought to give an even more comprehensive embodiment of amplitude than other non-parametric measures (Hatfield et al., 2004).

Executive Functioning Measures.

Digit Span Backward. In this task, the experimenter reads a

string of digits and the participant then immediately repeats them in reverse order . There are two sets of numbers per series length. Once the set of numbers is repeated correctly, the tester moves on to the next set. The total score corresponds with the longest number of digits repeated backwards correctly.

Trail Making Test B. This task consists of 25 circles distributed over one sheet of paper (Reitan, 1958). The circles are alphanumeric, with numbers ranging from 1-13 and letters ranging from A-L. The participant is asked to draw a line connecting each circle in an ascending order, while alternating numbers and letters (1-A-2-B-3-C…). The final score is based on the time necessary to complete the test.

Stroop Color-Word Test. In this task (Stroop, 1935), the participant is asked to name the color of the word that is on a piece of paper; for instance, the word "blue" may be printed in red ink. The correct answer would be "red" in this particular example. Scoring is dependent on how many colors the participant is able to correctly name within 45 seconds. The Stroop interference score is calculated by the difference in delay times of naming incongruent and congruent colors on the color-word test. A lower score indicates less interference when faced with incongruent words.

Verbal Fluency Task (FAS and Category-Animals). In this verbal fluency test (Delis et al, 2001; Delis et al., 2004), individuals are given three one minute time periods to come up with as many words beginning with each of the letters F, A, and S (FAS) and as many animals (Category-Animals) as they as the can in a one minute period. This is an executive function task in which the number of words and clustering, (using similarly sounding words), are measured.

Ruff Figural Fluency. In the Ruff Figural Fluency Test (RFFT), each participant is given a test booklet with 5 different timed parts. The participant is asked to draw as many unique designs as he or she can within 60 seconds for each of the 5 parts, by connecting dots in different squares provided in each section. Results are measured by how many unique designs are created by the participant (Ruff et al., 1987).

Recognition and Recall Memory Tests.

California Verbal Learning Test-II (CVLT-II). Different parts of this test measure different aspects of memory (Delis et al., 2000). For immediate recall, 16 words from 4 categories are presented to the participant. Each person is then asked to remember as many as possible in 5 consecutive efforts. For long recall, after 20 minutes have passed, the participant is asked to recall as many words as possible from the list of 16 originally presented to him or her. Finally, in the recognition trial, the participant is shown a list of words and asked which ones were on the original list.

Brief Visuospatial Memory Test (BVMT). In three learning trials, the participant is given a recall stimulus page with six geometric figures to look at for ten seconds (Cherner et al., 2007). The individual is then asked to draw as many of the figures as he or she can. After 25 minutes, the task is repeated. The participant is then asked to identify which of the 12 figures were included in the six geometric figures on the original recall stimulus page.

Data Analysis

Summary scores in each cognitive domain (executive functioning, working memory) were calculated by using z-scores based on the means of NCs from each neuropsychological test and then averaging them. PD and NC performance was then analyzed using a series of between group t-tests. For each t-test, group was the independent variable and summary scores for either cognitive domain were the dependent variables. The two groups were also compared on the three non-parametric circadian rhythm variables using t-tests mentioned above. Correlational analyses were used to examine the relationship between cognitive performance and circadian rhythm performance for each group.

Results
Cognitive Assessments

Independent samples t-tests were performed to examine group differences on individual cognitive assessments given to participants, as well as summary scores calculated for two cognitive

domains (executive functioning and working memory; see Table 1). Consistent with this study's hypothesis, analysis of cognitive task results revealed that PD patients performed significantly more poorly than NCs on multiple measures, including overall summary scores for executive functioning and working memory. Specifically, PD patients performed more poorly on the FAS letter and category fluency tests, trail making test B, Ruff figural fluency test, Stroop color word, CVLT-II total learning test, CVLT-II short delay test, CVLT-II long delay test, BVMT total learning test, BVMT long delay test, and BVMT recognition test. Significant differences in test results were not found between groups on the WAIS-III digit span backwards test, Stroop interference, or CVLT-III recognition test.

Circadian Rhythm Assessments

Independent samples t-tests were also performed to examine group differences with respect to the variables chosen to measure circadian rhythm stability (i.e., RA, IS, and IV). Results from circadian rhythm measures only partly supported the hypothesis that PD patients would show less stable rhythms than the NC group. Analysis showed a statistically significant difference in RA values between NC (M = .94, SD = .03) and PD (M = .88, SD = .10) groups, t(44) = 1.87, p < .007 (see Figure 1). There was not a statistically significant difference shown in IV values between NC and PD groups; t(44) = .60, p = .55, nor was there a statistically significant difference found in IS values between NC and PD groups; t(44) = 1.76, p = .09.

Correlations between Circadian Rhythm and Cognition

Pearson correlation tests were performed to examine the relationship between circadian rhythm dysfunction in PD patients, as measured by the circadian variables RA, IS, and IV; and executive functioning and working memory summary scores among PD patients. Results only partially supported my hypothesis that less stable circadian rhythms would be correlated with poorer performance on cognitive assessments.

There was a positive correlation between summary scores for executive functioning (M = -.57, SD = .61) and RA values (r = .41 p < .02; see figure 2); as well as IS values (r = .35 p < .04). No significant correlation was found between the PD group's executive functioning summary scores and IV values among PDs (M = .02, SD = .09) (r = -.02 p = .92).

There was not a significant relationship seen between working memory summary scores (M = -.92, SD = .77) and RA (r = .14 p = .43); IS (r = .12 p = .49); or IV values (r = .05 p = .78).

Discussion

This study examined the potential relationship between circadian rhythm dysfunction and cognitive impairment. The first hypothesis, stating that PD patients would perform more poorly than NCs on cognitive assessments, was mostly consistent with previous literature. PD patients performed more poorly on the majority of cognitive assessments, including summary scores for both executive functioning and working memory. Executive functioning deficits in PD patients has been widely evidenced in the literature (Zgaljardic et al., 2006; Verbaan et al., 2007; Stavitsky, Neargarder, Bogdanova, McNamara, and Golomb, 2011;Dirnberger & Jahashahi, 2013), while multiple studies have found evidence of PD patients having deficits in both executive functioning and working memory (McKinlay, Grace, Dalrymple-Alford, & Roger, 2010; Varanese, Perfetti, Ghilardi, & Di Rocco, 2011). PD patients showed poorer performance than NCs in the current study on Stroop color-word and Ruff figural fluency, which is consistent with the study by Miller and colleagues (2013), while they also performed more poorly on three of the four CVLT-II assessments, similar to deficits seen in CVLT-II assessment results from PD patients in Varanese and colleagues (2011) study.

The second hypothesis predicted that PD patients would exhibit less stable circadian rhythms than NCs. This hypothesis was only partially supported, as PD patients showed a less stable rhythm in terms of RA, but not in terms of IS or IV values. This is inconsistent with some of the literature. For example, as in the current study, RA values were shown to be lower (less stable) in PD patients than healthy controls in Whitehead and colleagues (2008)

study; however, in the same study, they also found that PD patients showed significantly higher IV values than healthy, age-matched controls, unlike what was found in the present study. Because there is a lack of research into circadian dysfunction in PD patients, it is not possible to understand definitively why this difference in IV exists. However, it has been shown that IV can be higher in older adults and is also more likely to be affected by age-related changes than the other variables used in this study (Huang et al., 2002). The mean age of PD patients in this study was 66.38 and the mean age of healthy controls was 62.17, while the mean age of PD participants in Whitehead and colleagues (2008) study was 73.36 and the mean age of healthy controls was 70.90. Whether or not PD patients have a higher likelihood of increased IV values (i.e., a more fragmented rhythm) as they age compared to similarly-aged healthy adults, and hence explains the different results, is worth examining. In addition, the disease could have progressed further in the PD patients from Whitehead and colleagues' (2008) study, than in the current one due to the age differences, possibly accounting for the difference in IV values. Because Whitehead and colleagues' (2008) study was the only one found examining PD patients' circadian rhythms using non-parametric methods, additional studies examining the age-related differences in IV values of PD patients is warranted.

There was not a significant difference in IS values between the PD and NC groups, which is consistent with much of the literature using nonparametric methods. For example, although Whitehead and colleagues (2008) found a significant difference in IV, there was not a significant difference in IS between the groups. This is also consistent with findings that IS is not affected by age. In fact, it has been shown that older adults often have higher, and therefore more stable, IS values (Huang et al., 2002). It has also been suggested that the regularity in which PD patients often have to take their medications and/or get treatment may act as additional zeitgebers, synchronizing agents for the circadian system (e.g., sleep/wake cycle, light/dark cycle, meal times). This, in turn, could make their days more synchronous, stabilizing IS values (Whitehead et al., 2008).

The third hypothesis, that a less stable circadian rhythm would be correlated with poorer performance on cognitive assessments among PD patients, was only partially supported as well. RA and IS were positively correlated with executive functioning summary scores, however, IV was not correlated with executive functioning. In addition, working memory was not correlated with RA, IS, or IV. A possible explanation for this could be that working memory could be less affected by disruptions in circadian functions than other executive tasks.

Limitations

One limitation of this study is of the inability to control exogenous factors such as meal times, light exposure, and schedule of activities, which can all act as zeitgebers and have an effect on the entrainment of circadian rhythms. Although not practical, an ideal study would control all of these factors. Suggested methods for this include a forced desynchrony protocol in which participants sleep for very long or short cycles, designed to bring out the circadian system's free running period. Other methods used include constant routine, bed rest, and multiple nap protocols (Wirz-Justice, 2007). Past studies examining circadian rhythm have also looked at variables such as melatonin secretion and core body temperature to measure circadian rhythm (Kräuchi, 2002; Bordet et al., 2003; Weinert & Waterhouse, 2007). Using these additional variables in order to strengthen the validity of circadian rhythm analysis would lend more strength to the current and future findings.

Conclusion

The present study examined the relationship between circadian rhythm dysfunction and impairments in executive functioning and working memory in PD patients. PD patients performed significantly more poorly in both cognitive domains. They also showed a less stable rhythm in terms of RA, but not in IS or IV. Among PD patients, RA and IS were positively correlated with executive functioning. Preliminary evidence from this study suggests that disrupted circadian rhythm in PD patients could be related to cognitive impairment. Gaining a better understanding of the role

Table 1. Cognitive performance of NC and PD groups.

	NC (*n* = 12)	PD (*n* = 34)	Significance
Executive Functioning Summary Score	-.007 (.43)	-.57 (.61)	.005
Verbal			
Letter Fluency (FAS)	57.58 (11.68)	39.50 (10.29)	.001
Category Fluency	54.92 (13.31)	45.03 (10.69)	.013
WAIS-III Digit Span Backward	9.16 (2.85)	7.79 (2.43)	ns
Visual			
Trail Making Test B (seconds)	65.20 (17.51)	119.0 (64.14)	.001
Ruff Figural Fluency	90.42 (23.28)	75.67 (16.25)	.021
Stroop Interference (index score)	-4.86 (6.36)	-4.28 (5.98)	ns
Stroop Color Word	39.08(8.43)	31.09(9.86)	.017
Working Memory Summary Score	.055 (.47)	-.918 (.76)	.001
Verbal			
CVLT-II total learning	57.42 (10.41)	42.81 (13.09)	.001
CVLT-II short delay	12.25 (2.96)	8.28 (3.25)	.001
CVLT-II long delay	12.5 (3.58)	9.37 (3.69)	.016
CVLT-II recognition	14.67 (1.50)	14.09 (1.78)	ns
Visual			
BVMT total learning	24.0 (6.51)	16.5 (6.55)	.002
BVMT long delay	9.67 (2.87)	7.31 (3.23)	.032
BVMT recognition	6.0 (0.0)	5.12 (.91)	.001

Note: Means (SD) are reported. NC= normal control; PD = Parkinson's diseaee; TMT = Trail Making Test; WAIS-III = Wechsler Adult Intelligence Scale III; CVLT-II = California Verbal Learning Test-II; BVMT = Brief Visual Memory Test; ns = not significant

circadian rhythm may play in cognitive impairment is important due to the negative impact both can play in an individual's quality of life.

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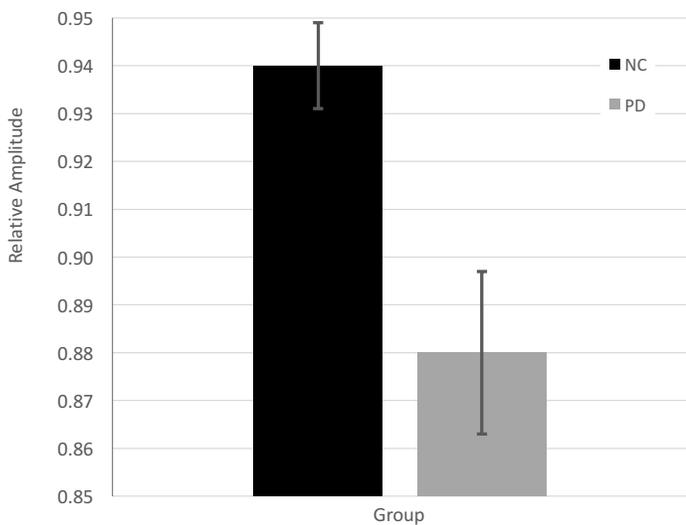
Figure 1. Bar graph displaying the difference in relative amplitude (RA) between participant groups. PD patients had significantly lower RA values ($M = .88$, $SD = .10$) than NCs ($M = .94$, $SD = .03$). A lower RA value suggests a less stable circadian rhythm.
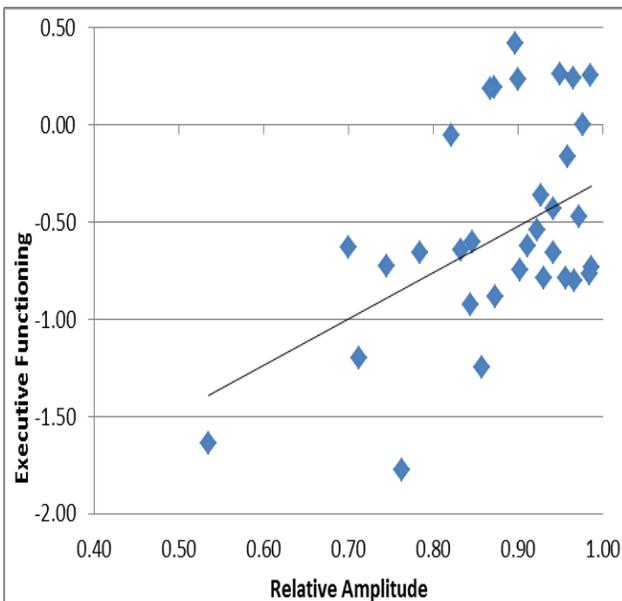

Figure 2. Scatterplot of relative amplitude (RA) and executive functioning summary scores. Results showed a significant positive correlation between the two variables ($r = .41$ $p < .02$)

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