Top Lang Disorders
Vol. 42, No. 3, pp. 193–211

Is There a Relationship Between Cortisol and Treatment Response in Chronic Aphasia?

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Purpose: To evaluate whether levels of cortisol, a stress-related hormone, predicted response to intensive speech–language intervention for individuals with chronic aphasia (IWA). Secondary analyses explored baseline cortisol levels, change following intervention, association between cortisol levels and aphasia severity, self-reported communicative distress, and chronic stress. **Method:** Afternoon salivary cortisol levels were measured in 14 IWA during the first and last weeks of a 4-week intensive speech–language intervention epoch. Behavioral outcome measures were collected pre- and postintervention. **Results:** Cortisol levels did not significantly predict treatment response in this sample of IWA, although a positive trend was present. Baseline cortisol levels were not abnormally elevated, did not change from pre- to postintervention, and were not significantly correlated with any of the behavioral outcome measures. **Discussion:** Although afternoon salivary cortisol levels did not robustly predict treatment response in this participant sample, future studies may be warranted that include IWA with elevated levels of cortisol at pretreatment.
Key words: *aphasia*, *biomarker*, *cortisol*, *predictors*, *treatment*

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Michelle Gravier discloses that she received a Competitive Pilot Project Award from the Veterans Health Administration VISN 4. Authors William D. Hula and Michael Walsh Dickey disclose that they received a VA Merit Award #I01RX000832. Jeffrey P. Johnson and Alyssa Autenreith have indicated that they have no financial and no nonfinancial relationships to disclose.

Author disclosures can be found at http://links.lww.com/TLD/A91.

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DOI: 10.1097/TLD.0000000000000291

INDIVIDUALS WITH APHASIA (IWA) following stroke experience higher levels of stress compared with their neurologically intact same-aged peers (Laures et al., 2003; Warner, 2010) and stroke survivors with no aphasia (Laures-Gore, 2012; Mitchell et al., 2017). This has often been attributed to the "linguistic anxiety" experienced by IWA associated with the expectation of errorful language production (Cahana-Amitay et al., 2011). In these studies, increased levels of stress have been documented via subjective patient report of perceived stress as well as objective physiological measures of stress (Laures-Gore et al., 2007). One commonly used physiological measure of stress is *cortisol*, a stress-related hormone (Bozovic et al., 2013; Hellhammer et al., 2009). Although under normal conditions cortisol levels follow a diurnal cycle, with peak levels reached shortly after awakening, followed by a decrease in levels throughout the day, chronic

stress can result in alterations in this cycle including cortisol levels that remain elevated throughout the day (van Eck et al., 1996; van Eck & Nicolson, 1994). Chronically elevated levels of cortisol can have a negative impact on cardiovascular health, contribute to impaired cognition, and exacerbate other psychological conditions such as depression, among other potential consequences (Lupien et al., 2007; McEwen & Seeman, 1999; Whitworth et al., 2005).

Importantly, elevated levels of cortisol have been shown to interfere with long-term potentiation (LTP), the mechanism by which synaptic connections are strengthened resulting in greater neural efficiency and, thereby, learning (Dinse et al., 2017; Sale et al., 2008). Language recovery for IWA, particularly in the chronic stage, is argued to rely on neuroplastic changes supported, in part, by LTP (Basilakos et al., 2022; Kiran & Thompson, 2019). As such, many speech–language interventions for aphasia incorporate principles of experience-dependent neuroplasticity known to induce LTP in order to maximize potential treatment-related gains (Crosson et al., 2019; see Kleim & Jones, 2008, for a review of these principles). For example, greater treatment intensity, the amount of practice per unit of time, has been shown to enhance neuroplasticity. This principle is one of the main proposed mechanisms of action of intensive aphasia therapy programs, typically defined as those providing at least 9 hr of therapy per week (Cherney et al., 2011; Pulvermüller & Berthier, 2008; Raymer et al., 2008). Supporting this idea, a recent meta-analysis found that the greatest clinical gains in overall language function and functional communication were associated with speech–language therapy provided at least 3 days per week (Brady et al., 2022). Furthermore, noninvasive brain stimulation approaches, such as repetitive transcranial magnetic stimulation that can induce LTP-like durable neuroplastic changes, are increasingly being studied as an adjuvant to aphasia therapy, with promising outcomes (Crosson et al., 2019; Saxena & Hillis, 2017).

Although speech–language intervention is effective (Brady et al., 2016), individual treatment response among IWA varies, even for those receiving intensive therapy (Code et al., 2010; Gravier et al., 2018; Pompon et al., 2017). A recent systematic review of individual participant responses to intensive interventions for aphasia reported that only a third of the participants showed a minimally detectable change at study exit (Menahemi-Falkov et al., 2021). Although the factors that contribute to this variability are likely numerous, and have been the subject of much recent attention (Doogan et al., 2018; Johnson et al., 2019), many of them, such as age and lesion size, are unmodifiable. On the other hand, factors that may contribute to an individual's neuroplastic capacity, such as cortisol levels, *are* modifiable. Mindfulness interventions, for example, have been shown to lower cortisol levels in patients with elevated cortisol levels with a previous cancer diagnosis (Bränström et al., 2013). Similarly, music therapy has been shown to lower cortisol levels in patients on hemodialysis, with a significantly lower 5-year mortality rate among patients who experienced greater decreases in cortisol levels compared with those with smaller decreases, highlighting the impact that lowering elevated cortisol levels may not just have on neuroplasticity but also overall health and wellness (Hou et al., 2017). As noted previously, given that IWA report higher levels of chronic stress on average, it may be the case that cortisol levels may be contributing to treatment response variability, with elevated levels resulting in less robust treatment effects.

No studies to date, to our knowledge, have investigated whether pretreatment (baseline) cortisol levels predict response to speech–language treatment in IWA, although one study has measured the effect of treatment on cortisol levels. Sharp et al. (2013) reported that significantly more IWA receiving an intensive aphasia treatment (5 days per week for 2.5–3 hr per session) had an increase in salivary cortisol from entry to the 1-week treatment mid-point, compared with an IWA

control group receiving traditional treatment (3 days per week for 45- to 60-min sessions). However, at the end of 2 weeks of treatment, there were no differences in cortisol levels between the two groups. The authors did not report whether cortisol values fell outside of the typical range, and participant-level data were not provided.

The usefulness of cortisol as a biomarker of chronic stress in IWA has received somewhat more attention. Based on the hypothesis that greater aphasia severity would be related to greater stress levels in IWA, Laures-Gore. (2012) measured salivary cortisol levels every 2 weeks for 10 weeks in IWA who were less than 6 months postonset of aphasia at the beginning of the study. No relationship was found between aphasia severity and salivary cortisol levels, and there were no significant group-level changes in cortisol levels over time despite improvements in aphasia severity. Although not statistically significant, there was a trend toward higher baseline salivary cortisol levels in the IWA for whom the study was initiated later postonset (>2.03 months) compared with those for whom it was initiated earlier, which the authors later suggested may have been due to increased awareness over time of the impact of aphasia on daily life (Laures-Gore & Buchanan, 2015). However, a later study from this group failed to find an association between salivary cortisol and either self-reported stress throughout the day or self-reports of chronic stress (Laures-Gore et al., 2019). Hunting Pompon et al. (2018) measured the association between self-report measures of stress in IWA and cortisol, using a novel method of evaluating cortisol levels in hair samples, and also found no significant association. Interestingly, none of the participants in this study had cortisol levels that exceeded the normal reference range despite some reporting moderate to high levels of chronic stress.

Other studies have focused on cortisol reactivity, the cortisol response to acute stressors, in IWA. Language tasks have been shown to induce other stress responses in IWA such as increased heart rate, respiratory rate, and skin conductance (Cahana-Amitay et al., 2015; Chih et al., 2021). Across a series of studies in which IWA were asked to perform a linguistic task (either an auditory vigilance task or speaking to an unfamiliar individual about their profession prior to their stroke, a task similar to the Trier Social Stress Test that is the standard protocol for inducing the psychosocial stress response; see Birkett, 2011 for details), IWA had similar cortisol reactivity as nonneurologically impaired control participants, despite reporting higher levels of perceived stress (Laures et al., 2003; Laures-Gore et al., 2007; Laures-Gore et al., 2010).

In sum, given the high prevalence of chronic stress among IWA, the stress hormone cortisol may play a role in contributing to treatment response variability by interfering with neuroplasticity when chronically elevated. However, this hypothesis has yet to be directly tested. Furthermore, findings regarding the prevalence of elevated cortisol in IWA are mixed, and the relationship between salivary cortisol levels and other psychosocial measures of stress remain underexplored. Given that evidence-based interventions to lower cortisol levels are relatively easily accessible, positive evidence that cortisol levels are associated with aphasia treatment response would support recommendations that IWA engage in these activities to maximize potential benefits of speech–language intervention. Furthermore, evidence that cortisol levels are associated with IWA's response to intensive aphasia treatment specifically would strengthen the hypothesized link between cortisol levels and LTP-like changes induced by intensive intervention (Basilakos et al., 2022; Crosson et al., 2019; Kiran & Thompson, 2019; Kleim & Jones, 2008).

Therefore, the primary aim of this study is to investigate whether levels of salivary cortisol predict response to intensive speech–language intervention. Secondarily, this study seeks to add to the evidence base surrounding the prevalence of elevated cortisol in IWA and the effect of intensive treatment on cortisol levels in IWA. Finally, this study follows a combined approach, as suggested

in the study by Laures-Gore and Buchanan (2015), by combining physiological (salivary cortisol levels), subjective (self-report measures of communicative distress and chronic stress), and behavioral measures (aphasia severity) to better understand the potential interactive effects in IWA.

METHODS

Participants

Fifteen IWA due to left-hemisphere stroke participated in this study. All participants receiving intensive speech–language treatment in the Pittsburgh Intensive Residential Aphasia Treatment and Education (PIRATE) program from October 2017 through September 2019, who indicated on their intake form that they were interested in learning about research opportunities, were screened for eligibility. Eligible participants were at least 18 years of age, at least 6 months postaphasia onset, with no reported history of neurodegenerative disease or neurological disorder aside from stroke. If screening criteria were met, the participants were contacted via their indicated preferred method (email or phone) and the study procedures were explained. Subsequently, written informed consent was obtained in person. One participant withdrew from the study prior to completion due to having to leave the area for personal reasons. No participants withdrew for reasons related to the study procedures. Although not included in the eligibility criteria, upon review of medical records, none of the participants were taking a prescribed corticosteroid medication at the time of study participation (e.g., prednisone). All study procedures were approved by VAPHS IRB (protocol Pro0475). Participant demographics for the 14 participants who completed the protocol are summarized in Table 1. Notably, as all PIRATE program participants are US military Veterans, and consistent with the Veteran population in general, a majority of the participants were male (13 males, 1 female). Gender has been linked to cortisol reactivity, with males typically exhibiting greater salivary cortisol responses following stressors than females (Smyth et al., 2013), and therefore

Table 1. Participant demographics

Participant	Age (Years)	Gender	Education (Years)	Handedness[a]	MPO
P1	67	M	14	R	54
P2	69	M	12	R	9
P3	69	M	12	R	6
P4	51	M	16	R	10
P5	31	M	14	L	29
P6	74	M	14	L	27
P7	69	M	12	R	7
P8	71	M	12	R	64
P9	41	M	20	R	43
P10	54	M	16	R	6
P11	44	M	16	R	42
P12	62	M	13	R	19
P13	58	M	14	R	20
P14	52	F	13	R	59
$N = 14$	$M = 58$, $SD = 13$	13 M; 1 F	$M = 14$, $SD = 2$	12 R; 2 L	$M = 28$, $SD = 21$

Note. MPO = months post onset of aphasia.
[a]Participant self-reported primary premorbid handedness: R = right, L = left.

some prior studies of cortisol reactivity in aphasia have elected to exclude female participants (Laures et al., 2003). In this study, in an effort to be as inclusive as possible, the participant was not excluded, but salivary cortisol data were evaluated for outliers.

Procedures

Assessment

As part of participation in the PIRATE program, the participants were assessed with a core battery of standardized speech and language measures including the Comprehensive Aphasia Test (CAT; Swinburn et al., 2004) and the Burden of Stroke Scale (BOSS; Doyle et al., 2004). The CAT contains a language battery that assesses performance in six domains (comprehension of spoken language, comprehension of written language, repetition, spoken language production, reading aloud, and writing), each of which yields a subscale T-score. The CAT *mean modality T-Score* (MMT; average of the language battery subscale T-scores) is a measure of overall aphasia severity and served as the primary language outcome measure to assess treatment response. The BOSS is a patient-reported health status assessment designed to quantify the burden of stroke across physical, cognitive, and psychological domains. The Communication Distress subscale is a sensitive measure of patients' stress regarding their communicative competence and their participation in communicative activities (Doyle et al., 2004). As noted previously, these types of psychosocial stressors are commonly associated with elevated cortisol levels (Birkett, 2011). The subscale consists of three questions all beginning with the phrase "How often do your difficulties communicating . . . ": (1) " . . . cause you to feel anxious, unhappy, or frustrated?," (2) "feel dissatisfied with yourself or your life?," and (3) "prevent you from doing the things in life that are important to you?" Responses are given on a 5-point scale from 1 "Not at all" to 5 "Completely," yielding a potential total score ranging from 3, indicating no communicative distress, to 15, indicating high levels of communicative distress.

An additional measure, the Modified Perceived Stress Scale (mPSS; Hunting Pompon et al., 2018) was administered to study participants to measure self-perceived levels of chronic stress, not limited specifically to communicative distress. The mPSS is an adapted form of a widely used self-report measure of chronic stress, the Perceived Stress Scale (PSS; Cohen et al., 1983) that uses simplified language and graphical supports to increase validity for IWA. The mPSS consists of 10 questions relating to perceived stress over the past month (e.g., item no. 6 "In the last month, how often have you felt you could not cope with all you had to do?") to which participants are asked to respond on a 0 ("Never") to 4 ("Very Often") scale. Hence, the potential total score ranges from 0, indicating lowest levels of perceived stress to 40, indicating the highest levels.

All assessments were administered at both program entry and exit (at least 3 weeks apart). See Table 2 for a summary of participant performance on the behavioral outcome measures.

Speech–language intervention

The PIRATE program is an intensive comprehensive aphasia program (for a thorough description, see Winans-Mitrik et al., 2014). Briefly, cohorts of 2–4 Veterans travel to Pittsburgh for the 4-week duration of the program and are provided with community housing and transportation (veterans residing in the local area are given the option to opt out of the housing and arrange their own transportation). The first $2\frac{1}{2}$ days are dedicated to program orientation and entry assessment, and the final $2\frac{1}{2}$ days are dedicated to exit assessment and program wrap-up. During the remaining program weekdays, the participants in the current study received 3 hr of individualized speech–language intervention during the morning session, from approximately 9 a.m. to 12 p.m. and 2 hr of group treatment and education during

Table 2. Behavioral outcomes

	Entry Assessment			Exit Assessment		
Participant	**CAT MMT**	**BOSS CD**	**mPSS**	**CAT MMT**	**BOSS CD**	**mPSS**
P1	52.00	3	1	52.50	3	0
P2	58.83	9	24	56.33	8	21
P3	50.33	14	18	54.33	10	15
P4	59.17	9	16	n/a	9	17
P5	59.17	7	11	59.33	6	7
P6	52.83	9	23	55.33	7	12
P7	60.33	8	18	60.33	10	23
P8	49.50	7	21	50.67	5	6
P9	39.33	10	16	41.33	11	29
P10	51.17	15	28	50.67	14	14
P11	41.33	15	22	40.67	14	30
P12	43.33	10	10	46.33	10	14
P13	51.33	7	6	53.50	6	0
P14	62.33	12	27	66.83	10	17
	$M = 52.21$, $SD = 7.26$	$M = 9.64$, $SD = 3.41$	$M = 17.21$, $SD = 7.90$	$M = 52.94$, $SD = 7.35$	$M = 8.79$, $SD = 3.19$	$M = 14.64$, $SD = 9.34$

Note. BOSS CD = Burden of Stroke Scale Communication Distress Subscale Score; CAT MMT = Comprehensive Aphasia Test Modality Mean T-Score; mPSS = Modified Perceived Stress Scale.

the afternoon session from approximately 2–4 p.m. Six of the 14 participants opted to participate in a separate research arm of PI-RATE in which they received only individual treatment consisting solely of semantically based naming treatment (for details, see Evans et al., 2021). The treatment schedule for these participants was otherwise identical. In total, all participants receive approximately 60 hr of speech–language intervention across the duration of the program.

Cortisol measurement

Saliva samples were collected on three subsequent afternoons during the first week ("entry") and last week of treatment ("exit") for a maximum of 6 samples. All samples were collected immediately following the conclusion of the daily treatment at approximately 4 p.m. As cortisol levels peak in the morning and fall to a more stable low level later in the day (Adam et al., 2017), afternoon sampling allows for a more stable measurement and is the most commonly used time point in published studies of cortisol and aphasia (Laures et al., 2003; Laures-Gore et al., 2007; Laures-Gore, 2012). Furthermore, collection of multiple samples at the same time of day on subsequent weekdays is recommended to minimize the influence of spurious factors, such as occasional assaying problems, on analyses (Smyth et al., 2013). Participants were instructed not to ingest caffeine, food, nicotine, or alcohol 2 hr prior to cortisol sampling. As participants were receiving speech–language therapy during that time, the treating clinician was instructed to ensure that this guideline was adhered to, or that deviations were noted. Samples were collected using a Sarstedt Salivette collection kit by a study staff member, who was gloved during the collection procedure. The collection kit contains a roll-shaped cotton tube that participants were instructed to chew for 2–3 min or until saturated. The swab was then placed into a plastic vial and sealed. After sealing, samples were labeled, double bagged, and delivered to the VA Pittsburgh Health Care System (VAPHS) Medical Center laboratory. Samples were retained in the laboratory refrigerator until sent out for analysis within 24 hr, according to standard clinical

Table 3. Study procedures time line

Program Day	PIRATE Program Procedures	Study-Specific Procedures
Day 1	Program Orientation Entry Assessment	Informed Consent Process
Day 2	(including CAT and BOSS)	Sample 1 Collection
		Administer mPSS
Day 3	Intensive individual or individual +	Sample 2 Collection
Day 4	group speech–language intervention	Sample 3 Collection
Days 5–16		
Day 17		Sample 4 Collection
Day 18	Exit Assessment (including CAT and	Sample 5 Collection
	BOSS)	Administer mPSS
Day 19	Program Wrap-up	Sample 6 Collection
Day 20		

Note. "Program Day" refers only to the weekdays on which treatment was provided. Treatment was not provided on the intervening weekends. CAT = Comprehensive Aphasia Test; BOSS = Burden of Stroke Scale; mPSS = Modified Perceived Stress Scale.

procedures. See Table 3 for a time line of the study procedures.

ANALYSIS

The 1–3 salivary cortisol values collected for each participant at each time point[1] were averaged to obtain an "average cortisol value" per participant and time point (see Table 4). This average value was used in all subsequent analyses involving cortisol. P4 was unable to complete the CAT at the exit time point due to emergency and therefore was not included in any analysis using the CAT Mean Modality T-Score (CAT MMT). All analyses were performed using R version 3.6.3 (R Core Team, 2020).

To address the primary aim, whether salivary cortisol levels predicted treatment response, a linear mixed-effects model was tested using the lme4 package (Bates et al., 2015) with CAT MMT as the dependent variable, including fixed effects of average cortisol levels (in μg/dl) and time point (entry, exit), and the random effect of intercept by participant. To determine the presence and prevalence of elevated cortisol levels in the participant sample, descriptive analysis was performed on the entry and exit cortisol levels to evaluate the range of values, which were then compared against the normal range for afternoon sampling (0.01–0.2 μg/dl) provided by the VAPHS laboratory. To determine whether cortisol levels changed from entry to exit, first a Shapiro–Wilk test of normality was performed. The distribution of values was found to be non–normally distributed ($W = 0.88407$, $p = .005$) and therefore a Wilcoxon signed rank test was used to test for significant differences between entry and exit cortisol values. Finally, to evaluate the strength of the relationship between cortisol levels and aphasia severity, self-reported communicative distress, or self-reported chronic stress, Pearson Product-Moment Correlations were performed.

RESULTS

The results of the linear mixed-effects model revealed a significant main effect of time point on CAT MMT ($\beta = 4.054$, $p = .029$, 95% confidence interval [CI: 1.09–7.0]) indicating that CAT MMT scores increased

[1]Only one sample was available for P5 at entry due to an insufficient quantity of saliva in the first two samples, and only two samples were available for P6 at exit, as the participant left early to keep a medical appointment. All three samples were available for all other participants and time points.

Table 4. Cortisol values

	Entry Samples				Exit Samples			
Participant	**1**	**2**	**3**	**Average**	**4**	**5**	**6**	**Average**
P1	0.041	0.03	0.027	0.033	0.031	0.025	0.033	0.030
P2	0.081	0.088	0.077	0.082	0.076	0.13	0.102	0.103
P3	0.057	0.095	0.036	0.063	0.063	0.038	0.048	0.050
P4	0.062	0.153	0.152	0.122	0.077	0.067	0.081	0.075
P5	QNS	QNS	0.07	0.07	0.071	0.16	0.059	0.097
P6	0.118	0.085	0.085	0.096	0.047	0.071	n/a	0.059
P7	0.072	0.061	0.086	0.067	0.057	0.108	0.06	0.075
P8	0.033	0.136	0.092	0.085	0.044	0.032	0.049	0.042
P9	0.01	0.039	0.046	0.025	0.057	0.048	0.143	0.083
P10	0.139	0.059	0.069	0.099	0.049	0.062	0.097	0.069
P11	0.05	0.056	0.059	0.053	0.045	0.1	0.039	0.061
P12	0.108	0.078	0.098	0.093	0.027	0.031	0.025	0.028
P13	0.335	0.055	0.084	0.195	0.065	0.064	0.085	0.071
P14	0.035	0.026	0.028	0.031	0.039	0.048	0.037	0.041
				$M = 0.079$, $SD = 0.044$				$M = 0.063$, $SD = 0.023$

Note. n/a = sample was not collected (see text for details); QNS = quantity not sufficient; an insufficient amount of saliva was present in the sample to perform the assay.

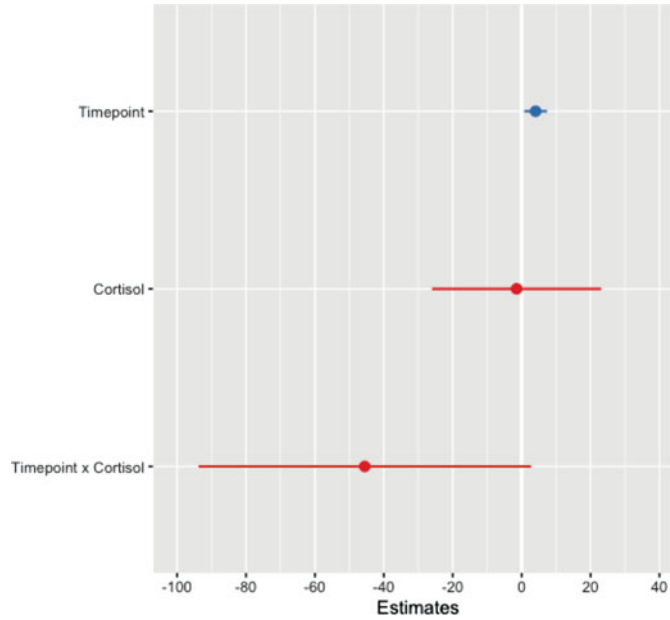

Figure 1. Regression model results. Plot of the estimates, and confidence intervals surrounding the estimates, of the fixed effects and their interaction from the linear mixed-effects regression model. Positive estimates are shown in blue and negative estimates are shown in red. This figure is available in color online (www.topicsinlanguagedisorders.com).

significantly from entry to exit. However, there was no significant main effect of average cortisol level on CAT MMT ($\beta = -1.47$, $p = .90$, 95% CI: −23.38 to 20.6). The interaction of time point and cortisol level was also nonsignificant ($\beta = -45.538$, $p = .077$, 95% CI: −88.44 to −2.33), although it approached significance, indicating that participants with lower levels of cortisol *may have* had greater gains in CAT MMT score compared with those with higher cortisol levels.[2] Using the simr package in R (Green & McLeod, 2016), the effect size of the fixed effect of cortisol in the model was estimated to be very large ($d = 1.5$) although a simulation revealed that approximately 24 participants would have been needed to achieve more than 80% power to detect an effect in a model comparison (i.e., the mixed-effects model including the interaction of time point and cortisol compared with the same model without the interaction). The distribution and homoscedasticity of the model residuals were evaluated using the lattice package in R (Sarkar, 2008), and no significant outliers were identified at $\alpha = .05$. The estimates of the fixed effects and confidence intervals are shown in Figure 1, and the predicted CAT MMT scores at entry and exit at a given average level of salivary cortisol are shown in Figure 2.

All average cortisol levels were within the normal range at both entry and exit. In addition, only one individual laboratory value fell outside of the normal range (P13 Lab 1, see Table 4) whereas the remaining samples for this participant were within the normal range. Of note, this sample was from a male participant and the samples from the female

[2]On the suggestion of an anonymous reviewer, follow-up analyses were performed with individual CAT subtest scores as the dependent variable in separate linear mixed-effects models, which otherwise were specified as described previously. Neither the main effect of average cortisol level nor the interaction between time point and cortisol level reached significance in any of the models.

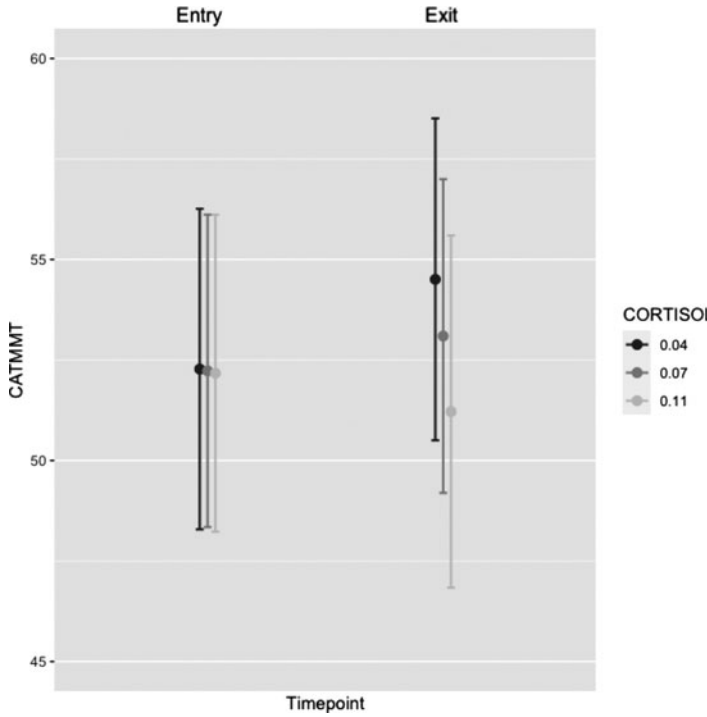

Figure 2. Predicted values of CAT MMT. Predicted values are indicated by the points and confidence intervals by the bars at entry and exit by average cortisol value (mean = dark gray, 1 *SD* below the mean = black, 1 *SD* above the mean = light gray). CAT MMT = Comprehensive Aphasia Test Modality Mean T-Score.

participant (P14) were neither outside of the normal range nor statistical outliers. Results of the Wilcoxon signed rank test revealed that, although cortisol levels were slightly lower at exit ($N = 0.063$, $SD = 0.023$) compared with entry ($M = 0.08$, $SD = 0.044$), this change was not significant ($V = 71$, $p = .27$). Entry and exit cortisol averages are shown in Figure 3. Cortisol levels were not significantly correlated with any of the behavioral outcomes at entry (CAT MMT: $r = .1$, $p = .72$; BOSS CD: $r = -.1$, $p = .67$; mPSS: $r = -.2$, $p = .52$) or exit (CAT MMT: $r = .1$, $p = .77$; BOSS CD: $r = .1$, $p = .65$; mPSS: $r = .3$, $p = .26$). BOSS CD and mPSS scores were significantly correlated at both entry ($r = .7$, $p = .006$) and exit ($r = .8$, $p = .001$), although no other outcome measures were correlated at either time point. The correlation matrix for entry is shown in Figure 4 and for exit in Figure 5.

DISCUSSION

Response to speech–language treatment for IWA depends in part upon neuroplastic changes in the brain, including the LTP of synaptic connections (Basilakos et al., 2022; Kiran & Thompson, 2019). Although it is widely accepted that speech–language treatment is effective, individual response remains highly variable (Brady et al., 2022), which suggests that IWA may vary in their underlying capacity for neuroplastic change. One potential source of this neuroplastic variability is the stress hormone *cortisol*, elevated levels of which have been shown to interfere with LTP (Dinse et al., 2017; Sale et al., 2008). Given that many IWA report high levels of chronic stress that are likely attributable in large part to their communication difficulties (Cahana-Amitay et al., 2011; Laures et al., 2003; Laures-Gore, 2012; Mitchell et al., 2017;

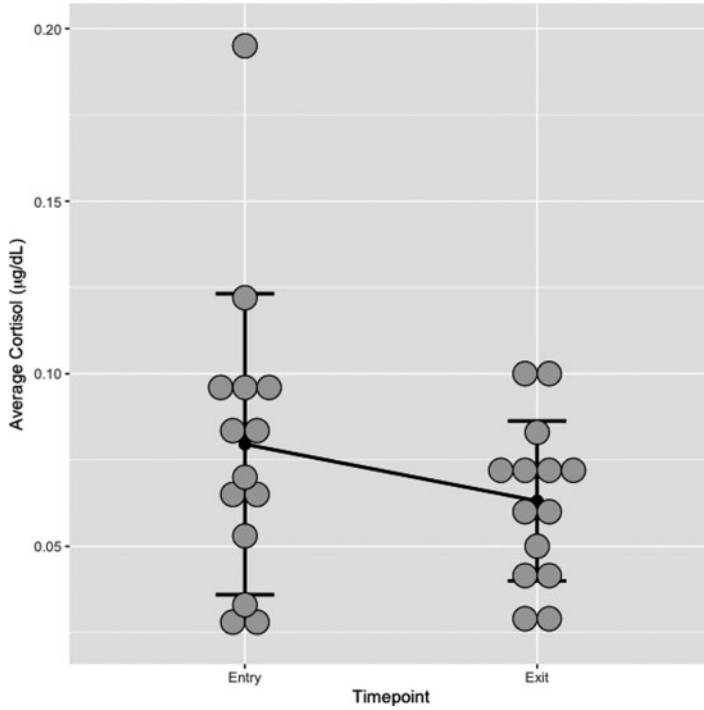

Figure 3. Cortisol levels at entry and exit with mean (black dot) and standard deviation (black bars). Individual average values by participant are indicated as gray dots. The mean and standard deviation at each time point are shown in black.

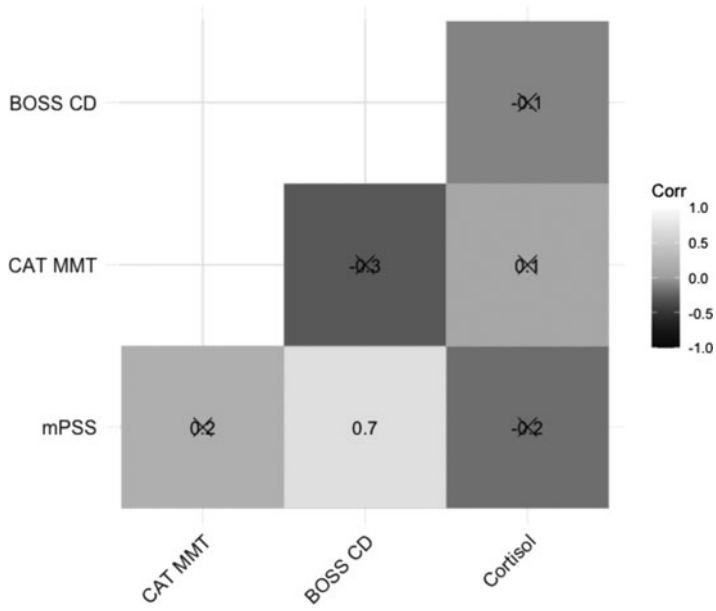

Figure 4. Correlation matrix of outcome measures at entry. Nonsignificant values are shown with an "X." BOSS CD = Burden of Stroke Scale Communication Distress Subscale Score; CAT MMT = Comprehensive Aphasia Test Modality Mean T-Score; mPSS = Modified Perceived Stress Scale.

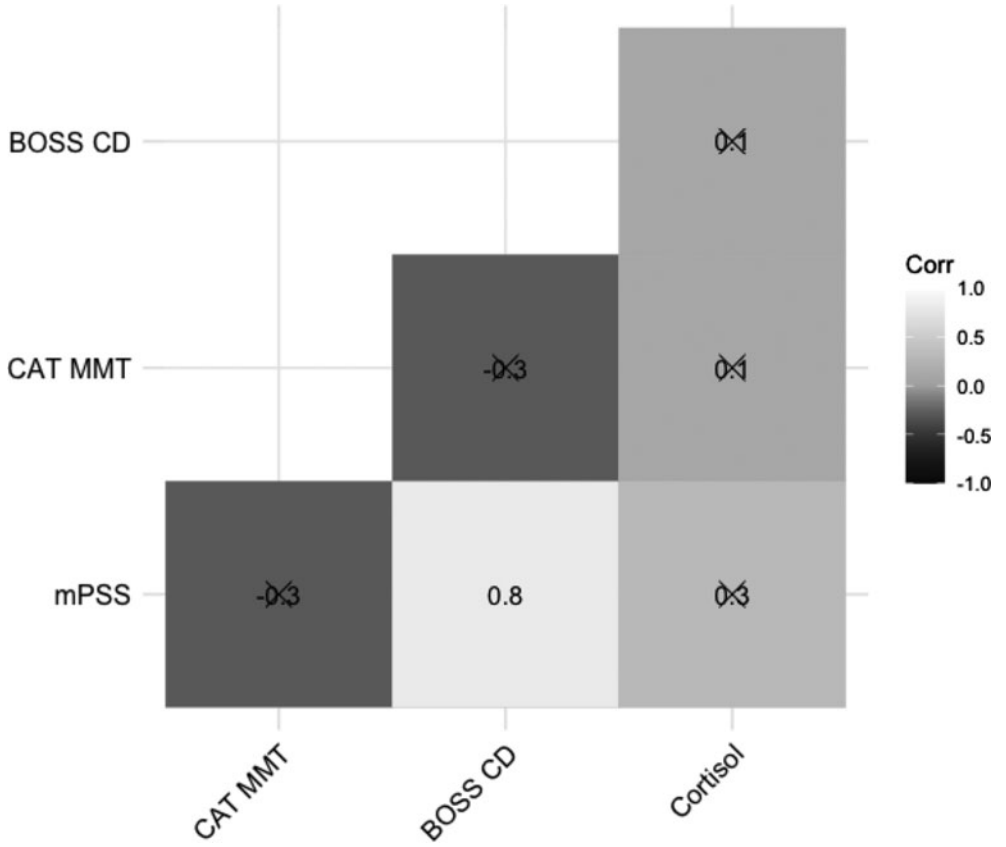

Figure 5. Correlation matrix of outcome measures at exit. Nonsignificant values are shown with an "X." BOSS CD = Burden of Stroke Scale Communication Distress Subscale Score; CAT MMT = Comprehensive Aphasia Test Modality Mean T-Score; mPSS = Modified Perceived Stress Scale.

Warner, 2010), it may be the case that the subsequently elevated cortisol levels result in less robust treatment effects for those individuals. Therefore, the primary aim of this study was to investigate whether levels of salivary cortisol predicted response to intensive speech–language intervention.

Consistent with prior reports, aphasia severity, as measured by the CAT MMT, improved following 4 weeks of intensive intervention (Evans et al., 2021; Gravier et al., 2018; Winans-Mitrik et al., 2014). Also consistent with prior reports, there was considerable variability in individual participant treatment outcomes (change in CAT MMT score from entry to exit; $M = 1.25$, $SD = 2.0$, range: -2.5 to 4.5). However, in our participant sample, average salivary cortisol was not found to robustly predict treatment outcomes, although a trend was present, and the effect size was large. Importantly, average salivary cortisol levels all fell within the normal range, with only one individual sample falling outside the range[3]. This may have been a result of participant "selection bias," given the

[3]This was the first sample taken at entry for this participant and was also taken at the end of a day in which multiple assessments were administered. As noted, the remaining samples for this participant were within the normal range, suggesting that the high value may have reflected acute changes in cortisol levels due to the assessment stressors. This highlights the importance of taking multiple samples to control for day-to-day variation and in considering the context in which samples were obtained.

constraints of the PIRATE program. That is to say that participants who were willing and able to travel to Pittsburgh to take part in the program (and thus had sufficient financial means, family support, and psychological well-being), and tolerate a month of intensive speech–language treatment, may have been experiencing less chronic stress than the population average. However, average participant scores on the mPSS in this study at entry ($M = 17.21$, $SD = 7.90$, see Table 2 for details) were actually slightly higher than the average of 75 community-dwelling IWA reported by Hunting Pompon et al. (2018) in their mPSS validation study, suggesting that in fact they were experiencing similar levels of chronic stress as other IWA. Notably, as discussed in the "Introduction," participants in the study by Hunting Pompon et al. (2018) also did not have elevated levels of cortisol as measured in hair samples and, in fact, many had values that were below the normal expected range. There is some evidence to suggest that when faced with repeated stressors, some individuals may "disengage," resulting in lower rather than higher levels of cortisol. For example, Laures-Gore et al. (2010) unexpectedly found that higher word productivity (WP; proportion of productive words in relation to total words) during the linguistic stressor task for IWA was associated with greater cortisol reactivity. They theorized that the IWA who had the most difficulty with the task may have disengaged, resulting in both lower WP and lower cortisol reactivity. This disengagement hypothesis is further supported by studies that have linked abnormally low cortisol levels in individuals with chronic posttraumatic stress disorder with disengagement coping strategies such as avoidance and emotional numbing (Mason et al., 2001). Future studies may consider incorporating a measure of task/therapy engagement to account for this possibility. Regardless of the underlying mechanism, it is possible that, with more representation at the higher end of the range of cortisol values, a significant positive relationship between salivary cortisol and treatment outcomes may be found.

Additional aims of this study included adding to the evidence base characterizing the effect of intensive treatment on cortisol levels in IWA, the relationship between salivary cortisol levels and aphasia severity, and self-report measures of communicative distress and chronic stress in IWA. In regard to the first item, the results here support and extend the findings of Sharp et al. (2013), in that 4 weeks (in comparison to Sharp's 2 weeks) of intensive treatment did not result in a significant change in cortisol levels. In addition, consistent with Laures-Gore (2012), salivary cortisol levels were not associated with aphasia severity[4], suggesting that "objective" language difficulty alone does not account for variability in the physiological stress response. However, self-reported chronic stress (mPSS scores) and communicative distress (BOSS CD scores) were strongly correlated at both entry and exit time points, even though the mPSS questions do not directly address communication. This robust relationship suggests that participants' overall perceived stress was likely related to their communication difficulties.

Although no significant relationship between afternoon salivary cortisol and treatment response was found in this study, it is also important to note that other cortisol measures may also be affected by chronic stress. As mentioned in the "Introduction," cortisol levels peak shortly after awakening, termed the "cortisol awakening response (CAR)," followed by a decline that becomes more gradual throughout the day, termed the "diurnal cortisol slope (DCS)," together forming the diurnal curve or rhythm. Elevation or alteration of salivary CAR has been related to chronic stress (Chida & Steptoe, 2009), as

[4]As shown in Figures 4 and 5, the results of the correlational analysis indicated that aphasia severity (as measured by CAT MMT) was also not significantly associated with chronic stress (mPSS score) or communicative distress (BOSS CD), suggesting that another factor, such as resilience, may play a role in determining how IWA respond to communicative difficulty.

has a flatter DCS (Doane et al., 2013). These patterns have also been linked with poorer mental and physical health outcomes including depression, inflammatory diseases, and mortality (Adam et al., 2017). A recent study, in fact, did find that the CAR was abnormal in a group of IWA, with higher mean levels at awakening compared with control participants, and a subsequent decline after awakening (Laures-Gore et al., 2019). Although not specific to IWA, the presence of a CAR predicted functional improvement among older adults in the post–acute rehabilitation setting (Fiorentino et al., 2012). In addition, a recent large prospective longitudinal study found that elevated *bedtime* salivary cortisol levels were associated with poorer cognitive functioning poststroke, even when controlling for stroke severity, demographic, and health factors (Tene et al., 2018). Therefore, future studies should consider obtaining multiple measures of cortisol throughout the day to determine whether CAR, DCS, or bedtime cortisol may more accurately predict treatment response.

If cortisol levels are found to impact response to intensive speech–language treatment in future work, it is unclear whether any of the cortisol-lowering interventions discussed in the "Introduction" would be similarly effective for IWA. The efficacy of mindful meditation (MM) has been evaluated in a small number of case studies with mixed results; some have reported improved psychological well-being, cognition, and even language (Dickinson et al., 2017; Laures-Gore & Marshall, 2016), whereas others have found little effect (Marshall et al., 2018; Orenstein et al., 2012). Other approaches to reducing stress and anxiety in IWA have also been trialed, including music therapy (Gadberry & Ramachandra, 2015), yoga (Bislick et al., 2022), and simulated laughter programs such as Laughter Yoga (Silverman et al., 2021) although physiological measures are rarely collected. Cortisol levels were measured in one MM study but did not change significantly following five sessions training (Marshall et al., 2018).

Brain-derived neurotrophic factor (BDNF), a protein that also plays a key role in synaptic plasticity including LTP (Fritsch et al., 2010), has also been explored in IWA. The presence of a polymorphism on the gene that encodes for BDNF production (a switch from valine, "val", to methionine, "met," in one or both alleles) results in a reduction in BDNF production (Egan et al., 2003). In a recent systematic review, IWA with the atypical met genotype were found to have poorer language recovery in both the acute and chronic stages (Lee et al., 2021). In one study, individuals with the met genotype benefitted less from speech–language intervention with adjunctive noninvasive brain stimulation than those without the met genotype (Fridriksson et al., 2018). As with cortisol, BDNF levels are modifiable and may be another potential target for adjunctive interventions to improve treatment outcomes in IWA. For example, yoga (Naveen et al., 2016), and aerobic exercise (Zoladz et al., 2008) have both been found to increase BDNF levels in neurologically unimpaired adults, although a recent study found no changes in BDNF after 5 weeks of either aerobic exercise or stretching in IWA (Harnish et al., 2018). Importantly, although they have different mechanisms of expression, levels of BDNF and cortisol are often inversely correlated, with individuals with the met allele having higher levels of cortisol and a larger cortisol stress response (Colzato et al., 2011; Schule et al., 2006), suggesting that BDNF and cortisol may play a complementary role. Supporting this idea, interventions that have yielded BDNF increases in neurologically unimpaired adults have also found correlated cortisol decreases (Naveen et al., 2016), although the relationship between BDNF and cortisol is yet to be explored in IWA. Future studies may also explore whether cortisol similarly predicts response to noninvasive brain stimulation approaches.

Limitations

As noted previously, the participant sample was limited to those IWA who were able and willing to tolerate a month of intensive

treatment, reducing the likelihood of including those experiencing high levels of chronic stress and thereby introducing selection bias. This bias may have contributed to the lack of abnormally elevated cortisol levels in this sample, although notably some participants did report high levels of perceived chronic stress. Furthermore, the sample was almost entirely male, which may have also biased the sample given that, in addition to the differences in cortisol reactivity noted previously, gender differences in basal salivary cortisol levels have been identified. Males are generally reported to have slightly lower levels of cortisol than females (Larsson et al., 2009) although this finding is not universal (Galvão-Moreira et al., 2016). The cortisol values of the single female participant in this study were, in fact, *below* the group average (1.1 *SD* below average at entry and 0.94 *SD* below average at exit); the opposite of the expected pattern. Although data from this one single participant can certainly not be said to be representative of all females with aphasia, it does suggest that gender effects on cortisol levels in IWA may deserve closer attention, particularly given that previous studies that have enrolled both participants of both genders have for the most part failed to find differences between baseline cortisol levels and/or reactivity in IWA compared with controls (Laures-Gore et al., 2007; Laures-Gore et al., 2010; Laures-Gore et al., 2012), whereas the study in which a significant difference was noted enrolled only males (Laures et al., 2003). Finally, the restricted range of salivary cortisol levels for participants in this study, in addition to the small sample size, may have obscured the relationship between cortisol and intensive speech–language treatment response, change in cortisol following treatment, and the relationship between salivary cortisol and behavioral measures of chronic stress and communication distress. Furthermore, these relationships may differ for treatment approaches, cortisol measures, and behavioral measures other than the ones studied here.

CONCLUSIONS

Although salivary cortisol levels did not significantly predict response to intensive speech–language treatment in this study, more studies are needed that include a larger number of participants with a wider range of both normal and elevated cortisol levels to ensure that analyses are sufficiently powered to detect an effect. In addition, the results are consistent with previous studies that have failed to find an effect of intensive treatment on cortisol levels (i.e., change in cortisol from pre- to posttreatment) and also support prior findings of a dissociation between cortisol levels and both subjective measures of perceived chronic stress and aphasia severity. Future research should consider utilizing other cortisol measures such as the CAR, and the DCS, to fully characterize the relationship between cortisol and treatment response. Furthermore, the contribution of cortisol should be considered alongside other physiological determinants of neuroplasticity, such as BDNF, to capture more variability.

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