Exploring associations between a biological marker of chronic stress and reported depression and anxiety in people with aphasia

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ABSTRACT

Purpose: Living with the communication impairment of aphasia can be stressful. Chronic stress, depression, and anxiety are intimately linked, may be more pervasive in people with post-stroke aphasia than the general population, and may influence cognitive function and treatment outcomes. In this project, we explored the psychological constructs of depression and anxiety and their associations with a biomarker measure of chronic stress in people with aphasia.

Method: Fifty-seven participants with aphasia completed measures of depression, anxiety, and provided a hair sample from which to extract the stress hormone cortisol. Pearson's product-moment correlational analyses were used to identify associations between depression, anxiety and long-term level of cortisol via hair sample.

Results: While cortisol level was not associated with depression and anxiety across this sample of people with aphasia, a post-hoc analysis showed a significant, positive correlation between a subset of participants with moderate and higher levels of depression and elevated cortisol level.

Conclusions: Chronic stress, depression, and anxiety have been little explored in people with aphasia to date, yet they are associated with future health consequences and impaired cognitive function, motivating further research as well as consideration of these factors in aphasia rehabilitation.

Key Words: aphasia, stress, depression, anxiety

Approximately two million people in the U.S. live with aphasia, a multi-modal impairment of language that can occur after stroke and other brain injury ("National Aphasia

Association," n.d.). Aphasia impacts an individual's ability to effectively communicate, participate in life, and overall emotional well-being (Code & Herrmann, 2003). Logically, struggles with daily communication may be chronically stressful (DuBay, Laures-Gore, Matheny, & Romski, 2011; Laures-Gore, Hamilton, & Matheny, 2007). When stressors persist over time, the body and brain adjust in ways that can be damaging to health and psychological well-being (McEwen, 1998; McEwen & Gianaros, 2011; Rice, 2011). Specifically, chronic stress has long been associated with the psychological disorders of depression and anxiety (Mazure, 1998; Tafet & Bernardini, 2003). Converging evidence links chronic stress, depression, and anxiety to the potential diminishment of memory, attention, and executive function (Bishop, 2009; McEwen & Sapolsky, 2005; Pittenger & Duman, 2008). This could have significant implications for PWA undergoing rehabilitation, since memory, attention, and related cognitive processes are necessary to attend to treatment tasks and maintain what is learned in treatment. In other words, a better understanding of chronic stress and its associations to depression and anxiety in PWA will help clinicians better differentiate language impairments from cognitive processing impairments stemming from psychological sources.

The following paragraphs will review literature on chronic stress, its links to depression and anxiety, and preliminary evidence of these psychological factors in stroke as well as aphasia.

Chronic Stress

Chronic stress can negatively affect health and wellbeing, and may also precipitate detrimental neurophysiological adaptations. As a key component of the biophysiological stress responses, the hormone cortisol becomes elevated when we perceive stress and helps trigger the "fight or flight" response. Repeated or persistent perceived stress may result in extended elevation of cortisol and a maladaptive prolongation of the biological stress response (McEwen,

1998, 2006; Pittenger & Duman, 2008). The resulting biophysiological adaptations can lead to increased risk of stroke, heart disease, immunosuppression, and psychological disorders (Cohen, Janicki-Deverts, & Miller, 2007; McEwen, 1998), as well as negatively influence centers of the brain important to cognition and memory (Lupien & McEwen, 1997; Sapolsky, 2015). Chronic stress appears associated with suppressed neurogenesis in the prefrontal cortex (PFC) and the hippocampus – regions which contain a high concentration of cortisol receptors and are central to cognition and memory (Bao, Meynen, & Swaab, 2008; McEwen & Gianaros, 2011; Pittenger & Duman, 2008; Tafet & Bernardini, 2003). In other words, significant and persistent stress may interfere with an individual's neuroplastic capacity in the hippocampus and the prefrontal cortex, and may therefore negatively affect memory and cognition (Lupien, Maheu, Tu, Fiocco, & Schramek, 2007; McEwen & Sapolsky, 2005; Sapolsky, 2015).

Cortisol is commonly measured as a biological indicator of acute and chronic stress levels. This hormone can be measured in saliva, plasma, and urine to capture acute levels of biological stress. While these are widely used biomarkers of acute stress, they may not be appropriate to measure chronic stress. For example, asking research participants to provide multiple samples over an extended period of time can be burdensome and prone to error. Cortisol extracted from hair, however, has been used as a biomarker of chronic levels of stress in both the general population as well as in some clinical populations (Stalder et al., 2017), and has been shown to correlate with acute measures of cortisol (Short et al., 2016). One centimeter length of hair, most often sampled from the posterior vertex of the scalp, contains approximately 1 month of cortisol levels and serves as a record of circulating cortisol over time (Manenschijn, Koper, Lamberts, & van Rossum, 2011; Sauvé, Koren, Walsh, Tokmakejian, & Van Uum, 2007). As a relatively novel measure of chronic levels of cortisol, hair assay has shown varying degree of

association with reports of perceived chronic stress, though significant associations have been reported in populations who commonly experience chronic stress, such as caregivers and unemployed persons (Stalder et al., 2017, 2014).

Chronic Stress, Depression, and Anxiety

While the link between depression and anxiety in the general population is well known (Lovibond & Lovibond, 1995; Löwe, Spitzer, et al., 2008), chronic stress, depression, and anxiety are also intimately linked (Bergdahl & Bergdahl, 2002; Cohen et al., 2007; Mah, Szabuniewicz, & Fiocco, 2016). The biological stress response, when prolonged over time, appears to overactivate neural circuitry in the amygdala (Pittenger & Duman, 2008), nuclei central to emotional appraisal of external and internal inputs. Furthermore, evidence of hippocampal atrophy has been observed in major depression and could contribute to several behavioral symptoms of major depression (Dranovsky & Hen, 2006; Gianaros et al., 2007). In other words, the structural remodeling of the brain that occurs with chronic stress may increase the likelihood of mood dysregulation and its associated symptoms. This consistent finding has led some to label the often co-occurring psychological impairments of depression and anxiety as "disorders of stress adaptation" (McEwen & Gianaros, 2011, p. 440).

Stressful life events and chronic adverse conditions are among the most powerful catalysts leading to depressive episodes, reported in both general and clinical populations (Cohen et al., 2007; Hammen, 2005; see Liu & Alloy, 2010; Whyte & Mulsant, 2002). A review, including 2,000 cases of major depression, found approximately 80% of depression diagnoses were preceded by life stressors (Cohen et al., 2007; Hammen, 2005; Mazure, 1998). Furthermore, in a large review, Lee and colleagues (2012) reported that perceived chronic stress was consistently and significantly correlated with measures of emotional variables, such as

anxiety (see also Bergdahl & Bergdahl, 2002; Mah et al., 2016). Depression and anxiety, like chronic stress, are tied to diminished cognitive abilities. For example, one of the diagnostic criteria of depression is a "diminished ability to think or concentrate" (American Psychiatric Association, 2013). People with depression often complain of difficulty with executive function (e.g., problem solving, attention, etc.) during everyday tasks, and exhibit prominent deficits in explicit memory (Pittenger & Duman, 2008). Anxiety disorders can lead to a diminished ability to attend and to inhibit distractions, and are associated with reduction in concentration and attention, as well as sleep disruption (American Psychiatric Association, 2013; Bishop, 2009; Kneebone et al., 2012), all of which may impede learning and memory.

Chronic stress, psychological associations, and stroke

Stroke is associated with a heightened stress response (Baune & Aljeesh, 2006; Dennis, O'Rourke, Lewis, Warlow, & Sharpe, 2000; Hilari et al., 2010; Kronenberg, Gertz, Heinz, & Endres, 2014; Laures-Gore et al., 2007), and this association is reflected in both biological (Barugh, Gray, Shenkin, MacLullich, & Mead, 2014; Fraguas et al., 2015) and perceptual measures of stress (Bruggimann et al., 2006; Dennis et al., 2000; Laures-Gore et al., 2007; Merriman, Norman, & Barton, 2007). Notably, elevated cortisol levels are associated with biological changes in the brain associated with stroke lesion in the first year post onset of stroke (Bustamante et al., 2014; Slowik et al., 2002).

While reported prevalence statistics are varied (e.g. Hadidi, Treat-Jacobson, & Lindquist, 2009), approximately one-third of stroke survivors suffer from depression according to a statement published by the American Heart Association (n.d.). While some depression interventions appear effective for stroke populations (Hackett, Anderson, House, & Xia, 2008), depression continues to be an enduring barrier to stroke recovery and rehabilitation outcomes

(Hackett & Pickles, 2014; Kronenberg et al., 2014; Kutlubaev & Hackett, 2014; Loubinoux et al., 2012).

General anxiety disorder is nearly as prevalent as depression after stroke. Specifically, one longitudinal study found approximately 22% of stroke survivors at the acute stage and 28% of stroke survivors at the chronic stage reported symptoms of clinical anxiety (Aström, 1996). In a more recently published systematic review on post-stroke anxiety, Campbell Burton and colleagues (2013) reported a rate of anxiety among chronic-stage stroke survivors to be 24%, though the authors believe this rate may be an underestimate. Interventions for the varied types of anxiety disorders within stroke populations are limited, even though anxiety may be associated with curbed treatment outcomes (Chun, Whiteley, Dennis, Mead, & Carson, 2018). Additionally, stroke survivors experiencing either or both anxiety and depression may have limited available psychological services compared to the general population (Campbell Burton et al., 2013), as well as an increase in mortality compared to psychologically well stroke survivors (Burvill et al., 1995).

Chronic stress, psychological associations, and aphasia

PWA report higher levels of stress than people without brain damage (Hilari et al., 2010; Laures-Gore et al., 2007; Parr, 1994), as well as fewer coping resources and a lower overall quality of life compared to stroke survivors with no aphasia (DuBay et al., 2011; Hilari, 2011). Laures-Gore and Buchanan (2015) have described factors that may influence stress reactivity in people with aphasia. While moment-to-moment language difficulties associated with aphasia may not uniformly generate a stress response, several individual factors, such as coping style and social support, interact with the perception of linguistic difficulties to generate biological and psychological responses to stress.

Depression and anxiety have been explored in PWA, though often separately (Døli, Helland, & Andersen Helland, 2017; Eccles, Morris, & Kneebone, 2017; Fucetola et al., 2006; Laures-Gore & DeFife, 2013; Laures-Gore, Farina, Moore, & Russell, 2017; Spencer, Tompkins, & Schulz, 1997). Depression is an acknowledged reaction to the onset of aphasia (Code & Herrmann, 2003) and may persist into the chronic stage of recovery (Hilari et al., 2010; Laures-Gore & DeFife, 2013; Laures-Gore et al., 2017; Spencer et al., 1997). Additionally, Fucetola and colleagues (2006) determined that depressive symptoms were predictive of functional communication – surprisingly, more than aphasia severity. That is, mood state was significantly associated with performance on a measure of communication in everyday life, with the reported mood states of anger, sadness, tiredness, and tension linked to poorer performance. Morris and colleagues (2017) reported the prevalence of anxiety among people with aphasia is approximately 44% compared to 18-25% for stroke survivors with no aphasia (Campbell Burton et al., 2013).

The originating study associated with the present paper found that participants with aphasia who reported higher levels of chronic stress also reported statistically significantly increases in depression and anxiety (Hunting Pompon et al, 2018). Unfortunately, clinical assessment protocols of aphasia typically do not include measures of chronic stress and psychological symptoms, and the study of these factors has not kept pace with research in other clinical populations. Since people with aphasia may be at a higher risk for experiencing chronic stress, depression and anxiety, it is essential to consider how these psychological variables may influence treatment efficacy. Specifically, chronic stress may precipitate depression and anxiety, and all three of these factors may negatively influence the neural substrates underlying cognition and memory, and therefore may diminish learning within the rehabilitation context, though this

association has yet to be explored. Indeed, several studies of stroke survivors (though not aphasia) have reported that depression appears to negatively impacted post-stroke cognitive rehabilitation outcomes (Gillen, Tennen, McKee, Gernert-Dott, & Affleck, 2001; Kutlubaev & Hackett, 2014; Robinson, 2003). Therefore, this project sought to address the following research question: Does a biological measure of chronic stress associate with reported depression and anxiety in people with aphasia?

METHODS

This correlational study investigated the relationships between a biological measure of chronic stress and the psychological constructs of depression and anxiety as part of a larger study that modified and validated a measure of chronic stress for people with aphasia (Hunting Pompon, Amtmann, Bombardier, & Kendall, 2018).

Participants

Fifty-seven participants (17 female) were included in the present study. These participants were drawn from a larger sample of 72 participants (Hunting Pompon et al., 2018), and included in the present study if they met the eligibility criteria to participate in the cortisol sampling portion of the overarching study (inclusion criteria: participants with at least 1 cm length of hair and who had not used hair dye within 8 weeks of the study session). Participants were recruited from the University of Washington Aphasia Registry and Repository and the VA Puget Sound Health Care System, at least 21 years of age, and at least one-year post-onset language-dominant hemisphere stroke resulting in aphasia (using the definition provided by McNeil & Pratt, 2001). Participants with a concomitant diagnosis of apraxia of speech and/or dysarthria were also included. Individuals excluded from participation were those who could not

complete the IRB-approved informed consent process; those with a diagnosis of a neurodegenerative or psychiatric impairment, active substance abuse, or adrenocortical dysfunction (e.g., Cushing syndrome); and those currently using systemic glucocorticoid medication (e.g., Prednisone).

Participants' mean age was 65.32 years (*SD* 10.54), mean education was 16.33 years (*SD* 3.40), and mean time post-onset of stroke was 86.00 months (*SD* 57.49). The reported races and ethnicities of these participants was African American (n = 1), Asian (n = 3), and Caucasian (n = 51; 1 of Hispanic ethnicity); two participants declined to report race and ethnicity. Each participant completed the Language Comprehension subtests of the Comprehensive Aphasia Test (CAT; Swinburn, Porter, & Howard, 2004). The mean raw score on the Auditory Comprehension subtests was 51.32 (*SD* 9.77) out of 66, and the mean raw score on the Visual Comprehension subtests was 46.56 (*SD* 10.62) out of 62. These mean raw scores are equivalent to T scores (mean = 50, *SD* = 10) of 52 and 53 respectively. This suggests that our sample of PWA closely mirrored the mean aphasia severity of the CAT reference sample. See Table 1.

Procedures

Each participant completed a 90-120 minute testing session. Approximately thirty percent of participants, selected randomly, completed a follow-up session approximately one week later to assess reliability of responses on two of the questionnaires (modified Perceived Stress Scale, and a visual analogue scale of stress; results are reported in Hunting Pompon et al., 2018).

Behavioral measures

After completing the informed consent process, participants completed language and vision testing (CAT, Auditory and Visual Comprehension Subtests and Line Bisection; Swinburn

Table 1

Summary of Demographic Information

	mean	T score	SD	range
Age	65.32	-	10.54	33 - 84
Education (years)	16.33	-	3.40	12 - 25
Time post onset (months)	86.00	-	57.49	12 - 228
Comprehensive Aphasia Test				
Auditory Comprehension subtests	51.32	52	9.77	22 - 66
Visual Comprehension subtests	46.56	53	10.62	9 - 61

Note: The mean, T scores, standard deviation, and range of raw scores on two compiled subtests of the Comprehensive Aphasia Test (Swinburn, Porter, & Howard, 2004): the Auditory Comprehension subtests (maximum score = 66), and the Visual Comprehension subtests (maximum score = 62). T scores are reported to show how the study sample compared to the published reference sample (mean = 50, SD = 10) of people with aphasia on these compiled subtests.

et al., 2004) as well as self-report questionnaires. We administered a modified version of the Perceived Stress Scale (mPSS; Hunting Pompon et al., 2018; based on Cohen & Janicki-Deverts, 2012; with permission from S. Cohen), the Patient Health Questionnaire (PHQ-8; Kroenke et al., 2009) to measure depression, and the General Anxiety Disorder scale (GAD-7; Spitzer, Kroenke, Williams, & Löwe, 2006) to measure anxiety. Both the PHQ-8 and GAD-7 are widely used diagnostic measures of emotional disorders with rigorous psychometric evidence of validity from various clinical populations (though not specifically aphasia). These measures are simply worded for clinical populations and use Likert scales with four or five response options. On all three measures, higher scores indicating greater symptoms of chronic stress, depression, or anxiety. For the PHQ-8, scores 5-9 indicate mild depression, scores 10-14 indicate moderate depression, scores 15-19 indicate moderate-severe depression, and scores 20-24 (max) indicate severe depression (Kroenke et al, 2001). For the GAD-7, scores 5-9 indicate mild anxiety, scores 10-14 indicate moderate anxiety, scores 15-21 (max) indicate severe anxiety (Spitzer et al, 2006).

Each questionnaire was read silently by the participant and read aloud by the examiner. To control for order effects, questionnaires were presented in one of three pseudorandom orders based on each participant's study code number. Questionnaires were administered using a communicative support hierarchy (Tucker, Edwards, Mathews, Baum, & Connor, 2012), a systematic approach to supporting comprehension and communication, and allowing for more complete participation for individuals with more severe impairment.

Biological measure

Participants provided a hair sample from the posterior vertex of the scalp to determine cortisol level. After identifying a small portion of hair to be sampled, and with the participant's approval of the specific sample location, an approximately 3 mm-diameter sample was clipped

close to the scalp. Each sample was cut to approximately 1-2 cm in length (proximal to scalp) representing 1-2 months of hair growth (Sauvé et al., 2007; Stalder et al., 2012; Wennig, 2000), contained within a labeled envelope, and stored at room temperature for several weeks until it was sent to a university biobehavioral health laboratory for processing using a specific assay protocol (Salimetrics High-Sensitivity Cortisol EIA kit; Salimetrics, LLC, State College, PA). The resulting levels of cortisol were compared against a published range of 17.7-153.2 pg/mg in a neurotypical adult sample (Sauvé et al., 2007).(Additional biomarker processing information is provided in Hunting Pompon et al, 2018.)

RESULTS

This sample of PWA yielded a mean depression scale score (PHQ-8) of 6.12 (*SD* 3.60), mean anxiety scale score (GAD-7) of 4.79 (*SD* 3.92), and a mean cortisol level of 20.82 pg/mg (*SD* 14.67 pg/mg). See Tables 2 and 3.

To determine the association between chronic cortisol level and measures of depression and anxiety, we conducted Pearson product-moment correlational analyses using the total score on the measures of depression and anxiety (PHQ-8 and GAD-7, respectively) and level of cortisol (pg/mg) from hair sample assay. Analysis results showed no significant correlation between the cortisol level and scores on either depression or the anxiety measures. Approximately 795 and 2,328 participants would have been required to detect a significant association between cortisol levels and, respectively, scores on measures of depression and anxiety. After a visual scan of participants' depression scores and cortisol results, we conducted

Table 2

Participant Descriptive Statistics: Behavioral Measures and Cortisol Level

Participant #	Depression score	Anxiety score	Cortisol level (pg/mg)
001	0	0	20.00
002	6	4	25.00
003	10	5	14.29
007	9	5	11.25
008	12	17	30.00
011	6	4	25.00
012	4	0	13.33
013	2	3	8.57
014	8	6	8.24
015	7	4	28.00
016	10	10	11.67
019	8	12	25.00
020	7	12	3.75
022	2	2	45.45
023	4	10	30.77
024	3	2	8.70
026	14	12	28.47
027	1	3	5.08
028	4	2	3.45
029	4	5	30.00
030	9	6	4.00
031	3	3	12.70
032	9	4	17.50
034	4	1	5.33
035	17	--	38.40
037	5	3	16.67
038	10	3	13.33
039	2	1	39.70
040	10	6	33.33
042	3	4	60.00
043	7	6	26.20
044	5	7	30.20
045	2	8	11.20
046	7	0	19.40
048	3	3	10.80
049	10	5	19.20
050	11	6	33.30
051	8	8	7.60

053	4	2	8.40
054	3	2	11.40
055	6	6	10.00
056	3	2	14.40
057	4	0	26.96
058	4	7	22.10
059	12	7	9.50
060	7	17	33.80
061	0	0	22.77
062	6	3	46.41
063	6	2	73.32
064	9	9	27.41
065	6	5	3.17
066	1	0	2.36
067	5	2	15.98
068	6	3	44.75
069	11	5	20.33
074	7	3	3.67
075	3	1	15.37
mean	6.12	4.79	20.82
SD	3.60	3.92	14.67

Note: Individual participant scores on the depression scale (PHQ-8; Kroenke et al., 2009) and the anxiety scale (GAD-7; Spitzer et al., 2006). On both scales, scores of 5-9 are considered "mild" and 10-14 "moderate." On the PHQ-8, scores of 15-19 are considered "moderate-severe" and 20-24 "severe." On the GAD-7, scores of 15-21 are considered "severe." Cortisol data reported in picogram/milligram (pg/mg); reference range for neurotypical adults is 17.7 – 153.2 pg/mg (Sauvé et al., 2007).

Table 3

Group Descriptive Statistics: Cortisol Levels and Behavioral Measures

	mean	**SD**	**sample range**	**ref. range**
Cortisol level (pg/mg)	20.82	14.67	2.36 – 73.32	17.7 – 153.2
Depression scale scores (PHQ-8)	6.12	3.60	0 - 17	0 - 24
Anxiety scale scores (GAD-7)	4.79	3.92	0 – 17	0 - 21

Note: Mean, standard deviation, sample range, and reference range on primary measures. Cortisol data reported in picogram/milligram (pg/mg); reference range published by Sauvé and colleagues (2007). Raw scores reported on depression scale (Patient Health Questionnaire-8; Kroenke et al., 2009) and anxiety scale (General Anxiety Disorder Scale-7; Spitzer et al., 2006).

a post hoc analyses which yielded a statistically significant, moderate Pearson's product-moment correlation between scores on the measure of depression and level of cortisol ($r(9) = .563$, $p < .05$) in the 19.3% of participants with moderate or greater levels of depression. No significant association between scores on the measure of anxiety and level of cortisol was found for the 12% of participants with moderate or greater levels of anxiety ($r(5) = .470$, $p = .14$).

Additional post-hoc analyses were conducted to explore other possible associations between the individual characteristics of sex, age, time post onset, education level, and aphasia severity and the constructs of focus. While cortisol levels were significantly different as measured by t-test between male and female participants (male $M = 23.97$ pg/mg; female $M = 13.41$ pg/mg; $p < .01$), Pearson product-moment analyses resulted in no significant associations between cortisol levels nor the behavioral measures (depression, anxiety) for male or female participant subgroups. A minimal significant inverse correlation ($r(55) = -.263$, $p < .05$) was found when examining age and score on the anxiety measure. In other words, older participants reported lower levels of anxiety. However, since these analyses involved multiple comparisons, a more conservative threshold for significance may be considered when interpreting these result (see Perneger, 1998).

DISCUSSION

The purpose of the present study was to explore depression and anxiety and their associations with a biological measure of chronic stress. This study was part of a larger research project that modified and validated a patient-reported measure of chronic stress for people with aphasia, and reported significant associations between perceived chronic stress, depression, and anxiety (Hunting Pompon et al., 2018). The present study's results revealed no significant

associations with either depression or anxiety and chronic levels of the stress hormone cortisol across the participant sample. A post-hoc analysis, however, showed a significant association between cortisol level and depressive symptoms in the subset of participants reporting a moderate or greater level of depression. The following paragraphs will discuss the depression and anxiety findings, the association (or lack thereof) between these psychological factors and the biological measure of chronic stress, as well as clinical implications and study limitations.

Depression findings

A large epidemiological study using the same measure of depression (PHQ-8) as the present study reported symptoms of moderate or greater depressive disorder (score of ≥10 of 24 maximum) in 8.6% of their general population sample (Kroenke et al., 2009). The proportion of participants in our sample reporting symptoms of moderate or greater depressive disorder was 19.3%. The proportion of participants reporting at least mild symptoms of depression was 59.6%. In other words, people with aphasia in the present study reported a higher prevalence of depressive symptoms compared to a large general population sample. This finding is meaningful; depressive symptoms in people with aphasia could have considerable effect on rehabilitation outcomes. Additionally, depression is associated with poorer functional communication (Fucetola et al., 2006) and changes in cognitive and memory processes (Pittenger & Duman, 2008), also evident in stroke survivors (Gillen et al., 2001; Kimura, Robinson, & Kosier, 2000; Kutlubaev & Hackett, 2014). Clinicians, researchers, and healthcare institutions develop and initiate language-based treatments for aphasia that depend on new learning. Logically, since chronic stress and depressive symptoms appear to interfere with an individual's capacity to learn, these constructs may therefore limit the success of aphasia rehabilitation.

Anxiety findings

A large general population study using the same measure of anxiety (GAD-7) as the present study reported symptoms of moderate or greater anxiety disorder in approximately 6% of the study sample (Löwe, Decker, et al., 2008) . In another GAD-7 validation study (Spitzer et al., 2006), the authors reported 23% of primary care patients indicated symptoms of generalized anxiety disorder (Spitzer et al., 2006). In our sample, 12% of participants reported moderate or greater anxiety symptoms (scores of ≥10 of 21 maximum), and 44.6% of participants reported at least mild symptoms of anxiety. In other words, this sample of participants appears to have a higher prevalence of anxiety symptoms compared to reports of the general population but less reported anxiety symptoms compared to patients currently seeking primary care. Other research reports that anxiety is frequently associated with stroke (Chun et al., 2018), extends into chronic recovery after stroke, and may be more frequent in people with aphasia (44%) compared to stroke with no aphasia (18-25%) (Campbell Burton et al., 2013; Morris et al., 2017). Cahana-Amitay and colleagues (2011; 2015) specified "linguistic anxiety" to represent the stress linked to poorer language performance, though this acute state of performance anxiety has not yet been explored relative to symptoms of general anxiety disorder.

Vytal and colleagues (2013) hypothesized that if cognitive resources are expended in part by anxious thoughts, the individual has less cognitive resources to perform intended tasks. If confirmed, this hypothesis could have significant implications for aphasia rehabilitation. If chronic stress and general anxiety interfere with a person's ability to attend to therapy and recall treatment items, in addition to the potential "linguistic anxiety" experienced with impaired language performance (Cahana-Amitay et al., 2011, 2015), these challenges may impede the success of treatment.

Associations with a Biomarker of Chronic Stress

We found no significant association between a biomarker of chronic stress (i.e., cortisol levels extracted from hair) and scores on measures of depression or anxiety in the participant sample. However, post hoc analyses provided additional information: a subset of participants with moderate and greater symptoms of depression (based on diagnostic cut-off scores; Kroenke et al., 2009) also had significantly higher levels of cortisol.

Prior research has reported evidence of cortisol elevation associated with depression diagnoses in the general population (Bao et al., 2008; Staufenbiel, Penninx, Spijker, Elzinga, & van Rossum, 2013; Tafet & Bernardini, 2003) and in samples of post-stroke participants (Barugh et al., 2014; Mitchell, 1997; Noonan, Carey, & Crewther, 2013). However, other stroke research has shown that cortisol levels may vary depending on site of lesion (Bao et al., 2008; Lueken et al., 2009), and relatively lower cortisol levels are sometimes found in people with post-stroke depression (Kwon, Kim, Lee, Sung, & Lee, 2015; Poll, Gilsbach, Hans, & Kreitschmann-Andermahr, 2013). Importantly, many studies measuring cortisol following stroke have been conducted with participants in the acute and sub-acute phases of stroke, when cortisol levels may be elevated due to an organic response to stroke-related inflammation, and not necessarily related to perceived stress (Bustamante et al., 2014; Slowik et al., 2002). Fewer studies have examined the link between cortisol levels and chronic stroke, depression, and anxiety (e.g., Hilari et al., 2010). Additional research is necessary to more fully understand the complex relationships between these factors in chronic stroke.

A related post-hoc analysis of the participants who reported a moderate or greater anxiety disorder (based on diagnostic cut-off scores; Kroenke et al., 2009) did not show a significant association between anxiety disorder and cortisol level. In other words, participants with at least a moderate anxiety disorder did not demonstrate elevated levels of cortisol. While there have

been a number of reports of acutely elevated cortisol levels associated with anxiety (Vreeburg et al., 2010), other research has reported an association between general anxiety disorder and relatively lower levels of the stress hormone cortisol (Staufenbiel et al., 2013; Steudte et al., 2011). In a recent meta-analysis of 124 published samples (N = 10,289; Stalder et al., 2017), participants with anxiety disorders had a 17% lower level of cortisol derived from hair. As it relates to people with aphasia, Cahana-Amitay and colleagues (Cahana-Amitay et al., 2015) reported a link between language performance-related anxiety and acute elevation of biomarkers of stress (heart rate, skin conductance) in a single case, proof-of-concept study. This association was not evident in the present study when examining moderate and higher anxiety and chronic levels of cortisol.

Importantly, people with more severe or persisting chronic stress, stress-related syndromes (e.g., chronic fatigue syndrome), and some forms of depression may not mirror the biophysiological response patterns of a relatively less stressed and psychologically well general population (Fries, Hesse, Hellhammer, & Hellhammer, 2005). This hypothesis may be reflected in our finding that descriptively, a large proportion of participants presented with significantly lower than typical levels of cortisol compared to some published norms (see Table 3; for additional discussion, see Hunting Pompon et al., 2018). A number of reports, including those based on animal models, connect the potential dysregulation of the biological stress response to stroke (de la Tremblaye, Raymond, Milot, Merali, & Plamondon, 2014), post-stroke depression (Kwon et al., 2015), psychological disorders in the general population (Kronenberg et al., 2014; Staufenbiel et al., 2013; Steudte et al., 2011), and as well as chronic fatigue, chronic pain, and other stress-related chronic syndromes (Fries et al., 2005). Notably, lower than typical acute cortisol levels were found in another study when comparing PWA to neurotypical adults

(Laures-Gore et al., 2007). In short, psychoneuroendocrine systems and their functioning, especially in chronic stroke, are complex and ripe for further exploration. Until more is known, using cortisol sampling alone to identify chronic stress, depression, and anxiety will be problematic.

Clinical Implications and Future Directions

Though people with aphasia appear more vulnerable to developing depression following stroke than people with stroke without aphasia (Code & Herrmann, 2003; Katerina Hilari & Byng, 2009; Laures-Gore et al., 2017), individuals with diagnosed psychological disorders are often excluded from clinical research in aphasia (Kendall & Nadeau, 2016; Wambaugh, Mauszycki, Cameron, Wright, & Nessler, 2013). This means the effects of currently used treatment programs for aphasia have not been examined for people with depression. At the same time, the inclusion, appropriate screening, and reporting of PWA in the post-stroke depression literature is highly variable (Townsend, Brady, & McLaughlan, 2007) in aphasia. When more is understood about chronic stress and psychological disorders and their influence on aphasia rehabilitation, more specific treatment planning, behavioral, pharmacological, counseling, and adjuvant interventions can be developed. Specifically, clinicians and clinical researchers may eventually become more equipped to differentiate between sources of impairment (linguistic vs. cognitive processes stemming from psychological factors), leading to more informed decisions about recommended interventions and more accurate predictions about treatment response. Furthermore, Bragoni and colleagues (2013) suggested anxiety symptoms and depressive symptoms may impact rehabilitation outcomes differently. While anxiety contributes to debilitating distraction, depression limits initiative/motivation and other executive functions.

Thus, it may be important to measure these constructs separately and explore targeted behavioral treatment and supports for individuals with different psychological profiles.

Understanding the neuropsychobiology of chronic stress and psychological disorders in aphasia may illuminate clinically relevant factors including varying recovery profiles. Questionnaires, surveys, interviews, diaries, and visual analog scales depicting mood states may provide some patient-reported information about stress levels and psychological symptoms (Fucetola et al., 2006), though we cannot yet connect these behavioral measures to the potential influence on treatment outcomes. While it appears the PHQ-8 and GAD-7 are feasible candidates for the identification of psychological symptoms in people with aphasia, measuring cortisol to help identify these factors may not yet be useful. Further research will help us understand the possible utility of measuring biomarkers underlying depression and anxiety, and identify the consequences of psychological factors on the arc of recovery and response to treatment in people with aphasia.

Limitations

The present project included several limitations. First, measuring cortisol as a biomarker of stress is a complicated venture, especially when interested in chronic levels of cortisol. Cortisol assay via hair to assess long-term cortisol levels is a somewhat novel methodology. A "gold-standard" approach for measuring chronic cortisol levels is not yet accepted, though measuring cortisol through hair is a less burdensome and error prone method for participants compared to daily acute cortisol sampling over a long period of time. Once we understand more about the emerging best practices for hair cortisol sampling and interpretation, we can clarify the relationships between this biological marker of chronic stress and psychological disorders. Additionally, sex, race, and ethnicity may associate with cortisol levels. For example, men and

people of African heritage often have higher hair cortisol values (Abell et al., 2016). This study did not include enough participant racial or ethnic heterogeneity to assess differences in cortisol levels between groups. While we found a significant difference between the cortisol levels of male and female participants in our study, sex differences were not apparent for any other measure of focus. Second, the scales of depression and anxiety used in this study have not been studied with people with aphasia. While both the PHQ-8 and GAD-7 scales have been simply written and well-validated for clinical and older adult populations, they were not developed specifically for PWA. Other scales of these psychological constructs have been developed PWA and their family caregivers: the Stroke Aphasic Depression Questionnaire-10 (SADQ-10; (Lincoln, Sutcliffe, & Unsworth, 2000; Sutcliffe & Lincoln, 1998) and the Behavioural Outcomes of Anxiety scale (BOA; Eccles et al., 2017; Linley-Adams, Morris, & Kneebone, 2014). Additional research will be useful to identify the strengths and challenges of each of these measures with PWA (see Laures-Gore et al., 2017 for an introduction to this research).

Additionally, the current project did not examine other life events, lesion site, additional stroke sequelae impacting emotional symptoms, premorbid psychological diagnoses, or anti-depression use. The use of anti-depressants in post-stroke depression populations is associated with a significant reduction in depressive symptoms (Chen, Patel, Guo, & Zhan, 2007). Participants receiving anti-depressant intervention may have been less likely to endorse depressive symptoms. Additionally, some anti-depressant medications act directly on biochemical components of stress and emotional regulation (e.g., norepinephrine, serotonin; Chollet et al., 2013), though the impact of anti-depressants on cortisol values is not yet well understood (Pariante, Thomas, Lovestone, Makoff, & Kerwin, 2004).

Conclusion

This project sought to explore associations between a biomarker of chronic stress, depression, and anxiety in people with aphasia. Long-term cortisol levels extracted from hair were not associated with patient-reported measures of depression or anxiety across the study sample but were evident in participants with moderate and higher levels of depression. These findings point to the complex underlying relationships of the psychoneuroendocrine systems that subserve chronic stress, depression, and anxiety.

Though there is continued interest in the psychological sequelae of stroke, there are many outstanding questions and gaps in our knowledge. Assessing chronic stress, depression, and anxiety in people with communication impairments remains a complicated venture. Relatively limited research regarding the prevalence of psychological disorders and related biopsychosocial factors, lack of psychometric data, and emerging measurement methodologies highlights this difficulty. Further exploration of how to assess psychosocial constructs in people with language impairment, as well as the influence of these factors on cognition and language impairment, will help improve assessment and intervention. Additionally, chronic stress, depression, and anxiety almost certainly impact aphasia rehabilitation outcomes. Future research is planned to examine the link between chronic stress, psychological disorders, and their influence on memory, cognition, and learning. Ultimately, further explorations of chronic stress, depression, and anxiety in aphasia may help us expand intervention efforts and provide patients with greater opportunities for therapeutic gains and improved quality of life.

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