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Diurnal cortisol and coping responses in close relatives of persons with acquired brain injury: a longitudinal mixed methods study

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Running Title: Cortisol and coping in relatives of persons with ABI

Abstract

Objective: To examine the impact of having a close relative experience a severe brain injury.

Design: Six-month longitudinal mixed methods concurrent embedded study. Quantitative data provided the primary database and qualitative data provided the secondary source.

Methods: Assessment included psychosocial factors of perceived stress, traumatic stress symptoms, coping, and social support in addition to salivary cortisol as a biological marker of stress. Written accounts of the experience were provided in response to an open-ended question. Participants composed 15 close relatives of adults with severe brain injury admitted to a specialist rehabilitation facility (mean age 49.4 years; SD 11.79). Assessments were conducted on admission, at six weeks, three months, and six months post admission.

Results: Quantitative data revealed high traumatic stress at admission with a non-significant decline at follow-up. Diurnal cortisol output declined significantly from baseline to all follow-up assessments. Coping subscales of acceptance and religion were repeated associated with cortisol indices at baseline, six weeks, three months, and six months follow up. Qualitative data revealed two themes; 'relational impact' and 'passage of time'.

Conclusions: Findings offer the potential for effective and timely intervention in family members of persons with severe brain injury.

Introduction

The effect of caring for a relative with acquired brain injury (ABI) can have substantial impact on psychological state, social relationships and well-being. Indeed, national guidelines have incorporated carer needs and support into recent documentation, including the NICE guidelines [1] and the DoH National Service Framework (NSF) for Long Term (Neurological) Conditions [2]. Quality Requirement 10 of the NSF 'Supporting Family & Carers' states that 'Carers of people with long term neurological conditions are to have access to appropriate support and services that recognise their needs both in their role as carer and in their own right' [2]. Research has also pointed to the discrepancy between the need to involve family members in rehabilitation and the clinical practicality of doing so [3]. In order to develop effective interventions which could be applied within existing services it is necessary to establish a better understanding of these needs. There has been little research which examines stress and coping in relatives during the earlier stages (first six months) following ABI. This is a period of significant turmoil, which also provides an opportunity for early assessment and a point of intervention which could benefit longer term adjustment. A multilevel analysis, set within the theoretical context of the stress and coping literature, would benefit understanding of this complex process.

Having a close relative experience an ABI is an example of an aversive stressor associated with multiple psychosocial stressors. Such an event may elicit an initial acute stress response followed by the experience of chronic enduring stress, and require significant life adjustment as it may frequently carry with it the responsibility of care-giving. The long term impact of caregiver burden in ABI has focused on psychological health outcomes, such as anxiety, depression, social isolation, and well-

being [4-8], as well as the need for family support to reduce these effects [9-12]. Using a questionnaire comparison of carer experience, those caring for adults with ABI were found to have poorer mental health and quality of life than those caring for an older cohort with dementia [13]. In the majority of studies examining the needs of the family of persons with ABI, social support or the lack of it, is one of the most important variables for both patient and family outcome [11,14-16], particularly that of emotional and informational support [17,18]. The role of close family is vital to patient rehabilitation and a sense of social isolation is one of the most significant obstacles with which the patient and family have to contend [19]. Similarly, a vital component of adaptation to life event trauma such as ABI in a family member, is the use of different types of coping responses [20]. Greater use of emotion focused coping, for example, has been associated with greater emotional distress [21].

ABI In the broader stress-health literature outside of ABI, the physical health impact of caregiving is also well documented, e.g. in dementia and HIV [22-24]. A wealth of research has been generated in this area with respect to the assessment of stress hormones, such as alterations in the diurnal pattern of salivary cortisol production following a stressful life experience. For example, despite paradoxical findings of extreme hypocortisolaemia in some cases of post traumatic stress disorder [25], both acute and chronic stress have been found to generate an initial increase in release of glucocorticoid stress hormones. Subsequent alterations in the daily pattern the stress hormone, cortisol, under chronic stress conditions, are influenced by psychological factors. There is now a strong body of evidence linking cortisol and stress responses with health outcome, through a flattening of the diurnal cortisol rhythm [26-28]. In their meta-analysis, Miller Chen and Zhou [29] identified a number of predominant influences on the hypothalamic pituitary adrenal (HPA) axis

stress response system. Of particular relevance here is whether or not the stressful experience involves a threat to the social self, the controllability of the stress, and the emotions elicited by the stress (e.g. shame) [29]. Most notably, these relate to the maintenance of a high yet flat diurnal profile of cortisol (less morning variation with higher than average afternoon/evening levels) in chronic stress which threatens physical integrity or is uncontrollable [29]. By contrast, diurnal peaks in cortisol during morning and afternoon/evening were noted under stressful conditions which pose a threat to the social self, in an effort to retain social standing [29]. A second recent meta-analysis concludes that whilst acute stress in naturalistic settings generates a stronger cortisol response than chronic stress, it is the latter that is potentially more damaging to long term health, via increased sensitivity of the HPA axis to future stress events [30]. There is also considerable evidence to suggest that the effect of trauma experience can lead to severe physiological alteration and health effects over time [31,32, 33]. Yet there is a general lack of prospective longitudinal research which specifically addresses the physiological effect of experiencing a naturalistic chronic stressor. The, experience of ABI in a close family member presents a fitting example of such stress.

Established research on coping under chronic stress has reported health benefits associated with the responses of acceptance, humour, and positive reframing, in contrast to harmful effects of responses based around denial, disengagement and avoidance [34]. Early work on coping also pointed to a ‘spiral’ of ‘reciprocal influence’ which occurs between coping and distress when the stress experience continues longitudinally [34]. The relationship between coping responses and cortisol has largely been based on experimental laboratory stressors, with limited work on naturalistic chronic stressors. In a recent study examining this link in a

healthy sample of middle aged civil service employees, the coping responses of ‘seeking social support ‘and ‘problem engagement’ (planning and positive reinterpretation) were individually associated with lower diurnal salivary cortisol output [35]. Using a challenge paradigm in which the HPA axis was pharmacologically activated, Abelson et al [36] further differentiate stressor characteristics of control, highlighting the importance of coping abilities to overcome HPA axis activation. The authors report a reduction in serum cortisol for participants provided with cognitive coping techniques (novelty reduction and explanation of drug effects) which was as effective as combining coping with control features [36].

Given the importance of the family in rehabilitation following ABI, the primary objective of the current study was to examine the psychological and biological impact of having a close relative experience an ABI. Specifically, we wanted to address links between the stress experience, coping responses, and availability of social support in close family members of persons with ABI newly admitted to a neurorehabilitation unit. It was hypothesised that stress levels would reveal a varied pattern of effects, reflecting the temporal aspect of the stress experience and would be attenuated by the psychosocial resources available to aid adaptation to this life event.

Methods

Research design

This study utilised a mixed methods concurrent embedded data collection design [37] in which quantitative data provided the primary database and qualitative data provided a supporting or supplementary role (see figure 1). This involved longitudinal repeated measures analysis employing four assessment points over a period of six

months: 1) within 1 week of the person with ABI being admitted to the Unit; 2) six weeks post admission; 3) three months post admission; and 4) six months post admission.

Insert figure 1 about here

Participants and procedure

Thirty close relatives of persons with ABI admitted to an in-patient specialist brain-injury rehabilitation facility in the south west of the UK were identified as meeting inclusion criteria and invited to participate in the study. Twenty-six of these initially agreed to participate but seven withdrew from the study prior to returning the first set of materials. Of the remaining 19, four participants were excluded due to inadequate return of samples and missing data. The retained cohort of 15 participants, composed nine parents (four mothers, five fathers), four spouses (one husband, three wives) and two daughters, mean age 49.4 years (SD 11.79), with 33.3% educated to degree level or above.. Participation rates declined to seven at assessment point two, with nine of the relatives returning data at time points three and four. Patients composed 11 cases of severe acquired brain injury, including four cases (36%) of traumatic brain injury (TBI), they were aged between 16 – 54 years (mean 29.9; SD 16.2), with a Glasgow Coma Score of 3-15 on admission (mean 8.7; SD 3.3), indicating severe brain injury. At each of the three follow-up time points, the patient cohort included two cases of TBI (22.2 – 28.6%). The study adhered to the ethical guidelines of the British Psychological Society (BPS) and was approved by the National Health Service (NHS)

Research Ethics Committee and by the University's Department of Psychology Research Ethics Committee.

Participants were required to be a minimum of 18 years of age and visiting a close relative who had been admitted to the unit following severe acquired or traumatic brain injury. A 'close' relative was defined as a relation who considered themselves to be interpersonally close to the person with ABI and/or had responsibility for care. Since the quantitative assessment included measurement of the stress hormone, cortisol, relatives were excluded from the study if they were taking oral steroid medication likely to interfere with cortisol assessment. Recruitment of relatives was conducted by the project research assistant within ten days following patient admission to the hospital. The assistant was based in the brain injury unit and recruited participants in conjunction with the team of clinicians who enabled referrals of relatives for the study during patient visits. Participants received an initial interview with the researcher in which the study procedure was explained and informed consent was taken. Demographic variables relating to the relative (including age, gender, and education) and medical status variables relating to the person with ABI (age, Glasgow Coma Index (GCI) at scene of injury and on admission to the unit) were assessed as possible covariates in analysis.

Quantitative assessment

(i) The following self report questionnaires assessing psychological stress and psychosocial resources were administered at the first and last assessment points:

- The 10-item Perceived Stress Scale (PSS) [38]. The PSS is a valid measure of global stress which the authors specify as being sensitive to current life stress as well as to expectations about future stress [39]. It contains items relating to thoughts and feelings about events being unpredictable, uncontrollable and overloading and

generates a total score for perceived stress. We measured the degree to which relatives appraised their global experiences over the last month to be stressful.

- The Impact of events scale (IES) [40]. This scale yields two factors, intrusion and avoidance, as well as a total score relating to post traumatic stress symptoms and has achieved good psychometric properties across a wide range of clinical and non-clinical populations [40,41]. Participants were asked to respond specifically in regard to the brain injury of their relative, thereby measuring the subjective impact of the experience.
- The Brief COPE [42]. A shorter version of the original COPE [43] containing 14 scales each composed of two items: self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self blame. A four point response scale was used, from 1 = 'I haven't been doing this at all' to 4 = 'I've been doing this a lot'. Instructions were phrased to elicit 'situational' coping in response to the relative's experience of the recent injury. Lower order coping subscales were used in analysis in order to explore the full range of coping responses.
- The Interpersonal Support Evaluation List (ISEL-12). A shortened version of the original 40-item version [44,45], which consists of three subscales: belonging (availability of people to do things with), appraisal (perceived availability to talk about difficulties) and tangible (perceived availability of practical or instrumental help) support, each composed of four items. This multidimensional support inventory utilises a four point response scale from 1 = 'definitely false' to 4 = 'definitely true' for each statement.

ii) A biological marker of stress. The hormone, cortisol, was collected from saliva at each of the four time points across the study, using the Salivette device, which consists of a sterile cotton swab held inside a plastic tube (Sarstedt, Germany). Salivary cortisol has proven to be a valid and reliable reflection of the unbound hormone in the blood [46] used extensively as a stress marker in biopsychosocial research [47]. Each participant received a salivary cortisol kit at each time point, comprising eight Salivettes, colour coded for time of day and enabled sampling four times per day across two consecutive days at 1) Awakening; 2) 12 noon; 3) 6pm and 4) 9pm. Responses for each time point were averaged across the two days in order to enhance reliability and validity of cortisol assessment. Sample collection was self administered by participants in their own homes following the baseline interview with a trained researcher. Saliva kits were accompanied by a sampling booklet, containing information on how to collect the sample, questions about medication taken leading up to or on the day of sample collection, duration and quality of sleep, times of waking and sample collection and any problems regarding sampling. Participants were instructed to choose the two consecutive days on which to provide their samples within seven days of receiving the materials. Samples were stored in participants' home freezer until completion of all samples at each time point, when the kit was returned to the hospital via first class post, and stored at -20 degrees until analysis (full assay details are provided in [48]). Two standard computations were used for area under the curve measurement of cortisol, reflecting total hormone output (AUC_G) and change over time (AUC_I - used here with respect to decrease and reflecting the degree to which cortisol observed a natural decline across the day) as recommended by [49]

Qualitative assessment

At the initial and final time points, participants were given the opportunity to provide a written response to the broad question ‘is there anything else that you would like to tell us about the influence that the recent injury of your relative has had on you?’

Participants were permitted to write as much or as little as they chose in response to this question and to return it by mail with the questionnaires.

Plan of Analysis

Quantitative data were analysed using SPSS V 14.0. Non parametric tests were employed due to sample size restrictions. Demographic and medical status variables were not significantly associated with the dependent cortisol indices and as such were not included as control variables in analyses. In order to assess within participant changes in cortisol across the 6 month study, variables were entered into a repeated measures Friedman’s ANOVA, with Wilcoxon tests used for posthoc comparisons. As the cortisol data were positively skewed, logarithmic transformation was applied prior to AUC calculation and analysis. Spearman’s correlations were conducted to assess relationships between psychosocial factors at admission and follow-up assessment points with biological stress responses at each of the four time points of the study. Qualitative data were assessed using Interpretative Phenomenological Analysis (IPA) in order to identify common themes. The qualitative data provided a rich source of narrative of the subjects’ lived experience of their situations [50]. The phenomenological analysis involved a detailed exploration of this data allowing for the dynamic of the interpretation of this by the researcher [51]. Triangulation of results was enabled using a comparison between quantitative and qualitative data.

Results

Quantitative analysis

Psychological stress and social support

Means and standard deviations for psychological stress and social support scores are given in table 1. There was no change observed in the perceived stress scores between admission and 6 months post. Traumatic stress symptom scores indicated high distress at admission. Whilst a decline was noted in the trauma scores and in the social support variables between the beginning and end of the study, the decline was not significant.

Insert table 1 about here

Adherence to requested sampling times was recorded as consistent across diurnal measurement points, with an average recorded time of 07.11 hrs (\pm 21 mins) for the awakening sample, 12:28 (\pm 18 mins) for the noon sample, 18:07hrs (\pm 19 mins) for the 6pm sample and 21:12 (\pm 21 mins) hrs for the 9pm sample.

Cortisol output (AUC_G) was significant across the four assessment points of the study (Chi-square = 14.02; $df = 3$; $p = 0.003$). Assessment of change in cortisol over time across the four assessment points of the study was non significant for diurnal change (AUC_I). Pairwise comparisons of cortisol AUC_G at admission and follow-up assessments using the Wilcoxon test revealed a significant effect (Bonferroni corrected for multiple comparisons, criteria of $p = 0.01$ used) for admission to six weeks ($z = -2.366$; $p = .018$), admission to three month follow-up ($z = -2.67$; $p = 0.008$) and admission to six months follow-up ($z = -2.67$; $p = 0.008$). The diurnal cortisol curves at each of the four assessment points across the study are illustrated in figure 2.

Insert figure 2 about here

Perceived stress and subscales of belonging, appraisal and tangible social support as measured directly through the ISEL were not significantly associated with cortisol indices. Total cortisol output was significantly correlated with IES avoidance (Spearman's $\rho = .71$; $p = 0.007$) and IES total (Spearman's $\rho = .59$; $p = 0.033$) at baseline, indicating an association of higher levels of post traumatic stress symptoms with greater cortisol output. At six month follow up there were no significant relationships found between IES scores and cortisol AUC_G . Trauma scores were not significantly associated cortisol AUC_I at any of the time points.

Coping as a psychological resource

Five of the fourteen coping responses reported at admission were significantly and consistently correlated with cortisol variables across measurement points. At admission, the responses of acceptance, instrumental support, planning and religion were all negatively associated with decline in cortisol across the day, indicating the use of these coping responses as adaptive. Acceptance and religion were also negatively correlated with total output indicating a smaller stress response when these types of coping responses were utilised. At six weeks following admission, the coping responses of acceptance and positive reframing were similarly negatively associated with total output of cortisol. At three months post admission, the coping responses of acceptance and of positive reframing were positively associated with cortisol decline, indicating a smaller diurnal change, but no effect was found for total cortisol output. At six months following admission, a positive association was again found for use of positive reframing and cortisol change across the day, whilst the use of religion was negatively associated with cortisol output. These correlations are reported in table 2. There were no significant changes in use of coping responses measured at the start

compared to the end of the study. However, examination of cortisol indices and coping responses at this final assessment revealed significant associations between acceptance and cortisol change ($\rho = -.81, p = .028$) and between the use of religion as a coping resource and total cortisol output ($\rho = -.88, p = 0.009$).

Insert table 2 about here

Qualitative Analysis

The participants in this study each shared the fact that a person they were close to had suffered a serious head-injury. The data was very limited in that it amounted to small fragments of text written in response to the one broad question yet all participants responded to this invitation to write about their experience, some writing extensively beyond the space provided.

The two themes that emerged in this analysis are presented here as ‘the relational impact’ and ‘the passage of time’.

The Relational Impact

When the participants were asked about the impact upon them of the critical illness of their close relative, their responses made significant reference to social relationships. Their accounts were predominantly relational as they described how both in the present and the future they were trying to make sense of a significant change in both their relative’s health status and the loss of their capacity to function as they had previously. The change in functional capacity amounted to a different person and a different relationship. There was significant uncertainty as to the extent of this change and the grief and bereavement involved.

Almost all of the participants described how the incident had significantly impacted (both positively and negatively) on their attachment relationships and on the way in which they related to others in general. The event appeared to intensify the participants' attachments, which for some was problematic, but for others was a palpable source of support. The participants described how events had brought them 'closer' to their relatives and to other members of their family, 'injury has brought close members of the family even closer' (E). For some, this closeness was positive. Participant (D) described his wife's illness as 'probably the ultimate test of a relationship...our mutual love is probably stronger than ever'. But not all the participants felt the same, for example, participant (H) found the 'test' of her relationship more problematic as not all of her feelings were positive, '...guilty about change of feelings about my husband in some regards'.

Participant (D) described how he drew upon his relationships for support, including the one with his ill wife. Her struggle with her illness helped him to manage the demands of the situation and defended him against depression. Not only did he worry for her, but he drew upon his relationship with her to give meaning to his own struggle to cope;

'I am fortunate in having close support from my three lovely step children, my own children, my ex-wife and several friends...it has helped me to provide support for my step children.....I felt I was dipping away [into depression] but the fact that my wife is fighting so much so hard lifts me out of it'.

This participant (D) included hospital staff in his supportive relationships, '...[staff] undoubtedly play a very large part in my ability to cope. Their considerable support is fundamental to me as well as to my wife...'.

Unlike (D), others, found the 'closeness' uncomfortable and the compelled sense of intimacy and proximity was problematic at times. For (C) there was tension between her concern for her son's condition and his reaction to what he felt was over-protective and intrusive behaviour '...I'm trying hard not to say the wrong thing...Was also very angry with me for asking him how he was too often...'. (G) described a similar difficulty with her father and how this extended to all of her close family '...I am much closer to dad, much more protective, often unnecessarily ...the same with the rest of the family'.

This increase in the intensity of the attachment in the participants' relationships, coupled with their limited ability to influence their relatives medical condition often left them frustrated, compelled to do more and aggressive;

'I am hungry for information on my son's progress probably unrealistically.....there is a feeling of impotence and a desire to help, whatever it helps, the frustration makes me short tempered, which I don't like...' (A).

Participants also described how their relative's illness had distorted their relationships and become a source of tension - with the needs of their ill relative competing with those of their other family members. '...feel very guilty that I can't be there for her all day every day, however with a 1 yr old and a family of my own I realise that this is not possible or helpful to me...' (E). Not all relationships were positive and (06) found the increased proximity with other family members very difficult and even repulsive as instead of feeling guilty that they could not spend more time with all their family, (B) felt angry that they were compelled to be with people that they disliked intensely. Intensity and closeness exposed difficult relationships and was not necessarily comfortable;

‘anger and frustration at the people also involved, their actions and comments and having to control myself from biting back at them. Having to spend time with in the company of people you are separate from in normal life and also people you have no liking for and would not spend time with in normal course of life...’ (B).

Similarly, participant (H), worried about the long-term effects on her relationships should her husbands behaviour change significantly. ‘...behaviour change in my husband...long term outcome...if friends will fall off...impact on our son...carrying the responsibility of parenting single handed’. She worried about becoming isolated and alone and later at the second interview described how this had affected her personally, leaving her feeling low in confidence, ‘...surprised at the lack of confidence I feel with other people, when I have normally been a very confident person...’.

The change in their relative’s health, functioning and dependency and the impact this would have on their relationships was prominent in the participants’ responses. Although asked about themselves their answers were set in the context of their relationships, the ‘we’ as opposed to the ‘I’. This situated their experience in a social and cultural phenomenon setting. It highlighted how the quality of life in critical illness and long term conditions is also a relational phenomenon where connectedness and attachment are important.

The passage of time

The participants’ experience changed over time and some described a clear distinction between the phases. This was defined by the medical status of their relative’s condition rather than any easing of the emotional burden. Participant (C) detailed a specific trajectory involving three phases, the acute ‘... on the critical list...’, sub-

acute ‘... off the critical list...’ and chronic ‘... the future...’. Each phase was typified by particular emotions:

‘acute phase has passed so shock, anger, etc, the usual feeling have all been dealt with’ (G);

‘the initial shock/numbness has evolved to feelings of positivity that she has survived but also fear/concern for her future life’ (E).

The demands of each phase were different but the duress involved, although it changed, did not appear to ease over time. For some, it increased during the sub-acute/chronic phase and worry over an uncertain future become intrusive:

‘as time has gone following mum’s injury I have found it much harder’ (E);

‘I worry greatly about how I will cope long term if my wife needs constant care at home’ (D);

‘It is now over a year since my wife became ill and I am surprised that stress levels have, in some way, increased’ (D).

Part of the demand of the chronic phase was the need to accept uninvited change and go through a process of adjustment and grief;

‘as time has gone it has also made me realise my mum as she was, is not coming back’ (E);

‘accepting new family situation and helping dad, the rest of the family and myself come to terms with the fact that things won’t be the same again’ (G).

The worry for the future was dominated by feelings of uncertainty about the development of their relative’s condition and their ability to cope with their needs;

‘out of the blue anxiety attack 9 months later i.e symptoms still emerging ...I’m trying so hard not to say the wrong thing’ (C);

‘it would be easier to cope if you could realistically set your sights’ (D);

‘very anxious about how I will cope when he comes home’ (H).

The chronic uncertainty often prompted them to live in the present, the here and now, ‘...do it now’ (F) and to recommend that others did so too and did not postpone anything they wanted to do to an indeterminate point in the future; ‘the best advice I have been given is to re-set my sights only on today as there is no benefit in panicking about the future’ (D).

The participants’ experience was typified by considerable worry and anxiety which changed over time and involved a significant impact on their relationships, ways of relating and social-connectedness.

Discussion

This study set out to longitudinally explore the complex nature of the experience of chronic stress and psychosocial resources, in close relatives of persons who had experienced a severe brain injury. Over time, we found a significant alteration in the biological stress indicator of cortisol output but not in diurnal cortisol decline. We interpret this as reflecting an initial acute stress response followed by a chronic stress effect. Overall, post traumatic stress symptoms and in particular the coping subscale of avoidance, were linearly associated with diurnal cortisol output at baseline, indicating high levels of initial psychological distress with some reduction at six months. Associations between the coping responses of acceptance and religion with cortisol output and diurnal decline indicate these to be adaptive coping mechanisms of particular relevance to this cohort. Qualitative analysis yielded two themes, relational impact and the passage of time, which are consistent with the pattern of quantitative data and provide further insight into the impact of the experience for the relatives.

The cortisol pattern observed reflects the acute/chronic compound nature of the stress experience referred to in previous research [30]. As the literature reporting

repeated cortisol measures in naturalistic studies of chronic stress is sparse, there is little with which to directly compare these findings. The significant correlations between the traumatic stress symptom subscale of avoidance and total IES score with cortisol output at baseline are comparable with findings from naturalistic stress studies of other chronic stress population [33]. The qualitative data support these findings, with written reports of profound distress including feelings of worry, alienation, apprehension, loss of confidence, guilt and anger, grievance and senselessness. The trajectory of phases mentioned by one participant was particularly poignant with respect to the theme of 'passage of time'. These phases are consistent with the cortisol pattern observed: high cortisol output at admission, followed by the significantly lower level of cortisol at 6 weeks, then the gradual increase at three and 6 months follow up, as concerns for the long term future created further anxiety. A complex relationship was observed between psychological coping resources and cortisol across the six months of the study. The COPE subscales of acceptance, instrumental support, planning, positive reframing, and religion revealed consistent significant associations with cortisol activity across the four assessment points, with religion and acceptance being the most notable. All associations were negative, indicating that use of these coping responses were individually associated with lower diurnal output of cortisol and/or greater change in diurnal cortisol, with the exception of acceptance and positive reframing at the three month follow-up. The change in direction of effect at the three month assessment is also in accordance with the qualitative data mentioned above. Acceptance and positive reframing subscales of the COPE are both coping measures that have previously been associated with beneficial effects in other chronic illness populations [34] and could be viewed as 'problem engagement' responses in a similar way to those reported by O'Donnell et al [35], as well as being consistent with

other coping research specifically relating to brain injury [21]. The change in direction of effect at three months reflects the non-linear trajectory in the adaptation to rehabilitation in this population and indicates the contextual importance of coping. Similarly, results associated with the coping response of turning to religion are in accordance with other more in depth studies which have reported similar associations with lower cortisol in other populations experiencing chronic stress from illness [52-54].

The lack of effects relating to the COPE subscales of emotional/ instrumental social support and cortisol levels is not consistent with previous research which has found the use of social support coping to be associated with lower cortisol in healthy participants [35]. However, the qualitative data highlights the importance of the relational impact of having a relative experience brain injury. In writing about their experience, participants refer to a range of social networks including family, hospital staff, and friends, with a focus on the emotional context of support, with elements of social belonging, consistent with other research [17]. That the qualitative rather than the quantitative data in this study yielded important findings relevant to social support indicates the appropriateness of such a mixed methods approach with this population. Given the lack of research examining coping strategies and their effect on HPA axis functioning [30,35] these effects are of interest. Coping strategies certainly compose an important part of the 'stressor mosaic' referred to in previous research [30] and the naturalistic longitudinal elements highlighted here require further investigation at both quantitative and qualitative levels.

The embedded design of this study enabled us to examine the complex issues associated with a family member experiencing a brain injury from three perspectives: quantitative psychosocial, quantitative biological and qualitative. The triangulation of

these results yielded a number of important and clinically relevant findings encompassing both the psychological and physiological effects of the trauma experience on family members. However, a number of limitations exist in the current study. It is acknowledged that the quantitative findings need further replication and exploration with a larger sample size in future studies in order to more precisely understand the relationships between psychosocial factors and cortisol observed in this study. In particular, the attrition rate (40%) reflects the difficulty of following such a difficult to study population longitudinally. Given the intake of patients to long term rehabilitation units such as the facility used in this study, findings need replication across a multisite study in order to obtain a sufficiently large initial cohort. Statistically the studied was underpowered and as such findings are only speculative and caution must be exercised in generalising even within other ABI populations. It is also acknowledged that a control group was not included for comparison in the design of this study, rather the participants served as their own controls. Participants in this study were repeatedly assessed whilst undergoing a known stressor and in this respect the study also constitutes a longitudinal developmental design [55]. Whilst there is a certain amount of utility in this design, and broad comparisons can be made to cortisol levels in other studies, future research incorporating a control group would be beneficial for a number of reasons. Inclusion of a control group of participants not experiencing an ABI life event in a relative, as well as inclusion of comparison groups representing other types of injury would be necessary to more fully explore the quantitative relationships reported here. Future research with a larger number of participants would also enable within group comparisons by age, sex and generational relationship of the relative, which were not possible with the current sample size. Whilst questionnaire assessment was fruitful, particularly in relation to coping

responses, the generalised measurement of stress and social support were less useful for this population. Refinement of questionnaires to utilise those most valid for this specific population is necessary, particularly for tapping relevant mechanisms of social support. An assessment of other co-occurring life event stress would also enable the potential to disentangle ABI related stress from other non-ABI related acute and chronic stressors. Future research would benefit from expanding the qualitative assessment to include an in-depth interview where psychosocial concepts can be probed, particularly in relation to coping responses. The small amount of qualitative data means that it needs to be approached very tentatively and that any interpretation is seen as speculative. However, the responses were very rich in content and suggest that there would be substantial value in more extensive interviewing.

This naturalistic, mixed methods longitudinal approach to the study of biopsychosocial adaptation in relatives of persons with ABI has served as a useful proof of concept. Triangulation of results enables a multilevel approach to an often neglected and difficult to study population. This study offers the potential to guide clinical intervention following injury when relatives of persons with ABI are themselves potentially vulnerable to the experience of trauma. In conclusion, we have demonstrated the complexity of psychosocial and endocrine consequences using a model of acute/chronic stress exposure in the early stages following ABI in a family member. We propose that in conjunction with larger studies and more in depth assessment, these findings may help assist the development of effective and timely intervention in family members. The relevance of these findings for future research, and implications for the support of relatives via interventions to improve health and well-being are important for both relative(s) and person with ABI.

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Declaration of Interest

No conflicts of interest.

Figure Legends

Figure 1. Study design showing four testing points over six months duration

Figure 2. Mean and SEM of salivary cortisol over four diurnal samples across the four time points of the six month study.

Table 1. Means and standard deviations for stress and social support at baseline and follow-up

Measure	Baseline (n = 15)	Six month follow-up (n = 9)
	Mean (SD)	Mean (SD)
Perceived stress total (PSS)	19.87 (6.19)	19.87 (4.22)
Post traumatic stress symptoms (IES)		
Intrusion	12.31 (8.97)	10.62 (5.45)
Avoidance	8.38 (7.29)	6.12 (4.61)
Total	20.69 (14.47)	16.75 (9.38)
Social support (ISEL)		
Appraisal	13.40 (3.20)	12.87 (2.59)
Belonging	12.60 (1.72)	12.5 (1.77)
Tangible	13.33 (2.38)	12.7 (2.66)

Table 2. Correlation (Spearman's rho) between coping responses at admission and cortisol (area under the curve (AUC) total output and change over time) at each assessment point across study

Coping response variable	Admission to Unit		Post Admission Follow-Up					
	Within 10 days	6 Weeks	3 Months		6 Months			
	(n = 15)	(n = 7)	(n = 9)		(n = 9)			
	<i>AUC_G</i>	<i>AUC_L</i>	<i>AUC_G</i>	<i>AUC_L</i>	<i>AUC_G</i>	<i>AUC_L</i>	<i>AUC_G</i>	<i>AUC_L</i>
Acceptance	-.64**	-.38	-.85*	-.19	-.24	.70*	-.23	.17
Instrumental Support	-.19	-.52*	.24	.07	.01	.12	-.01	.37
Planning	.043	-.52*	.05	.13	.36	-.02	.05	.45
Religion	-.69**	-.58*	.20	.09	.24	.34	-.75*	-.44
Positive reframing	-.35	-.49	-.87*	-.39	.28	.73*	.21	.88**

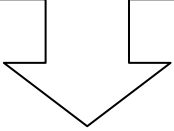
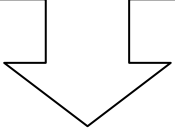
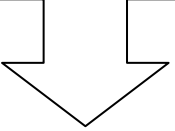
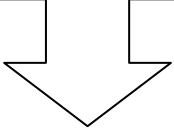
Time points

Baseline
Patient admittance
to RNHRD (within
one week)

Follow-up 1
Six weeks post
admission

Follow-up 2
Three months post
admission

Follow-up 3
6 months post
admission



T1 T2 T3 T4

Assessments

- Psychosocial questionnaires*
- Salivary cortisol assessment
- Open-ended question – written response

- Salivary cortisol assessment

- Salivary cortisol assessment

- Psychosocial questionnaires*
- Salivary cortisol assessment
- Open-ended question – written response

