Plasma Cortisol Levels and Illness Appraisal in Deficit Syndrome Schizophrenia

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Abstract

Research investigating the association between negative symptoms and plasma cortisol levels in individuals with schizophrenia has produced inconsistent findings. This study investigated whether deficit syndrome schizophrenia (characterised by high levels of primary negative symptoms) is associated with comparatively high morning plasma cortisol levels, more negative appraisals about illness and higher levels of depression. Participants were 85 individuals diagnosed with schizophrenia and 85 individuals with no history of contact with psychiatric services matched for age and gender. All participants provided fasting 9.00am plasma cortisol samples. There were no significant differences between the schizophrenia and control participants in plasma cortisol levels. The Proximal Deficit Syndrome method was used to identify individuals with deficit syndrome schizophrenia. Contrary to what had been hypothesised, participants with deficit syndrome schizophrenia had significantly lower plasma cortisol levels than both non-deficit syndrome participants and control participants. Participants with the deficit syndrome reported significantly less negative appraisals about illness (assessed by PBIQ) and lower levels of depression (assessed by BDI-II). Differences in cortisol levels continued to trend toward significance when levels of depression were controlled for. The patterns of illness-related appraisals and plasma cortisol levels raise the possibility that the deficit syndrome could be a form of adaptation syndrome.

Key words

Psychosis, Symptoms, Depression, Deficit syndrome, Cortisol, Stress

1. Introduction

The negative symptoms of schizophrenia reflect a diminishment in a set of basic human capacities required for psychosocial function and acceptable quality of life. They include reductions in the intensity of emotional experience, volition, emotional expression and overall richness of internal experience and thought and are strongly associated with poorer concurrent (Milev et al., 2005; Wittorf et al., 2008), and prospective levels of social and vocational function (Weinberg et al., 2009). Importantly, these deficits appear to be more resistant to current interventions than other symptoms of schizophrenia (Buckley and Stahl, 2007).

One barrier to understanding the roots of negative symptoms, and thereby refining and developing treatment, is that negative symptoms may result from any of a number of different factors. Persons may, for instance, withdraw or demonstrate a paucity of affect as a consequence of impairments in attention that disrupt the processing of relevant stimuli and render social experiences too difficult to negotiate, whilst others might manifest no deficits in attention (Lysaker et al., 2009). One response to this dilemma has been to distinguish Primary from Secondary negative symptoms. As defined by Carpenter and colleagues (Carpenter et al., 1985) *Primary* negative symptoms are directly linked to the pathophysiology of psychosis and so should be relatively stable over time, while *Secondary* negative symptoms are a reflection of processes related to, but not central to, psychosis such as medication side effects, positive symptoms, depression or under-stimulation. Building on this work, Kirkpatrick et al. (1989) developed the *Schedule for Deficit Syndrome* that distinguishes individuals with schizophrenia and primary negative symptoms (i.e. *deficit* schizophrenia) from those individuals without primary negative symptoms (*non-deficit* schizophrenia). A recent overview, suggests that the deficit syndrome can be detected in approximately 15-20% of individuals diagnosed with schizophrenia (Buchanan, 2007). Evidence of the validity of this construct includes findings that it is linked to poorer outcome (Tek et al., 2001).

One of the key assumptions regarding the deficit syndrome is that it is not a reaction to distress or a response to psychological or social problems. Instead, deficit symptoms are cast as a general kind of loss of psychological vitality, something in the spirit of Kraepelin who offered the visual metaphor of a candle's flame slowly dimming. In support of this, individuals with deficit syndrome have been found to have less depression, and lower levels of suicidal ideation, and are less likely to misuse drugs (Tek et al., 2001). Regarding positive symptoms, there is evidence individuals with deficit syndrome experience less frequent social-themed delusions, but not more pronounced levels of psychosis (Tek et al., 2001).

An important gap in the literature relates to the need to examine whether the deficit syndrome is linked with biomarkers of stress. One such biomarker is plasma cortisol. Research has linked the

hypothalamic-pituitary-adrenal (HPA) axis to the expression of vulnerability for schizophrenia (Walker et al., 2008). Hypercortisolemia and the administration of corticosteroids have been associated with increased risk for psychosis (Perantie and Brown, 2002). However, a systematic review by Bradley and Dinan (2010) indicated that of the 77 studies that had compared basal cortisol levels in individuals diagnosed with schizophrenia with controls, less than half (44.2%) found that individuals with schizophrenia had significantly higher basal cortisol levels. It is possible though that some studies included in the review were not sufficiently powered to find significant differences between the groups. Research has also investigated associations between basal cortisol levels and the symptoms of psychosis. Belvederi Murri et al. (2012) conducted a systematic review of 28 studies investigating basal (i.e. not under psychosocial or pharmacological challenge) cortisol levels in individuals with schizophrenia. The vast majority of the studies (n = 24) investigated plasma cortisol levels. The review concluded that the associations between clinical symptoms and plasma cortisol were mixed and inconsistent and that this may be a consequence of the heterogeneity populations (particularly with regard to illness phase) recruited and the methodologies used (Belvederi Murri et al., 2012). Positive correlations were noted between basal plasma cortisol and positive symptoms in some studies (Christie et al., 1986; Keshaven et al., 1989; Rybakowsi et al., 1991), whereas no significant correlations were noted in others (Zhang et al., 2005; Iancu et al., 2007; Goyal et al., 2004; Yilmaz et al., 2007). Studies mainly recruiting individuals with chronic schizophrenia found positive associations between basal plasma cortisol levels and the severity of negative symptoms (Altamura et al., 1989, Kaneko et al., 1992, Shirayama et al., 2002, Zhang et al., 2005, and Iancu et al., 2007). Yet, other studies found no significant association between plasma cortisol and negative symptom levels (Yilmaz et al., 2007; Montelone et al., 1999; Venkatasubraminian et al., 2007; Garner et al., 2010). Similarly positive correlations were noted between basal plasma cortisol depressive symptoms (Halari et al., 2004; Keller et al., 2006), but not others (Munro et al., 1984; Monteleone et al., 1992; Strous et al., 2004; Rybakowski et al., 1991). Distinguishing clinically between depression and negative symptoms (particular *secondary* negative symptoms) can cause clinical confusion (Tarrier, 2005). It is striking that to date, no studies have investigated whether plasma cortisol levels are related to *primary* negative symptoms.

Lysaker and Lysaker (2010) highlighted how the experience of schizophrenia can lead to diminishments in *self-experience* (i.e. the first-person dimension of schizophrenia). Recently, Henriksen and Parnas (2014) have suggested that the anomalous nature of the self-experiences of individuals diagnosed with schizophrenia give rise to deficits in insight. To date there has been a paucity of research investigating how the deficit syndrome might be related to subjective appraisals that individuals make about the impact that their illness has had on their lives. Research has indicated that the deficit syndrome is associated with significantly worse scores on measures of insight, defeatist attitudes, and asocial beliefs than the non-deficit syndrome (Beck et al., 2011). Negative

appraisals of illness have been associated with anxiety, depression and hopelessness in schizophrenia (Birchwood et al., 2000; Gumley et al., 2004; Karatzias et al., 2007; White et al., 2007). Understanding whether the deficit syndrome is associated with negative appraisals about illness seems important for both understanding the phenomenology of the deficit syndrome, as well as developing effective treatments and forming therapeutic relationships with persons living with this condition.

This study sought to determine whether individuals with schizophrenia had significantly higher levels of cortisol relative to a control group of individuals with no history of contact with psychiatric services. In addition, the study sought to determine whether those with the deficit syndrome schizophrenia, relative to those with non-deficit syndrome schizophrenia, would have: i) significantly higher plasma levels of cortisol; ii) elevated levels of depression, and iii) more negative appraisals about their illness.

2. Materials and Method

2.1 Participants

Participants were individuals with diagnosis of DSM-IV (APA, 1994) schizophrenia as recorded in their notes and adjudged by the Consultant Psychiatrist responsible for their care to be presenting with a clinical impression of stability (i.e. no current exacerbation of psychotic symptoms, and no change in general clinical state for 6 months before testing). These individuals (n = 99) were predominantly outpatients recruited from a psychiatric day hospital and a variety of residential schemes in the Northern Health and Social Care Trust, Northern Ireland. There were also a small number of inpatients (n = 8). The inpatients had been in hospital for some time and would have been discharged if it were not for difficulties in finding them appropriate accommodation. Of the 107 individuals approached, 2 decided not to participate and 1 withdrew following the first assessment session.

The Research Psychiatrist (M.McC.) administered the SCID-I (First et al., 1994) diagnostic interview to confirm diagnoses of schizophrenia. Four participants were subsequently excluded because they met DSM-IV criteria for schizoaffective disorder rather than schizophrenia. Consequently, data were gathered on 100 participants with schizophrenia. Of these, 15 further participants were excluded because they were taking medication that could alter hypothalamic-pituitary-adrenal axis functioning (e.g. exogenous steroid medications which suppress normal cortisol production) and/or medications that alter steroid metabolism (including barbiturates, phenytoin, rifampicin, and/or the female contraceptive pill). Of the 85 participants, 77.6% were male (n = 66) and 22.4% (n = 19) were female. All were outpatients.

A control group of 100 individuals with no history of contact with psychiatric services were recruited from a local GP practice for comparison with the participants diagnosed with schizophrenia. Eighty-five of these participants were matched with the participants diagnosed with schizophrenia on the basis of age and gender. All of the control participants were also free from the aforementioned medications that could alter cortisol levels.

2.2 Procedures

The study received approval from the Research Ethics Committee, Royal Victoria Hospital on behalf of Queens University Belfast and all participants signed informed consent. The Brief Psychiatric Rating Scale and the Scale for the Assessment of Negative Symptoms were administered by an experienced research clinician (M.McC.). The Beck Depression Inventory and Personal Beliefs about Illness Questionnaire were administered by the first author (R.W.). In addition to providing plasma samples, the control participants also completed the Beck Depression Inventory.

The Proximal Deficit Syndrome (PDS) method (Kirkpatrick et al., 2000) was used to establish caseness for Deficit Syndrome on the Brief Psychiatric Rating Scale (Overall and Gorham, 1988). Consistent with claims about the prevalence of the deficit syndrome (Buchanan, 2007; Kirkpatrick et al., 2000), the 'deficit syndrome group' consisted of all cases in the top 15 percent of the range of PDS scores (PDS score $\geq$ 1, n = 13). The non-deficit syndrome group consisted of all cases in the lowest 50 percent of PDS scores (PDS score $\leq$ -2, n = 46, 54%). All other participants were excluded from the analyses (PDS score of -1 or 0, n = 26, 31%).

2.2.1 Cortisol Assay

Fasting plasma samples from all participants were collected at 9.00am by the research clinician (M.M^{c}C). All participants were instructed to abstain from unusual physical activity or stress for a period of 24 h prior to blood sampling. Plasma cortisol levels were determined by radioimmunoassay (RIA) using a Serano RIA kit. The assay was performed in accordance with the manufacturer's instructions. Each sample was run in duplicate. The sensitivity was 1 ng/ml, intra- and inter-assay variation coefficients were 4.3% and 8%, respectively. Participants were provided with £10 to compensate for any costs associated with transport to provide cortisol samples. The time of awakening, caffeine consumption and smoking (which can all affect morning neurosteroid levels) of participants diagnosed with schizophrenia and control participants was controlled for.

2.2.2 Chlorpromazine dose equivalents (CPZeq)

The CPZeq is a measure of the relative antipsychotic potencies of neuroleptics. The daily dose of antipsychotic medication prescribed to each patient was converted into milligram equivalents of chlorpromazine according to conversion factors derived from the literature (Davis, 1976; Rey et al., 1989; Woods, 2003). Total CPZeq was constructed by calculating a total daily dose of each antipsychotic listed in the medical file. Then each converted antipsychotic-specific CPZeq amount was added to arrive at a total dose.

3. Measures

Symptoms

Psychiatric symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1988) and the Scale for Assessment of Negative Symptoms (Andreasen, 1989). These scales are widely used for clinical and research purposes and demonstrate sound reliability and validity. The Beck Depression Inventory (BDI-II; Beck et al., 1996) was used to assess levels of depression. The BDI-II has been shown to demonstrate sound reliability and validity (Beck et al., 1996).

The Personal Beliefs about Illness Questionnaire (PBIQ Birchwood et al., 1993) was administered. The questionnaire has 5 subscales. The *Entrapment* subscale assesses the extent to which the participants feel they have control over their illness. The *Attribution: self versus illness* subscale measures the extent to which the participants feel to blame for their illness. The *Loss of autonomy* subscale assesses the extent to which the participants feel that the illness is affecting their capacity for independence. The *Humiliating devaluation of self* subscale examines whether the participants regard the illness as a source of shame. Lastly, the *Humiliating need to be marginalized* subscale assesses the participants' belief in the social segregation and control of the mentally ill. All 16 items on the PBIQ have a 4-point response scale: strongly disagree, disagree, agree, and strongly agree. Higher scores on each of the subscales represent more negative illness appraisals. The PBIQ has been shown to demonstrate sound psychometric properties (Birchwood et al., 1993).

All statistical analyses were performed using SPSS-14. The normality of the data was assessed using Kolomogorov-Smirnov statistics and where appropriate Mann-Whitney tests and Independent T-tests were used to compare different groups. The cortisol data for both the participants with schizophrenia and the control participants were checked for outliers using Hoaglin and Iglewicz (1987) *Outlier Labelling Rule*. No outliers were detected in either group. Analyses of covariance (ANCOVA) were used to investigate the potential impact of age, length of illness, and depression on between group differences in cortisol levels.

3. Results

3.1 Participants diagnosed with schizophrenia vs. control participants

The participants diagnosed with schizophrenia had a mean total score of 14.68 (SD = 8.81) on the BPRS, 35.86 (SD = 18.98) on the SANS, 9.26 (SD = 10.48) on the BDI-II and 6.31(SD = 5.16) on the BHS. The control participants had a mean score of 5.58 (SD = 6.86) on the BDI-II, which was significantly lower than the participants diagnosed with schizophrenia ($t = 2.693$, $df = 167$, $p = 0.008$).

The median plasma cortisol level for individuals diagnosed with schizophrenia was 335.00 nmol/L (IQR = 268.50 – 412.00). This was lower than the median level of 360.00 nmol/L (IQR: 259.75 – 438.25) for control participants but this difference was not statistically significant (Mann-Whitney U = 3789.00, $Z = 0.689$, $p = 0.491$). There were no significant differences between the plasma cortisol levels of male and female participants in either the schizophrenia and control groups.

3.2 Participants diagnosed with schizophrenia

Correlational analyses were conducted to determine if the plasma cortisol levels of the individuals diagnosed with schizophrenia ($n = 85$) were associated with their age, BPRS, SANS, PBIQ subscales, and BDI-II. The α-value was adjusted using the False Discovery Rate (Benjamin et al., 2006). Results indicated that there were no statistical significant correlations. Similarly plasma cortisol levels were not significantly correlated with the age and BDI-II scores of the control participants ($n = 85$).

Individuals diagnosed with schizophrenia with deficit syndrome had significantly lower levels of cortisol than did individuals with non-deficit syndrome (287.85 nmol/L compared to 362.26 nmol/L respectively) ($t = -2.16$, $df = 57$, $p = 0.035$). Relative to individuals with non-deficit syndrome, the deficit syndrome group had significantly lower scores on the Brief Psychiatric Rating Scale ($Z = -2.66$, $p = 0.008$). There were no significant differences between the groups on the SANS. The deficit syndrome group was also receiving significantly lower levels of anti-psychotic medication as assessed by chlorpromazine equivalent doses ($Z = -2.10$, $p = 0.033$) than their non-deficit syndrome counterparts. Fisher's Exact Test indicated that there was no significant difference in the proportion of individuals in the deficit and non-deficit syndrome groups currently taking anti-depressant medication ($p = 0.246$). In addition, Fisher's Exact Test indicated that there was no significant difference in the proportion of individuals taking typical vs. atypical antipsychotic medication between the deficit and non-deficit syndrome groups ($p = 0.516$).

Table I provides details of between group comparisons that were made between participants with deficit syndrome and those with non-deficit syndrome. Relative to participants with non-deficit syndrome, the individuals with deficit syndrome had significantly lower scores on the *Entrapment* ($Z = -2.16$, $p = 0.031$), *Attribution: Self vs Illness* ($t = -2.62$, $df = 35.58$, $p = 0.013$), *Loss of Autonomy* ($Z = -2.41$, $p = 0.016$), and *Humiliating Devaluation of Self* ($Z = -3.07$, $p = 0.002$) subscales of the PBIQ but not the *Humiliating Need To Be Marginalized* subscale. The deficit syndrome group had significantly lower scores on the BDI-II ($Z = -4.76$, $p < 0.001$) than did the non-deficit participants.

The individuals with deficit syndrome also had significantly lower plasma cortisol levels (median = 271 nmol/L, IQR = 239.00 – 355.00 nmol/L) than did the control participants (median = 360.00 nmol/L, IQR = 259.75 – 438.25 nmol/L) (Z-score 2.10, $p = 0.036$).

INSERT TABLE I

3.3 Covariate analyses:

The difference between the deficit-syndrome and non-deficit syndrome participants in cortisol levels continued to be statistically significant when levels of BPRS rated psychiatric symptoms ($F = 6.05$; $df = 1,56$; $p = 0.02$) and participants' age was controlled for ($F = 4.88$; $df = 1,56$; $p = 0.031$). Similarly, the difference in plasma cortisol levels between the deficit-syndrome and non-deficit syndrome participants was a trend approaching significance when depression was controlled ($F = 3.48$; $df = 1,56$; $p = 0.07$). The differences between the groups on the subscales of the PBIQ became non-significant when BDI-II score was controlled for.

4. Discussion

The current paper sought to advance understanding about the relationship between cortisol levels and negative symptoms of schizophrenia. Some previous studies have found that higher plasma cortisol levels are associated with higher levels of both negative symptoms (e.g. Shirayama et al., 2002; Zhang et al., 2005), whereas other studies failed to find any significant correlation between these variables (e.g. Venkatasubraminian et al., 2007; Garner et al., 2010). The study sought to address inadequacies in previous research, which could not rule out the possibility that secondary negative symptoms (linked to medication side effects, positive symptoms, depression or under-stimulation) were confounding the relationship between cortisol levels and primary negative symptoms. Specifically, 9.00am fasting plasma cortisol levels of individuals with deficit syndrome of schizophrenia

(characterised by high levels of primary negative symptoms) were compared with the cortisol levels of individuals with non-deficit syndrome. With this being the first research to focus on primary negative symptoms, the study findings have important implications for advancing understanding about the relationship between plasma cortisol levels and negative symptoms.

Analyses indicted that individuals with deficit syndrome had significantly lower levels of plasma cortisol than did those individuals without deficit syndrome. Indeed, the plasma cortisol levels of individuals with deficit syndrome were significantly lower than those of the control participants. This was the opposite of what has been hypothesised. The cross-sectional nature of this research, limits the extent to which assertions can be made about precisely why individuals with deficit syndrome would have significantly lower levels of plasma cortisol. Mondelli et al. (2010) previously found a significant negative correlation between the number of stressful life events and basal cortisol levels in individuals experiencing first-episode psychosis, compared to a significant positive correlation between the number of stressful life events and cortisol level for control participants. Mondelli et al. (2010) claimed that individuals with schizophrenia who had experienced pronounced levels of life stress (such as childhood trauma) may actually hypo-secrete cortisol. Similarly, Braehler et al. (2005) reported that schizophrenia patients who had experienced childhood trauma were observed to have lower 24-hour salivary free cortisol than their counterparts who had not experienced any substantive childhood trauma. Furthermore, cortisol levels were significantly negatively correlated with levels of emotional and sexual abuse (Braehler et al., 2005). In a systematic review of the available evidence, Bradley and Dinan (2010) proposed that extreme childhood trauma could account for the variation in basal cortisol levels observed in individuals with schizophrenia. Research investigating cortisol levels in individuals diagnosed with Post-Traumatic Stress Disorder (PTSD) suggest that the *type* and *chronicity* of the stressor are linked with cortisol levels (Meewise et al., 2007). For instance, people with PTSD due to physical or sexual abuse had lower cortisol levels than controls suggesting chronic trauma that starts in early development may be also related to a chronic suppression of cortisol function to compensate for periods of hypercortisolemia (i.e. increased cortisol responsiveness to stressors) (Bremner et al., 2003). Unfortunately, the current study did not assess the level of trauma that the participants had experienced, so the association between past trauma and deficit syndrome could not be explored.

This is the first study to investigate whether there are differences in how participants with and without the deficit syndrome appraise their illness. Birchwood et al. (2000) have proposed that appraisals of illness (including themes such as loss, entrapment and humiliation) can give rise to depression. Consistent with this, strong associations have been noted between negative appraisals about illness and depression in individuals diagnosed with schizophrenia (Birchwood et al., 2000; White et al., 2007). In the current research, participants with deficit syndrome made significantly less negative

appraisals about their illness, and had significantly lower levels of depression than their non-deficit syndrome counterparts. This pattern of findings was the opposite of what had been hypothesised. When the level of depression was controlled for, the differences between the deficit/no-deficit syndrome participants in the appraisals about illness became non-significant.

Peralta et al. (2014) recently found no significant difference in levels of depression between individuals with deficit syndrome compared to non-deficit syndrome. However, the significantly lower levels of depression observed in individuals with non-deficit syndrome in the current study, are consistent with Beck et al.'s (2011) findings. Beck et al. (2011) proposed that the deficit syndrome may constitute a form of 'safe haven' whereby individuals experience a state of social with-drawl that protects them from experiencing failures and disappointments. When considered in the context of the conclusions drawn by Beck et al. (2011) and Bremner et al. (2003), the findings of the current study raise the possibility that the deficit syndrome may be the result of a succession of adaptations to life stress, and that reduced plasma cortisol levels displayed by individuals with deficit syndrome could be due to a suppression in cortisol production in response to prolonged hypercortisolemia.

We have recently proposed that negative symptoms of psychosis are a consequence of long-standing experiences of social defeat (White et al., 2013), and it may be that the deficit syndrome represents an end state where the individual behaves in a manner that minimises social interactions and the associated stress that this can cause. The lower levels of cortisol, less negative appraisals about illness and lower levels of depression evident in the deficit syndrome participants in the current study may be a reflection of how comparatively unperturbed they currently are by the experience of schizophrenia. It is important to highlight that alternative interpretations cannot be ruled out, and it is equally possible that the comparatively low levels of plasma cortisol in the deficit syndrome group are indicative of low premorbid levels of cortisol secretion. Although speculative, claims that deficit syndrome may represent a form of adaptation syndrome characterised by hypo-secretion of cortisol do merit further investigation.

There are a number of potential confounding factors that need to be considered when investigating the relationship between cortisol levels and primary negative symptoms. First, there is the issue of depression. Previous research with individuals diagnosed with schizophrenia has indicated that plasma cortisol levels were correlated positively and significantly with depression (Halari et al., 2004; Keller et al., 2006), yet other research noted no significant association (e.g. Monteleone et al., 1992; Strous et al., 2004). In the current study, the level of negative symptoms (as assessed by the SANS) was not correlated with plasma cortisol levels. Contrary to what had been hypothesized, individuals with deficit syndrome had significantly lower levels of depression than their non-deficit syndrome counterparts. Analyses indicated that when the level of depression was controlled for the differences

in plasma cortisol levels between the deficit and non-deficit syndrome trended towards significance. This suggests that the differences in cortisol levels between the deficit/non-deficit syndrome participants were largely independent of differences in levels of depression.

Positive symptoms may also impact on plasma cortisol levels. Correlations have been found between basal plasma cortisol and positive symptoms in some studies (e.g. Keshaven et al., 1989; Rybakowsi et al., 1991), but not others (Iancu et al., 2007; Yilmaz et al., 2007). In the current study the non-deficit syndrome participants had significantly higher levels of psychiatric symptoms as assessed by the BPRS than did the deficit syndrome participants. However, differences between the two groups in plasma cortisol levels remained significant when the levels of psychiatric symptoms were controlled for, suggesting that the differences in plasma cortisol levels between the groups were not directly linked to these symptom levels.

Another potential confounding factor relates to the use of antipsychotic medication. Atypical antipsychotic medications have been shown to reduce plasma cortisol levels in some studies (Hatzimanolis et al., 1998; Markianos et al., 1999; Scheepers et al., 2001), but not all (Breier et al. 1994). In the current study the deficit syndrome group had significantly *lower* levels of plasma cortisol than their non-deficit syndrome counterparts. This was in spite of the deficit syndrome group receiving significantly *lower* doses of antipsychotic medication. There were also no significant differences between the groups in the proportion of individuals taking typical vs. atypical antipsychotic medication. These findings suggest that the pattern of difference between the groups in plasma cortisol levels were not linked to antipsychotic medication. Smoking has been shown to have an effect on cortisol (Jansen et al., 1998). As we did not record the smoking status of all participants in the current study, it is unclear to what extent this might have impacted on findings. Lastly, research indicates that night-shift work can impact on levels of cortisol secretion (Nui et al., 2011). Unfortunately, information about night-shift work was not gathered from any of the participants.

The morning cortisol levels observed for the schizophrenia and control groups in the current study are largely consistent with those obtained in a previous study by Ritsner et al. (2004). Contrary to what had been hypothesized, analyses indicated that there were no significant differences between participants diagnosed with schizophrenia and the control participants. The lack of a significant difference in cortisol levels between participants diagnosed with schizophrenia and control participants is however consistent with some previous studies (Lee et al., 2001; Kaneda et al., 2002; Ritsner et al., 2004), but not others (Ritsner et al., 2006). The current study has shown for the first time that individuals with deficit syndrome have significantly lower levels of plasma cortisol than a group of control participants. The precise reasons for this remain unclear. The systematic review by Bradley and Dinan (2010) concluded that overall people diagnosed with schizophrenia tend to experience

elevated levels of cortisol secretion relative to control participants. However, the authors point out that some studies found that cortisol levels were actually lower in the schizophrenia group compared with control participants. Although this heterogeneity in the research findings may be due to the confounding impact of medication or environmental factors, the findings of the current study raise the possibility that characteristics of the individuals' experience of schizophrenia (e.g. deficit syndrome vs. non-deficit syndrome) may be contributing to the lack of consistency in the research findings.

It is important to acknowledge that the current study had a number of limitations. Plasma cortisol assays were used. For some individuals the drawing of blood can be stressful and this can inadvertently lead to an increase in cortisol levels. Future research could seek to replicate the current findings by using a salivary assay strategy, which is associated with lower levels of stress (Kirschbaum and Hellhammer, 1994). The current study only used a single sampling time. The diurnal patterning of cortisol secretion can provide important indications about potential dysfunction in the hypothalamic-pituitary-adrenocortical (HPA) axis (Nicolson, 2007), but this was beyond the scope of the current study. The *cortisol awakening response* (CAR) has been operationalized as the absolute change in cortisol levels from awakening to a fixed time point (e.g., 30 minutes) after waking. To improve accuracy, future research should utilize repeated measures of HPA activity such as the CAR or an analysis of the diurnal slope of cortisol levels. Similar to other research (e.g. Beck et al., 2011), the current study used the Proxy for Deficit Schedule (PDS; Kirkpatrick et al., 2000), a measure that derives deficit scores directly from BPRS ratings. Consequently, the present study did not use the gold standard assessment i.e. the Schedule for the Deficit Syndrome (SDS; Buchanan, 2007). However, PDS scores have been found to correspond highly with ratings on the SDS (Buchanan, 2007). As has been the case with previous studies (e.g. Beck et al., 2011), the number of participants in the current study that met criteria for the deficit syndrome was comparatively small. Future studies should look to recruit larger numbers of individuals who meet criteria for the deficit syndrome. The cross-sectional nature of the current study also limits understanding about how changes in deficit syndrome are temporally related to changes in appraisals about illness, depression and cortisol. Future longitudinal research could investigate these interactions.

4.1 Conclusions

Previous studies have provided mixed data on the relationship between schizophrenia and biological indices of stress adaptation such as cortisol levels. The purposive analysis of stress biomarker profiles in individuals with deficit syndrome used here has generated data suggesting that the deficit syndrome is marked by lower plasma cortisol levels, significantly less negative appraisals about illness, and lower depression compared to non-deficit syndrome. There is also a need to extend the current

findings by longitudinally exploring the interaction between deficit syndrome, premorbid trauma, stress responses, and appraisals about illness.

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Declaration of interest

The authors have no interests to declare over the last two years.

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Table I. Comparison of deficit vs. non-deficit participants

Variable			Deficit (N = 13)	Non-deficit (N = 46)	Group Comparison		
Gender	Male	N (%)	11 (84.60)	35 (76.10)	0.43	1	.512
	Female	N (%)	2 (15.40)	11 (23.90)			
Cortisol (nmol/L)		Mean (SD)	287.85 (80.88)	362.26 (116.32)	t = -2.16	57	.035*
Chlorpromazine equivalents (CPZeq: mg)		Median (IQR)	150.00 (96.00 – 250.00)	310.00 (237.50-416.75)	Z = -2.10	N/A	.033*
Symptom Ratings							
BPRS		Median (IQR)	8.00 (5.00 – 16.00)	16.50 (11.00 – 23.00)	Z = -2.66	N/A	.008**
SANS Total		Mean (SD)	41.38 (21.99)	36.09 (18.05)	t = 0.88	56	.379
Beck Depression Inventory		Median (IQR)	0.00 (0.00-3.50)	11.50 (5.75 – 19.50)	Z = -4.76	N/A	.000***$
Personal Beliefs about Illness							
Entrapment		Median (IQR)	9.00 (7.00 – 10.50)	10.00 (9.00 – 13.25)	Z = -2.16	N/A	.031*
Attribution: Self vs. illness		Mean (SD)	8.15 (1.52)	9.67 (2.71)	t = -2.62	35.58	.013*
Loss of autonomy		Median (IQR)	6.00 (5.00 – 7.00)	8.00 (6.00 – 9.00)	Z = -2.41	N/A	.016*
Humiliating devaluation of self		Median (IQR)	6.00 (5.00 – 7.00)	8.00 (6.00 -9.00)	Z = -3.07	N/A	.002**$
Humiliating need to be marginalized		Median (IQR)	4.00 (4.00 – 4.50)	4.00 (4.00 – 5.25)	Z = -0.93	N/A	.351

BPRS = Brief Psychiatric Rating Scale, SANS = Scale for Assessment of Negative Symptoms

* $p < 0.05$

** $p < 0.01$

*** $p < 0.001$

$ Significant according to the False Discovery Rates (Benjamin et al., 2006)

The study investigated plasma cortisol levels in individuals with schizophrenia.

Participants with deficit syndrome were compared with those with no deficit syndrome.

Participants with deficit syndrome had significantly lower levels of plasma cortisol.

Participants with deficit syndrome made less negative appraisals about illness.

Participants with deficit syndrome were significantly less depressed.