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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 (characterized 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 9.00 a.m. 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 hypothesized, 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.

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

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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; Keshavan et al., 1989; Rybakowski 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; Monteleone et al., 1999; Venkatasubramanian et al., (2007); Garner et al., 2011). Similarly positive correlations were noted between basal plasma cortisol and depressive symptoms in some studies (Halari et al., 2004; Keller et al., 2006), but not others (Munro et al., 1984; Monteleone et al., 1999; 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 till 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, 2013 have suggested that the anomalous nature of the self-experiences of individuals diagnosed with schizophrenia give rise to deficits in insight. Till 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., 2013). 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 who were 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 ($n=100$) 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