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# Pituitary volume reduction in schizophrenia following cognitive behavioural therapy

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ABSTRACT

Cognitive behavioural therapy (CBT) for psychosis (CBTp) aims to lower the stress of psychotic symptoms. Given that the pituitary is involved in stress regulation, CBT-led stress reduction may be accompanied by a change in pituitary volume. This study aimed to determine whether CBTp reduces pituitary volume in schizophrenia. The relation between pre-therapy memory and CBTp-led pituitary volume change was also examined given that poor memory relates to a blunted cortisol awakening response, denoting impaired stress response, in schizophrenia. Pituitary volume was measured at baseline in 40 schizophrenia or schizoaffective disorder patients and 30 healthy participants before therapy. Pituitary volume was measured again 6–9 months after patients had either received CBTp in addition to standard care (CBTp + SC, $n = 24$), or continued with standard care alone (SC, $n = 16$). CBTp + SC and SC groups were compared on pituitary volume change from baseline to follow-up. Pre-therapy memory performance (Hopkins Verbal Learning and Wechsler Memory Scale – Logical memory) was correlated with baseline-to-follow-up pituitary volume change. Pituitary volume reduced over time in CBTp + SC patients. Additionally, pre-therapy verbal learning correlated more strongly with longitudinal pituitary volume reduction in the CBTp + SC group than the SC group. To conclude, CBTp reduces pituitary volume in schizophrenia most likely by enhancing stress regulation and lowering the distress due to psychotic symptoms.



## 1. Introduction

The pituitary plays a key role in physiological stress regulation. Stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis to release corticosteroids from the hypothalamus and anterior pituitary (Appiah-Kusi et al., 2015). In turn, the hypothalamus and anterior pituitary stimulate cortisol release from the adrenal glands that lowers stress reactivity. Through a negative feedback loop, high plasma cortisol lowers hypothalamus and pituitary activity. The neural diathesis-stress model of schizophrenia posits that a genetic predisposition to schizophrenia combines with an accumulation of environmental factors, including psychosocial stress, that disturb the homeostasis of the HPA axis (Pruessner et al., 2017; Walker et al., 2008). This disturbance results in HPA axis hyperactivity and elevated cortisol level that affect glucocorticoid receptors in the hippocampus and medial prefrontal cortex, and increases dopamine release and prominent psychotic symptoms.

Stress regulation is implicated in cognitive behavioural therapy for psychosis (CBTp), because CBTp reduces distress due to psychotic experiences (National Institute of Health and Clinical Excellence, 2014, NICE Clinical Guideline 178). CBTp helps patients to modify their thoughts, become aware of their reactivity to stressful situations, and think less threateningly about psychotic experiences (National Institute of Health and Clinical Excellence, 2014). CBT changes appraisal of psychosocial stress and lowers cortisol levels in patients with generalized anxiety disorder by helping patients to generate strategies to overcome anxiety (Rosnick et al., 2016). Poorer parental bonding at childhood relates to lower cortisol awakening response in patients with first-episode psychosis (Pruessner et al., 2013). Certain acute psychosocial stressors (e.g. performing cognitive tasks) result in sustained cortisol elevation in schizophrenia (Nugent et al., 2015), while other social stressors (e.g. public-speaking and job interviews) decrease cortisol levels (Bradley and Dinan, 2010; Ciufolini et al., 2014). Consequently, increased emotional reactivity to daily life stressors relates to larger pituitary volume in patients with psychosis (Habets et al., 2012). However, lower pre-CBT urinary cortisol relates to CBT-led reduction in symptom severity in people with depression (Thase et al., 1996).

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Pituitary volume is reflective of HPA axis structure and function, stress and psychosis severity. Greater perceived distress from adverse life events relates to smaller pituitary volume in people who have a first or second degree relative with schizophrenia (Cullen et al., 2015). Greater pituitary volume relates to higher plasma cortisol level three years later in healthy adolescent boys (Kaess et al., 2013). Also, greater pituitary volume relates to higher nocturnal cortisol in patients with depression or bipolar disorder (Axelson et al., 1992). In schizophrenia, the pituitary enlarges at the prodromal and early stages; then, it atrophies over the chronic stage (Shah et al., 2015; Atmaca, 2014). Moreover, pituitary enlargement relates to less improvement of psychotic symptoms in early psychosis (Garner et al., 2009; Takahashi et al., 2011). Nonetheless, evidence for the relation between pituitary volume and HPA axis function in schizophrenia is scarce and contradictory.

### 1.1. The role of memory in HPA axis activity and CBTp responsiveness

Memory may be associated with stress regulation and HPA axis function. Cortisol is a glucocorticoid, which binds to glucocorticoid receptors in the hippocampus and prefrontal cortex where memory is formed and stored (Wingenfeld and Wolf, 2011). Cortisol binding to glucocorticoid receptors in the hippocampus lowers HPA axis activity (Jacobson and Sapolsky, 1991). Excessive endogenous and exogenous cortisol impairs memory in healthy people (Wingenfeld and Wolf, 2011). In patients with first-episode psychosis and children at risk for psychosis, blunted cortisol awakening response (denoting the physiological arousal due to the sleep-wake transition) relates to poorer memory (Aas et al., 2011; Cullen et al., 2014). Perhaps, poor HPA axis function can damage the hippocampus and diminish memory (Karanikas and Garyfallos, 2015; Wingenfeld and Wolf, 2011). To our knowledge, no study has investigated the association between memory and pituitary volume in schizophrenia patients. There is, however, evidence of positive associations between pre-therapy verbal memory and CBTp response (Penades et al., 2010), and larger hippocampal volume and CBTp response (Premkumar et al., 2009). Larger hippocampal volume is consistently associated with better verbal memory in schizophrenia (Antonova et al., 2004).

The aims of the present study were to determine whether CBTp reduces pituitary volume, and whether pre-therapy memory relates to CBTp-led pituitary volume reduction. Firstly, it was hypothesized that CBTp would reduce pituitary volume, because CBT helps patients to find stress regulation strategies and CBT reduces cortisol level (Rosnick et al., 2016). Secondly, it was hypothesized that better pre-therapy memory would relate to greater pituitary volume reduction in patients receiving CBTp, because good memory in patients receiving CBTp could lower stress-related cortisol level.

## 2. Methods and materials

### 2.1. Participants and design

Participants were 40 patients with a DSM-IV non-affective psychosis diagnosis (First et al., 2002) recruited from the South London and Maudsley NHS Foundation Trust; 24 patients received CBTp plus standard care (CBTp + SC), and 16 patients received standard care only (SC). Thirty healthy participants matched on age, sex and number of years in education, who reported no mental disorder history, were recruited from the same geographical area as the patients. Participants in this study have previously been examined for the neural effects of CBTp (Kumari et al., 2011). Patient inclusion criteria were: (1) a DSM-IV diagnosis of schizophrenia or schizoaffective disorder, (2) willingness to receive CBTp, (3) a stable dose of antipsychotic drugs for at least two years and their current antipsychotic drug for at least three months, (4) a score above 60 on the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and (5) having at least one distressing positive symptom, i.e. scoring three or more on a PANSS positive item. In addition, CBTp + SC patients were those who were referred to and accepted for CBTp by the Psychological Interventions Clinic for Outpatients with Psychosis (PICuP) at the South London and Maudsley NHS Foundation Trust. By following opportunistic sampling, the psychiatrists in the participating psychiatric services recommended suitable patients to be allocated to the SC group. The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee approved the study. All participants provided written informed consent.

CBTp aims to reduce distress, depression, anxiety and hopelessness by minimizing interference arising from psychotic symptoms (Fowler et al., 1995). Therapy was delivered weekly or fortnightly (as preferred by the patient) over an average of 16 individual one-hour sessions for 6–9 months. In initial sessions, the therapist engaged the patient by forming a therapeutic relationship and focusing on the patient's needs. Standard care consisted of typical and atypical antipsychotic medication and six-monthly care plan assessment reviews delivered by a case management team, with a view to recovery. The case management team included a dedicated care coordinator who saw the patient at regular intervals, a psychiatrist and other specialists, such as a clinical psychologist and occupational therapist.

### 2.2. Clinical and memory assessments

Experienced psychiatrists (DF and APA) diagnosed the patients using the Structured Clinical Interview for DSM-IV (First et al., 2002), blind to the type of intervention patients received (CBTp + SC or SC). The psychiatrists assessed patients' symptom severity using the PANSS (Kay et al., 1987) before and after CBTp, or 6–9 months after baseline in the SC group. Trained doctoral-level researchers assessed participants' pre-therapy memory blind to the hypotheses being tested. Participants were assessed on Wechsler Memory Scale – III Logical Memory (WMS-LM, Wechsler, 1998) and Hopkins verbal learning test (HVLT, Shapiro et al., 1999). In WMS-LM, participants listened to two stories read by the examiner and recalled the stories immediately (immediate recall) and then, half an hour later (delayed recall). Immediate and delayed recall scores were calculated by scaling the raw scores to the age-related norms of the test. In HVLT, participants listened to a list of 12 words read out by the researcher three times. Participants recalled the list each time. Verbal learning was calculated as the total number of freely recalled items across the three trials.

### 2.3. Pituitary and whole brain volumetry

T1-weighted structural magnetic resonance imaging brain scans were acquired in the axial plane with 1.5 mm contiguous slices from a 1.5 Tesla NV/i Signa scanner (General Electric, Milwaukee, Wisconsin) at the Centre for Neuroimaging Sciences, King's College London (TR = 18 ms, TI = 450 ms, TE = 5.1 ms, flip angle = 20° with one data average and a 256 × 256 × 128 voxel matrix). Patients were scanned at baseline and follow-up, while healthy participants were scanned at baseline only. Volumetry was performed manually using the MEASURE programme based on the Cavalieri principle (Barta et al., 1997). The Cavalieri principle states that the volume of an object may be estimated by sectioning it with a set of uniformly spaced parallel planes and measuring the cross-sectional area of the object on each plane (Barta et al., 1997). Trained researchers measured the pituitary (DB, AS and PPK) and whole brain volume (PPK) blind to group membership and treatment allocation. Novice raters achieved 95% accuracy against a trained rater's measurement of the region of interest on ten test brain scans before beginning to measure the study participants' brain scans. The pituitary was defined as a hyper-intensity adjacent to the posterior pons on the sagittal view, with clearly defined anterior and posterior boundaries (Klomp et al., 2012; Tien et al., 1992). The infundibular stalk was excluded from the segment (Fig. 1). The whole brain included the cerebral cortex, namely frontal, temporal, parietal and occipital lobes, and the subcortex, namely the basal ganglia and thalamus (DeLisi et al., 1995).

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