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Pituitary Volume in People with Chronic Schizophrenia: Clarifying the Roles of Serious Violence and Childhood Maltreatment

Minal Bipin[a#], Preethi Premkumar[b#], Mrigendra K Das[c], Jennifer YF Lau[d], Alex L Sumich[e], Veena Kumari[a,f*]

[#]Joint first authorship

[a]Division of Psychology, Department of Life Sciences, College of Health, Medicine and Life Sciences, Brunel University London, UK
[b]Division of Psychology, School of Applied Sciences, Southbank University of London, UK
[c]Flinders University, Australia
[d]Department of Psychology, Institute of Psychology, Psychiatry and Neuroscience, Kings College London, UK
[e]Division of Psychology, School of Social Sciences, Nottingham Trent University, UK
[f]Centre for Cognitive Neuroscience, College of Health, Medicine and Life Sciences, Brunel University London, UK

Corresponding author: Veena Kumari, Division of Psychology, Department of Life Sciences, & Centre for Cognitive Neuroscience, College of Health, Medicine and Life Sciencs, Brunel University London, Uxbridge, UK. Email: veena.kumari@brunel.ac.uk

Abstract

Aberrations in stress-linked hypothalamic-pituitary-adrenal axis function have been independently associated with schizophrenia, antisocial behaviour and childhood maltreatment. In this study, we examined pituitary volume (PV) in relation to childhood maltreatment (physical abuse, sexual abuse, neglect) in men (i) with schizophrenia and a history of serious violence (n=13), (ii) with schizophrenia but without a history of serious violence (n=15), (iii) with antisocial personality disorder (ASPD) and a history of serious violence (n=13), and (iv) healthy participants without a history of violence (n=15). All participants underwent whole-brain magnetic resonance imaging. Experiences of childhood maltreatment were rated based on interviews (for all), and case history and clinical/forensic records (for patients only). There was a trend for smaller PV, on average, in schizophrenia patients (regardless of a history of violence), compared to the healthy group and the ASPD group; other group differences in PV were non-significant. Sexual abuse ratings correlated negatively with PVs in ASPD participants, but no significant association between childhood maltreatment and PV was found in schizophrenia participants. Our findings are consistent with previous evidence of smaller-than-normal PV in chronic schizophrenia patients, and suggest that illness-related influences may mask the possible sexual abuse-smaller PV association, seen here in ASPD, in this population.

Keywords: sexual abuse, physical abuse, violence, MRI, stress

1. Introduction

There is epidemiological evidence of an increased risk of serious violence and aggression in people with schizophrenia and antisocial personality disorder (ASPD), relative to the general population (Eronen et al., 1998; Arseneault et al., 2000; Yu et al., 2012; Fazel et al., 2014). Amongst personality disorders (PDs), ASPD is most strongly associated with a risk of violence (review, Yu et al., 2012). Individuals who as children suffered maltreatment (physical, psychological or sexual abuse, neglect), compared to those who did not, are also more likely to commit violence towards themselves and others (reviews, Perepletchikova and Kaufman, 2010, McMahon et al., 2018; Smyth et al., 2017; Li et al., 2019) and have an increased risk of developing a range of mental disorders, including psychosis and ASPD (e.g. Bendall et al., 2008; Bebbington et al., 2011; Dhakal et al., 2019; Munitz et al., 2019; Pandey et al., 2020). Several brain regions known to be responsive to stress (e.g., the prefrontal cortex, hippocampus) are found to be aberrant in people with schizophrenia (reviews, Honea et al., 2005; Dietsche et al., 2017), ASPD (reviews, Bassarath, 2001; Yang and Raine, 2009), a history of violence (review, Dolan et al., 2014), and childhood maltreatment (review, McCrory et al., 2010). An important structure in this context is the pituitary gland: when a stressor stimulates the corticotrophin-releasing hormone in the hypothalamus, it acts on the pituitary gland causing it to produce the adrenocorticotropic hormone (ACTH). The ACTH then stimulates the adrenal cortex to raise the concentration of cortisol, the stress hormone (Chrousos and Gold, 1992). It has been proposed (Hankin, 2005; Haltigan et al., 2011) that the link between childhood maltreatment and development of various mental disorders may be explained by the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis.

To date, there is no empirical investigation of the pituitary gland in the context of childhood maltreatment or serious violence in adults with a diagnosis of schizophrenia. Still, evidence of pituitary volume (PV) changes ancillary to HPA axis dysregulation in schizophrenia may concur with evidence of a compromised PV in schizophrenia arising from stress. A larger PV is seen during the prodromal and early phases, and a smaller PV is seen during the chronic phase of schizophrenia, in many (but not all) studies (reviews, Pariente, 2008; Atmaca, 2014; Anastassiadis et al., 2019). Larger PV is also reported to correlate with positive schizotypy and to predict conversion-to-psychosis in people at familial high risk (Büschlen et al., 2011; Shah et al., 2015). Within the group of children with a family history of schizophrenia, those exposed to physical punishment show a smaller PV compared to those not exposed to physical punishment (Cullen et al., 2015). It has been suggested that acute or short-term stressors typically activate HPA axis and result in increased cortisol levels but chronic stressors eventually make the HPA axis hypoactive (i.e., lower basal cortisol), or generally hyperactive (higher basal cortisol) albeit with a reduced capacity to respond (i.e., a blunted cortisol response) to further stressors (reviews, Guilliams and Edwards, 2010; Anastassiadis et al., 2019). Structural properties of the pituitary are found to correspond with stress-linked HPA axis regulation (e.g., larger PV predicts greater cortisol release; Kaess et al., 2013). Therefore, larger PV seen in first-episode psychosis may indicate a hyperactive HPA axis (Büschlen et al., 2011; Takahashi et al.,

2013; review, Borges et al., 2013) due to stressful psychotic symptoms, such as threatening voices (Mueser et al., 2010), while smaller PV in chronically-ill patients may indicate a hypoactive/aberrant HPA axis due to prolonged stress in association with persistent symptoms and adverse psychosocial experiences (Dinan, 2004), as well as direct pharmacological actions of antipsychotic medication (review, Anastassiadis et al., 2019).

Cortisol hypo-reactivity to stress is also seen in association with antisocial behaviour (review, Fairchild et al., 2018). In children and adolescents, a lower level of cortisol upon awakening is associated with antisocial personality traits, including oppositional (Platje et al., 2013), externalising (Haltigan et al., 2011) and disruptive behaviours (Fairchild et al., 2018). A blunted cortisol response has been seen in people with a history of childhood maltreatment (Bunea et al., 2017) and found to predict adult antisocial behaviour in children who suffered sexual abuse (Shenk et al. 2010). HPA axis dysfunction may also be a marker of poor treatment outcomes in populations at risks of antisocial behaviour (van de Wiel et al., 2004; Schoorl et al., 2017). Thus, childhood maltreatment may be a risk factor for altered HPA function, and thereby pituitary structure and function.

The present study represents the first attempt, to our knowledge, to investigate the PV in relation to a history of serious physical violence and childhood experiences of maltreatment in people with a chronic schizophrenia illness. Our main aims were to examine (i) the PV of chronic schizophrenia patients with and without a history of serious violence, compared to each other as well as non-violent healthy controls, and (ii) the association between the severity of childhood maltreatment (physical and sexual abuse, general neglect) and PV in people with chronic schizophrenia. Furthermore, to understand the association between childhood maltreatment and PV in general in people with a history of violence versus, specifically, in those with chronic schizophrenia and a history of violence, we studied a group of ASPD patients who had a similar history of serious violence and were from the same clinical setting as the group of schizophrenia patients.

Based on earlier findings of reduced PV in chronic schizophrenia patients (Anastassiadis et al., 2019), and associations between HPA axis dysfunction and antisocial behaviour (Fairchild et al., 2018) as well as childhood maltreatment (Bunea et al., 2017), we hypothesized that schizophrenia patients would, on average, have smaller PV compared to healthy participants, and that this effect would be more pronounced in schizophrenia patients with, compared to those without, a history of serious physical violence. We further hypothesised that ASPD patients would have smaller PV, compared to healthy participants, and that childhood maltreatment severity would correlate negatively with PV in both SZ and ASPD groups.

2. Methods

2.1 *Sample and design*

The study used a cross-sectional design involving: (i) men with schizophrenia and no history of violence (SZ; n=15), (ii) men with schizophrenia and a history of serious violence (VSZ; n=13), (iii) men with ASPD and history of serious violence (ASPD, n=13), and (iv) healthy men with no history of a mental disorder or violence (healthy participants, HP; n=15) (Table 1). All participants were studied on one occasion. The sample had been assessed as part of a larger project that provided data for previous investigations of other brain areas in relation to childhood maltreatment (Kumari et al., 2013, 2014). The use of the magnetic resonance imaging (MRI) brain scans and other participant data for the purposes of current investigation was approved by the College of Health, Medicine and Life Sciences Research Ethics Committee, Brunel University London.

All included participants were required to (i) be aged between 18–50 years, (ii) be free of current substance abuse, (iii) have no history of a head injury or neurological conditions, and (iv) be fluent in English and able to provide written informed consent. The participants in the VSZ group were required to meet symptom criteria for schizophrenia and have a history of serious violence, but no co-morbid diagnosis of ASPD (see Diagnosis and Assessments). Those in the ASPD group were required to meet symptom criteria for ASPD (cluster B, DSM-IV) and have a history of serious violence, but no co-morbid diagnosis of schizophrenia. Of 13 ASPD patients, 8 had co-morbid antisocial and borderline PDs, 3 had co-morbid antisocial, borderline and paranoid PDs, 1 had antisocial, borderline and histrionic PDs, and 1 had ASPD without other co-morbid disorders. Although all participants had been free of alcohol and substance misuse for a minimum of two years (confirmed by regular random urine screens in secure hospitals), there was a history of previous substance abuse, especially in the two patient groups with a history of serious violence, based on the information gathered during interviews and notes in case files. Specifically, in the SZ group, 2 patients had a previous history of using cannabis and 1 of using cannabis and lysergic acid diethylamide (last use was more than 10 years prior to study participation). In the VSZ group, 2 patients had a history of cannabis dependence, 2 of alcohol dependence, 1 of solvent misuse, 1 of alcohol dependence and polysubstance misuse, and 1 patient had a history of alcohol as well as polysubstance misuse (cannabis, ecstasy, lysergic acid diethylamide and amphetamine). In the ASPD group, 2 patients had a history of alcohol dependence, 1 of alcohol and cannabis dependence, 2 of alcohol dependence and polysubstance misuse, and 5 patients of alcohol as well as polysubstance misuse.

All SZ patients were recruited from South London and Maudsley Trust Hospitals. All ASPD and VSZ patients were recruited from specialist high (Broadmoor Special Hospital) and medium security (Denis Hill unit, Bethlem Royal Hospital) hospitals in England. These specialist hospitals provide security and treatment to mentally ill people who require compulsory detention, because of their violent and dangerous tendencies and the risk of violence to others, under the 1983 Mental Health Act (England & Wales; http://www.legislation.gov.uk/ukpga/1983/20/contents). Healthy participants were recruited through local advertisements.

2.2 *Diagnosis and assessments*

The diagnosis of schizophrenia was determined using the Structured Clinical Interview for DSM IV Axis I disorder (First et al., 1995). The diagnosis of ASPD was determined using the Structured Clinical Interview for DSM IV personality disorders (First et al., 1997). These diagnoses were made by an experienced psychiatrist (MD). A negative history of mental illness in healthy participants was confirmed using the Structured Clinical Interview for DSM-III-R—Non-Patient Edition (Spitzer et al., 1990).

The history of violence in VSZ and ASPD participants was determined based on their clinical and forensic records and rated by MD using the Gunn and Robertson criminal profile (Gunn and Robertson, 1976). The ratings were based on the frequency of serious violence over lifetime (score 0–4) and the severity of the most recent violence act (score 0–4). A cut-off score of 5 was used for inclusion in the VSZ and ASPD groups, indicative of an index fatal or near fatal act of violence against another person and at least one other episode of at least moderately serious violence. For SZ and HP participants, any evidence of actual violence against another person, whether or not it had led to a criminal conviction, was taken as an exclusion criterion.

Ratings of sexual abuse, physical abuse and neglect for all patients were based on information extracted from case history, clinical records, and forensic records as well as information gathered during an interview by an experienced psychiatrist (MD) following the methods used by Raine and colleagues (1998) in a forensic sample. For each patient, sexual abuse, physical abuse and neglect were rated by MD based on the information available for all sources on a 5-point scale (0 = none, 1 = minimal, 2 = partial, 3 = substantial, 4 = extreme). In addition, all information for 40-50% of the sample in each patient group was rated independently by another investigator (VK). There was high agreement (>90%) between the ratings by MD and VK. For healthy participants, childhood maltreatment ratings were based only on information gathered during an interview by MD. Additionally, SZ and VSZ participants were assessed on symptoms using the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) and their current antipsychotic use was noted (Table 1). Lastly, all participants were assessed using the National Adult Reading Test (Nelson and Willison, 1991) to estimate their IQ.

*** Table 1 about here ***

2.3 *Stereological volumetric ratings of the pituitary gland*

MRI scans were acquired using a 1.5 Tesla GE NV/i Signa system (General Electric, Milwaukee WI, USA) at the Maudsley hospital (London, UK). First, a series of sagittal fast gradient echo scout images were acquired and then a 3-D inversion recovery-prepared fast spoiled GRASS sequence was applied to obtain whole brain T1-weighted images in the axial plane with 1.5 mm contiguous sections with the following specifications: TR = 13.8ms, TI = 450ms, TE = 2.8ms, flip angle = 20 degrees, FoV = 24cm. Prior to performing volumetry, all brain images were re-aligned horizontally

with reference to the anterior commissure-posterior commissure plane, and vertically with reference to the inter-hemispheric fissure, to ensure that all brain scans were similarly oriented in a 3-dimensional space. Volumetric ratings of the pituitary were then obtained manually using the MEASURE programme which calculates regional volumes based on the Cavalieri principle (Barta et al., 1997).

All ratings were performed by a single trained rater (MB), who had high intra-rater reliability and inter-rater reliability against an experienced MEASURE rater (PP). Inter-rater reliability was deemed to be achieved when the rater (MB) obtained 95% accuracy with previously rated PVs (by PP) on 10 practice scans. To prevent observer bias, the rater (MB) was kept blind to the participant group membership. The same parameters as in Premkumar et al. (2018) were used with the PV defined as a hyperintensity adjacent to the posterior pons on the sagittal view, with clearly defined anterior and posterior boundaries (Klomp et al., 2012; Tien et al., 1992; Figure 1). Ratings were carried out mainly in the coronal view starting at the anterior end of the pituitary, with the infundibular stalk excluded from the segment.

*** Figure 1 about here ***

2.4 *Data analysis*

All statistical analyses were carried out using SPSS v26, with significance level set at $p \leq 0.05$ unless stated otherwise.

Non-parametric analyses (Kruskal-Wallis tests) were used to test for a difference in age and NART-IQ between SZ, VSZ, ASPD and HP groups. The SZ and VSZ groups were compared on age at illness onset, illness duration, symptoms, medication dose (in chlorpromazine equivalents) and PV using Kruskal-Wallis tests. A Kruskal-Wallis test was then used to test for the effect of Diagnosis in PV [HP, schizophrenia (SZ and VSZ combined since they had comparable PV, see Results), ASPD], followed by further Kruskal-Wallis tests to assess differences between HP and schizophrenia (combined), HP and ASPD, and ASPD and schizophrenia (combined) groups; the results of these pair-wise comparisons were evaluated using Bonferroni-corrected *p* values.

The associations between childhood maltreatment (ratings of sexual abuse, physical abuse and neglect) and PVs in the SZ, VSZ and ASPD were examined using Spearman rank-order correlations. Given the high comorbidity between sexual and physical abuse, the strength of the (significant) correlation between the sexual abuse and PV (see Results) was re-evaluated using the partial correlation (non-parametric Spearman) (Reynolds, 1974) after controlling for the effect of physical abuse. The statistical significance of these correlational analyses was evaluated using Bonferroni-corrected *p* values. There was no case with a substantial or extreme rating of physical abuse, sexual abuse or neglect in the HP group (Results, Table 1). Thus, correlational analyses were not run within this group.

3. Results

3.1 *Sample characteristics*

As shown in Table 1, the four study groups had similar ages (p = 0.61) and IQ (p = 0.12). The SZ and VSZ groups were comparable on age at illness onset (H = 0.51, df = 1, p = 0.47), duration of illness *(*H = 0.19, df = 1, p = 0.66), positive symptoms (H = 1.29, df = 1, p = 0.25) and negative symptoms (H = 1.23, df = 1, p = 0.27), but the SZ group had higher levels of general psychopathology (H = 13.5, df = 1, p < 0.001). All SZ and VSZ patients were on typical and/or atypical antipsychotics, with no significant difference in dose when converted to chlorpromazine equivalents (H = 0.87, df =1, p = 0.35) (Table 1). No ASPD participant was on antipsychotic medication.

There was a high frequency of participants having experienced childhood physical abuse in the ASPD (84.61%) and VSZ (61.53%) groups, with physical abuse varying in severity from minimal to extreme in the VSZ group and from partial to extreme in the ASPD group (see Table 1). Childhood sexual abuse was also common in the ASPD group (69.23%), but not in the VSZ group (15.38%). Among the ASPD participants who experienced sexual abuse, participants varied in the amount of childhood sexual abuse they had experienced from minimal to extreme. Childhood neglect was prevalent in both the ASPD (76.92%) and VSZ groups (51.84%), with severity varying from minimal to substantial in the VSZ group and from minimal to extreme in the ASPD group. There were few cases of physical/sexual abuse and neglect in the SZ group, and even fewer cases in the healthy group (Table 1). Most cases of sexual abuse also reported physical abuse. Consistent with this pattern, physical and sexual abuse ratings were positively correlated with each other (across all, *rho* = 0.674, p < 0.001).

3.2 Group differences in PV

The VSZ and SZ groups did not differ in PV (H = 0.06, df = 1; p = 0.8). The analysis involving the HP, SZ and VSZ combined, and ASPD groups showed a main effect of Diagnosis (H = 6.84, df = 2, p = 0.03). Pairwise comparisons to probe this effect revealed a trend for smaller PV, on average, in schizophrenia patients (combined), compared to healthy participants (H = 4.8, df = 1, p = 0.03; Bonferroni-corrected p = 0.09) as well as ASPD patients (H = 4.07, df = 1, p = 0.03; Bonferroni-corrected p = 0.09) (Figure 2). The ASPD and HP groups did not differ (H = 0.45, df = 1; p = 0.5).

*** Figure 2 about here ***

3.3 *Association between childhood maltreatment and PV*

Sexual abuse ratings correlated negatively with PVs in the ASPD group (*rho* = -0.735, p < 0.004; Bonferroni-corrected p = 0.04) (Table 2). The strength of this correlation reduced only slightly after controlling for physical abuse ratings, although it lost formal statistical significance after applying a Bonferroni correction (partial *rho* = -0.724, p = 0.008; Bonferroni-corrected p = 0.08). No significant

associations were found between PVs and maltreatment ratings (sexual abuse, physical abuse, neglect) in the VSZ or SZ groups (all *p*-values > 0.30). In schizophrenia groups, current symptoms or antipsychotic dose (in chlorpromazine equivalents) were also not correlated with PVs (all *p*-values > 0.30). Age was not associated with PV when examined across the entire sample (rho = -0.12, *p* = 0.4).

*** Table 2 about here ***

4. Discussion

The findings revealed, on average, a trend for smaller PV in schizophrenia patients (with or without a history of serious violence), compared to the healthy as well as the ASPD groups. Our hypothesis of a more marked PV reduction in schizophrenia patients with a history of violence (VSZ), compared to those without a history of violence (SZ), was not supported. Similarly, our hypothesis of a significantly smaller PV in the ASPD group, compared to the healthy group, was not confirmed. Greater severity of sexual abuse correlated significantly with smaller PVs in the ASPD group, but no such correlations were found between PV and physical abuse or general neglect in the schizophrenia or ASPD groups.

4.1 *Pituitary volume in schizophrenia: the role of violence*

Our finding of a trend for smaller-than-normal PV in SZ patients is consistent with the findings of previous studies showing smaller PV in chronic schizophrenia patients and, as mentioned earlier (Introduction), this effect may be related to prolonged stress exposure as well as to long-term antipsychotic use (reviews, Pariente, 2008; Atmaca, 2014; Anastassiadis et al., 2019). Antipsychotic use has been associated, in a dose-dependent manner, with PV reduction at higher doses in first-episode psychosis patients (Nicolo et al., 2010). While a decrease in PV that brings it close to the normal range can be seen as helpful and adaptive, the functional significance of a smaller-than-normal PV is difficult to infer and complicated by illness chronicity. Nonetheless, we (Premkumar et al., 2018) previously observed a reduction in PV in chronic schizophrenia patients (no overlap with the current sample) who had shown improvement in medication-resistant distressing symptoms following 6-8 months of cognitive behaviour therapy for psychosis (CBTp) without accompanying change in antipsychotic medication. Thus, smaller-than-normal PV in antipsychotic-treated schizophrenia patients may reflect HPA axis hypo-reactivity as a coping mechanism, in addition to other illness or medication-related influences. However, longitudinal investigations that incorporate functional MRI and behavioural correlates of PV are needed to fully understand the behavioural and clinical meaning of smaller-than-normal PV in chronic schizophrenia, as smaller brain volume may not necessarily mean hypofunction (Antonova et al., 2004).

We did not find a significant effect of a history of violence on PV in schizophrenia or ASPD. While any violence-related effect in PV of people with schizophrenia may have been masked by illness or

medication-related influences, the fact that even ASPD participants did not differ significantly from healthy participants suggests that PV is perhaps less implicated in serious violence, compared to some other brain structures. For example, reduced volumes of the hippocampus (Barkataki et al., 2006), thalamus (Kumari et al., 2013) and the anterior cingulate (Kumari et al., 2014) were found in the current sample of ASPD and VSZ participants compared to the SZ and/or healthy participants, and the volumes of these regions also showed an inverse association with the severity of sexual and/or physical abuse (Kumari et al., 2013, 2014). Interestingly, HPA-axis dysfunction in relation to antisocial behaviour has been observed more consistently in children than adults (Fairchild et al., 2018). It is conceivable that HPA-axis-mediated impaired stress regulation (alone) is more relevant to milder and frequently displayed forms of reactive aggression in children than serious physical violence in adults.

4.2. Pituitary volume and childhood maltreatment

There was a negative association, as expected, between sexual abuse ratings and PV in ASPD participants. This observation is consistent with previous data (review, Fairchild et al. 2018) and suggests that greater stress and HPA-axis dysfunction are more strongly associated with sexual abuse, compared to physical abuse or general neglect. In future, it would be valuable to fully assess childhood maltreatment, including emotional abuse and emotional neglect, and examine it comprehensively in relation to HPA-axis dysfunction, risk for antisocial behaviour and mental health problems (Kumari, 2020). Future studies of changes in PV and other stress-linked brain structures in first-episode and prodromal populations in relation to childhood maltreatment history, risk of future aggression, and antipsychotic treatment outcomes within a single study would be extremely informative, given earlier findings showing the importance of HPA-axis function as predictors of antisocial behaviour and poor treatment outcomes in young people (Fairchild et al., 2018).

4.3 *Symptoms in SZ vs VSZ*

The VSZ group, on average, had lower general psychopathology symptoms compared to the SZ group. This finding, as discussed previously (Kumari et al., 2006), most likely related to VSZ patients living in secure hospitals (for two years or longer) and being closely monitored for medication-compliance whereas SZ patients lived in the community with continued exposure to adverse psychosocial experiences. Symptoms or medication dose, however, showed no direct relationship with PV in this study.

4.4 *Limitations*

This study had several limitations. First, it was carried out using an existing data set with relatively small sample sizes. Second, there was a limited range of sexual abuse in schizophrenia groups to meaningfully examine its association with PV. Third, MRI data were acquired using 1.5T scanner which has limited spatial resolution and, as a result, we did not examine the subdivisions of the pituitary gland (Musumeci et al., 2015). Our method of measuring whole PV, however, conforms to

that of most studies conducted-to-date in schizophrenia samples (Anastassiadis et al., 2019). Forth, our methods of collecting information on childhood experiences of maltreatment might have resulted in underestimation of such experiences, especially in healthy participants or any patients for whom we did not have detailed records. Fifth, there was a high frequency and diverse nature of previous alcohol and substance abuse history in ASPD participants which, although not surprising (Hatzitaskos et al., 1999; Chavez, 2010), does not allow us to disentangle the effects of sexual abuse in PV from those of a history of alcohol and substance abuse. Sixth and last, the study was limited to men. The findings thus may not be applicable to women, given previously reported sensitivity of PV to gonadal hormones (Wong et al., 2014). Further studies with larger samples of men and women with, or at risk of, SZ and ASPD, and using sophisticated markers of HPA axis function, higher field-strength MRI (e.g., 3T) for improved image quality, and expanded assessment of childhood maltreatment using standardised instruments are required to confirm and extend our findings.

4.5 *Conclusions*

In conclusion, the findings show a trend for reduced PV in people with a chronic schizophrenia illness, regardless of a history of serious violence. The association between childhood abuse and smaller PVs, seen here in ASPD, may be lost in chronic schizophrenia patients due to additional sources of chronic stress, or other illness- and medication-related influences.

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Contributors

Minal Bipin performed manual ratings of the pituitary gland and contributed to the first draft of the manuscript. Preethi Premkumar supervised manual ratings of the pituitary gland and contributed to statistical analysis and writing the manuscript. Mrigen Das performed the clinical diagnostic interviews and childhood maltreatment ratings. Alex Sumich contributed to MRI data acquisition and critically reviewed the manuscript. Jennifer Lau critically reviewed the manuscript. Veena Kumari developed the study and contributed substantially to statistical analysis and the writing of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Table 1

Participant characteristics classified by study group.

	SZ (n=15)	**VSZ (n=13)**	**ASPD (n=13)**	**HP (n=15)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Age (years)	34.47 (7.49)	34.46 (4.94)	33.50 (10.45)	32.13 (7.47)
NART IQ	98.93 (13.39)	96.38 (13.92)	96.36 (9.69)	106.87 (16.09)
Violence Score*	1.20 (1.32)	6.15 (1.46)	6.57(1.34)	0.47 (0.83)
Duration of Illness (years)	11.20 (7.58)	12.15 (7.32)	N/A	
PANSS: Positive Symptoms	12.00 (3.96)	10.77 (4.86)		
PANSS: Negative Symptoms	20.07 (5.40)	17.85 (5.24)		
PANSS: General Psychopathology	32.73 (5.82)	23.77 (5.64)		
PANSS: Total	64.80 (10.45)	52.85 (13.11)		
Chlorpromazine Equivalents (mg/day)	539.16 (299.77)	426.66 (227.60)		
Childhood Maltreatment	**N (%) [severity]**	**N (%) [severity]**	**N (%) [severity]**	**N (%) [severity]**
Physical abuse	2/15 (13.33%) [1 minimal, 1 partial]	8/13 (61.53%) [3 minimal, 1 partial, 2 substantial, 2 extreme]	11/13 (84.61%) [2 partial, 5 substantial, 3 extreme]	2/15 (13.33%) [1 minimal, 1 partial]
Sexual Abuse	1/15 (6.66%) [1 partial]	2/13 (15.38%) [1 minimal, 1 substantial]	9/13 (69.23%) [2 minimal, 1 partial, 2 substantial, 4 extreme]	1/15 (6.66%) [1 partial]
General Neglect	5/15 (33%) [3 minimal, 2 partial]	7/13 (51.84%) [1 minimal, 1 partial, 5 substantial]	10/13 (76.92%) [1 minimal, 2 partial, 1 substantial, 4 extreme]	1/15 (6.66%) [1 minimal]

NART= National Adult Reading Test; *As measured by Gunn and Robertson Scale
SZ= Non-violent Schizophrenia; VSZ= Violent Schizophrenia; ASPD= Antisocial Personality Disorder; HP = Healthy Participants

Table 2
Correlations [rho (*p*)] between abuse ratings and pituitary volumes.

	SZ N=15	VSZ N=13	ASPD N=13
Physical abuse	0.139 (0.622)	-0.174 (0.570)	-0.347 (0.246)
Sexual abuse	0.087 (0.758)	0.314 (0.295)	**-0.735 (0.004)**
Neglect	-0.199 (0.477)	0.143 (0.641)	0.094 (0.760)

Figure 1

Rating of the pituitary on (a) the axial (top left), (b) sagittal (top right) and (c) coronal (bottom right) views as seen from a mid-sagittal slice of the brain.

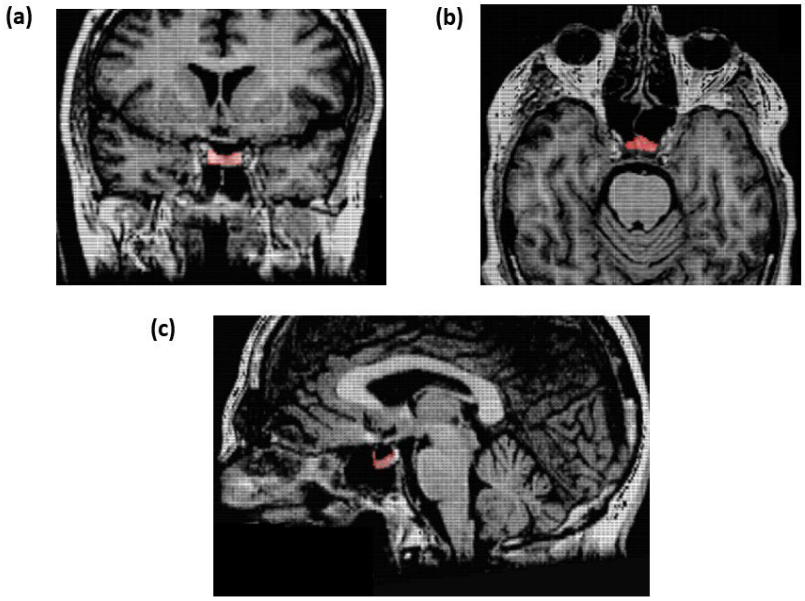

Figure 2

Mean pituitary volumes (in mm^3; error bars display +1 SEM) in the four study groups (SZ = non-violent schizophrenia; VSZ = violent schizophrenia; ASPD = antisocial personality disorder; HP = healthy participants).