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Pituitary volume in individuals at elevated risk for psychosis: A systematic review and meta-analysis

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ABSTRACT

Background: Pituitary volume (PV) abnormalities, representing one of several markers of hypothalamic-pituitary-adrenal (HPA) axis dysregulation, have been observed in psychosis, with variable patterns across illness stages. Typically, enlargements characterise first-episode patients, with reductions observed in those with chronic illness relative to healthy controls. Findings in high-risk populations have been inconsistent, highlighting the need for an updated review of the evidence.

Methods: We searched PubMed, PsycINFO, and EMBASE for studies examining PV in high-risk [clinical high-risk (CHR), family history of psychosis (FHx), schizotypal personality disorder (SPD), and psychotic-experiences (PEs)] and healthy individuals. Random effects models were used to examine group differences in PV (Hedges g) with stratified analyses and meta-regression employed to investigate the effect of high-risk category, transition status, age, sex, and antipsychotic medication.

Results: Ten studies, yielding 11 effect sizes, were eligible for inclusion. Overall, high-risk individuals had significantly larger PV relative to healthy controls ($g = 0.16$ [95% CI: 0.01 to 0.32] $p = 0.04$), despite showing a reduction in whole brain volume ($g = -0.17$, [95% CI. −0.30 to −0.03] $p = 0.020$). Individual sub-group analyses for CHR and FHx groups showed no significant differences relative to controls; however, larger PV increases characterised those who later transitioned to psychosis ($g = 0.55$, [95% CI. 0.06 to 1.04] $p = 0.028$). Larger effect sizes were positively associated with the proportion of high-risk individuals receiving antipsychotic medication.

Conclusions: PV enlargements characterise high-risk individuals and are more pronounced among those who later develop psychosis. We provide recommendations for future studies.

1. Introduction

The neural diathesis-stress model of schizophrenia posits that psychosocial and biological stressors, acting via the hypothalamic-pituitary-adrenal (HPA) axis, may further elevate the risk of psychosis in those with a pre-existing vulnerability (Walker et al., 2008; Walker and Diforio, 1997). Whilst the presence of abnormal cortisol profiles among individuals with, and at elevated risk for, psychosis provides evidence to support the model, methodological complexities (including, psychotropic medications, sex differences, cross-sectional designs, and heterogeneity in cortisol measurements) lead to inconsistent findings (Pruessner et al., 2017). Pituitary gland volume (PV) provides an alternative marker of HPA axis function, with enlargements thought to indicate HPA axis hyperactivity through an increase in the size and number of corticotroph cells producing adrenocorticotropic hormone (Pariante, 2008). Consistent with the elevated basal cortisol levels observed in this population, previous meta-analyses indicate increased PV in those with first-episode psychosis (FEP) relative to healthy individuals (Borges et al., 2013; Nordholm et al., 2013) In contrast, reduced PV has been observed in chronic schizophrenia (Pariante et al., 2004; Upadhyaya et al., 2007), perhaps reflecting pituitary hypoplasia caused by repeated episodes of HPA axis hyperactivity. The extent to which these abnormalities are present among individuals at high-risk for psychosis, however, is currently unclear.

High-risk studies typically examine one of four main groups: (1) clinical high-risk (CHR), also known as ultra high-risk (UHR) or the at-risk mental state (ARMS), predominately characterised by attenuated psychotic symptoms (Fusar-Poli et al., 2013; Yung et al., 2005); (2) family history of psychosis (FHx), typically defined as the presence of a first-degree relative with psychosis [i.e., offspring or siblings of those with psychosis (Niemi et al., 2003)]; (3) schizotypal personality disorder (SPD), characterised by perceptual distortions and eccentric behaviour (American Psychiatric Association, 2013; World Health

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Organization, 1992); and (4) psychotic experiences (PEs), also known as psychotic-like experiences or subclinical psychotic symptoms (Nelson et al., 2012). Transition rates among these groups are varied. Meta-analytic evidence shows that 36% of individuals at CHR transition to psychosis within the first three years of clinical presentation (Fusar-Poli et al., 2012). Although less extensively studied, similar transition rates (25–40%) have been reported in longitudinal studies of individuals with SPD (Fenton and McGlashan, 1989; Nordentoft et al., 2006; Woods et al., 2009). Lower transition rates have been observed in those with a FHx of illness, with a recent meta-analysis reporting that 12% of individuals with a parent with schizophrenia develop the same illness in adulthood (Rasic et al., 2014). Similarly, whilst longitudinal studies indicate that individuals experiencing PEs (e.g., hallucination- and delusion-like symptoms) are at an increased risk of developing psychosis relative to the general population (Kaymaz et al., 2012), the transition rate is notably lower (0.56%). Establishing whether PV abnormalities characterise some, or all, of these groups is an important step to understanding the role of HPA axis dysregulation in the onset of psychosis.

Previous reviews have provided preliminary evidence for PV abnormalities in high-risk groups. Aiello and colleagues conducted a systematic review of CHR and FHx populations, reporting enlarged PV in both groups (Aiello et al., 2012). Similarly, a subsequent systematic review and meta-analysis reported a trend for larger PV in CHR individuals who later transitioned to psychosis compared to healthy controls (Nordholm et al., 2013); however, FHx and PE groups were not examined. An updated review reported heterogenous findings in CHR, FHx, and SPD groups, with studies reporting that PV was enlarged, reduced, or no different relative to healthy controls (Pruessner et al., 2017). However, studies were not obtained systematically, and no meta-analysis was conducted; thus, the magnitude and consistency of any effects remains unclear. Moreover, important potential confounds such as sex, antipsychotic medication, and transition status were not statistically examined.

Pituitary volume is not the only indicator of HPA axis activity. Meta-analytic evidence shows that basal cortisol levels (one of the most widely-studied indictors of HPA axis function) are elevated among those at CHR (Chaumette et al., 2016), with similar elevations also reported in those with SPD (Mittal et al., 2007; Walker et al., 2001; Weinstein et al., 1999). However, there is less consistent evidence for the cortisol awakening response (CAR), thought to represent the response to a mild, natural stressor (i.e., awakening), independent from basal cortisol. A recent meta-analysis reported that individuals with psychosis and schizophrenia, but not those at CHR, were characterised by a blunted CAR relative to controls (Berger et al., 2016), tentatively suggesting that this aspect of HPA axis dysregulation does not emerge till later in illness. Such findings are consistent with the tonic/phasic model of HPA axis dysfunction (Shah and Malla, 2015) which proposes that the HPA axis may become overwhelmed by chronic hyperactivation (represented by basal cortisol) eventually leading to a maladaptive response to stressors.

Perhaps unsurprisingly, given the contribution of stress to multiple psychiatric disorders, HPA axis dysregulation is not specific to psychosis. Indeed, PV abnormalities have also been reported in bipolar disorder (Delvecchio et al., 2018; Takahashi et al., 2009a), major depression (Kessing et al., 2011), panic disorder (Kartalci et al., 2011), and obsessive-compulsive disorder (Atmaca et al., 2009). Whilst it may be possible to differentiate psychosis from other neuropsychiatric disorders using a combination of PV and other stress-response biomarkers, a psychosis-specific 'stress-signature' has not yet been identified. Determining the extent and nature of pituitary volume abnormalities among individuals at elevated risk for psychosis may help with this endeavour.

Given that research in high-risk groups has burgeoned in recent years, there is a need for an updated review of the evidence in this population. We therefore conducted a systematic review and meta-analysis which aimed to (1) systematically appraise studies examining PV in high-risk individuals and controls; (2) determine the magnitude and consistency of effects using meta-analytic techniques; and (3) formally examine sources of heterogeneity (high-risk definition, transition status, age, sex, and antipsychotic medication exposure) on effect sizes by means of stratified analyses and meta-regression.

2. Method

The protocol for this systematic review and meta-analysis was prospectively registered on PROSPERO (CRD42018108098), our search strategy and reporting complied with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Stroup et al., 2000).

2.1. Search strategy

The search was conducted independently in August 2018 by two researchers (T.S.S. and A.E.C.) within PubMed, PsycINFO, and EMBASE using the following terms: [(((pituitary gland) OR pituitary volume)) AND (((((((((schizotypal personality disorder) OR schizotypy) OR psychotic experiences) OR psychotic-like experiences) OR subclinical psychotic symptoms) OR subclinical psychosis) OR non-clinical psychosis)) OR ((((schizophrenia) OR psychosis)) AND ((((((((((relatives) OR offspring) OR sibling) OR family history) OR genetic risk) OR at risk mental state) OR ultra high risk) OR clinical high risk) OR prodrome) OR high risk)))]. No restrictions were applied for year of publication or language. Reference lists of studies and reviews were manually searched to identify additional studies. Only studies published in peer review journals were included, conference abstracts were excluded.

2.2. Study selection

We included observational studies (case-control) which compared pituitary gland volumes in those at high-risk for psychosis and controls. We defined "high-risk" participants as those who met criteria for "clinical high-risk" for psychosis [also known as "ultra high-risk" or individuals with an "at-risk mental state"; (Yung et al., 2005)], individuals at familial risk for psychosis (defined by a family history of the illness; FHx), those who met diagnostic criteria for schizotypal personality disorder (SPD), or youth who presented with psychotic-experiences (also known as psychotic-like experiences or non-clinical psychotic symptoms). Studies with no control group or overlapping samples were excluded (where we included the larger study sample). A.E.C and T.S.S double rated studies for inclusion/exclusion, study authors were contacted where necessary to resolve disagreements.

2.3. Data extraction

Two researchers (T.S.S and A.E.C.) independently extracted data from eligible studies. This included: year of publication, sample size, mean age of participants, participant sex, percentage of participants who received antipsychotic medication, recruitment method, high-risk definition, pituitary gland tracing software, PV mean and standard deviation (SD) per group, and mean and SD for whole brain volume (WBV) or total intracranial volume (TIV). The researchers were not blind to the names of authors, journals, or institutions. To pool data within studies reporting effect sizes separately for males and females, we extracted raw data and computed a combined mean and pooled SD using the Hedge's method for calculating SDs (Hedges, 1981). We contacted authors via email where information was missing (Habets et al., 2012; Mondelli et al., 2008; Nordholm et al., 2018; Romo-Nava et al., 2013; Takahashi et al., 2009b, 2013) and all but one responded and provided the necessary information. Any