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The role of cortisol and prolactin in the pathogenesis and clinical expression of psychotic disorders

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ABSTRACT

For many years, the study of the psychotic phenotpe and approach to treatment of schizophrenia has been focused on positive psychotic symptoms, although the functional outcome is more clearly associated with negative and cognitive symptoms. Recently, there has been a growing interest in identifying biomarkers associated with these symptoms at early stages of the illness, including the risk of psychosis in vulnerable individuals (at-risk mental states [ARMS]). In this paper, the role of cortisol and prolactin in the clinical expression of psychosis will be reviewed. In examination of the role of these hormones and the risk of developing a psychotic disorder in ARMS individuals, previous studies have suggested potential roles for both cortisol and prolactin. The study of cognitive abilities in recent-onset psychotic patients has suggested that affected cognitive domains differ depending upon the studied hormones: cortisol (processing speed, verbal and working memory) and prolactin (processing speed), with several studies suggesting that there are sex-differences in these associations. All of these results suggest that both cortisol and prolactin contribute to the pathogenesis and clinical expression of psychotic disorders.

1. Introduction

Psychotic disorders are relatively prevalent mental illnesses (3% lifetime prevalence) that cause abnormal thinking and perceptions (van Os et al., 2010) and constitute a major health burden worldwide (Vigo et al., 2016). The subtype of psychotic disorder may be difficult to diagnose at the onset of the illness due to the heterogeneity of the presentation of symptoms (Peralta et al., 2013). In most cases, patients with psychotic symptoms requiring psychiatric treatment will develop a recurrent and chronic mental disorder in the following years, with schizophrenia, bipolar disorder, schizoaffective disorder and psychotic depression being the main long-term psychiatric diagnoses. Although the study of the psychotic phenotype and treatment approach has been focused on positive psychotic symptoms (delusions, hallucinations, disorganized speech) for many years, other symptoms such as negative (blunted affect, poverty of speech, avolition, anhedonia, asociality) and cognitive symptoms are more clearly associated with the functional outcome of psychotic disorders (Carbon and Correll, 2014). Cognitive alterations are shared by different psychotic disorders although they are more prominent in people with schizophrenia (Bora et al., 2009). These alterations involve neuropsychological domains related to neurocognition (attention, memory, processing speed, executive function) and social cognition. Importantly, all of these cognitive alterations are present at early stages of the illness, even before the emergence of the psychotic outbreak (Fusar-Poli et al., 2012a).

The search for biological markers related to the onset and clinical expression of schizophrenia and other psychotic disorders has received substantial research efforts for many decades, although clinically translatable biomarkers in psychiatry have been elusive (Venkatasubramanian and Keshavan, 2016). Stress has been an enduring element in theories and models of the aetiology of psychosis, with perspectives on stress broadening to include both psychosocial and biological factors (Holtzman et al., 2013; Walker and Diforio, 1997). When exploring the role of stress-related biomarkers on psychotic

Abbreviations: ACTH, corticotrophin; ALSPAC, Avon Longitudinal Study of Parents and Children; APS, attenuated psychotic symptoms; ARMS, at-risk mental state; BDNF, brain-derived neurotrophic factor; BLIPS, brief limited intermittent psychotic symptoms; CAR, cortisol awakening response; DHEAs, sulphate dehydroepiandrosterone; DST, dexamethasone suppression test; FEP, first-episode psychosis; GRD, genetic risk and deterioration; HPA, hypothalamic-pituitary-adrenal; HS, healthy subjects; IL, interleukin; MMP, metalloproteinase; NAPLS, North American Prodrome Longitudinal Study; ROP, recent-onset psychosis; TRH, thyrotropin-releasing hormone

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disorders at early stages of the disease, hypothalamic-pituitary-adrenal (HPA) axis hormones have been the most studied. Previous studies suggest the presence of HPA axis hyperactivity and a blunted HPA axis response to stress at the onset of psychosis (Borges et al., 2013). However, recent studies also suggest a potential role for other stress-related hormones such as prolactin (Ittig et al., 2017), that is increased in drug-naïve patients with schizophrenia or related psychoses (Gonzalez-Blanco et al., 2016).

The current narrative review aims to address the role of HPA axis hormones and prolactin on the pathogenesis and phenotype of psychotic disorders. It also aims to include an integrative discussion of previous studies from our group focused on these hormones. Studies on inflammatory markers will also be discussed due to the close relationship between inflammation and some hormones, particularly HPA axis hormones and prolactin (Brand et al., 2004; Soria et al., 2017). The role of these hormones in psychotic disorders will be reviewed in two parts: 1) vulnerability to psychosis and 2) negative and cognitive symptoms. Some results from experiments examining the associations between positive symptoms or the comparison of different stages of illness will be referenced when discussing the vulnerability to psychosis (part 1).

2. Vulnerability to psychosis: roles for cortisol, prolactin and inflammation

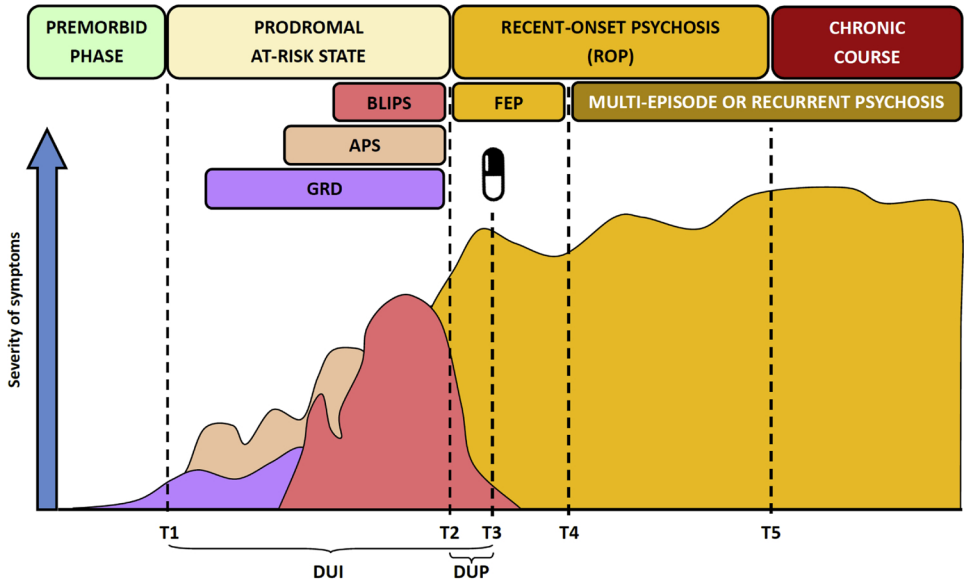
2.1. Moving towards an earlier stage of the illness: at-risk mental states studies

Schizophrenia and other related psychoses are developmental disorders that share the presence of prodromal symptoms that can last many months before the onset of the psychotic illness (Holtzman et al., 2012). In first-episode psychosis (FEP), a deterioration in social relationships may be present during the first 2–3 years; this critical period presents an important opportunity for secondary prevention (Birchwood et al., 1998). Furthermore, one of the variables that is more clearly associated with a poorer prognosis is the duration of untreated psychosis (DUP) (Marshall et al., 2005). For this reason, early intervention in the field of psychosis has shifted to the detection of people at risk for psychosis (Fig. 1), leading to the creation of the operational criteria for diagnosing at-risk mental states (ARMS), also known as ultra-high-risk (UHR). The most widely used approach includes three subgroups of ARMS (Fusar-Poli et al., 2015): 1) attenuated psychotic symptoms (APS), 2) brief limited intermittent psychotic symptoms (BLIPS), and 3) genetic risk and deterioration (GRD) criteria (defined as first-degree relatives of those with psychotic disorders or schizotypal personality disorder with reduction in social functionality). A meta-analysis including 4227 ARMS individuals (Fusar-Poli et al., 2015) indicated that APS criteria is the most prevalent subgroup (85%) when compared to the prevalence of the criteria for the BLIPS (10%) and GRD (5%) subgroups. The rate of psychosis transition also differs by diagnostic groups, with the transition risk at two years greater for those in the BLIPS diagnostic group (39%) than for those in the APS (19%) or GRD (3%) subgroups. Some authors (Schultze-Lutter et al., 2010) have recommended the use of a combination of ARMS criteria with basic symptoms (subtle, subclinical self-experienced disturbances in thought, speech, and perception processes that are rarely perceivable from the outside) in order to increase the sensitivity of the screening for vulnerable individuals.

As ARMS individuals are followed-up with Early Intervention Services for Psychosis, they offer a great opportunity for conducting clinical research regarding the potential contribution of biological markers to the development of psychosis in vulnerable individuals. This narrative review will address the contribution of HPA axis hormones, prolactin and inflammatory markers in the development of psychosis in people with an ARMS diagnosis, as well as discuss previous studies from our group in relation to this topic.

2.2. HPA axis

For many decades, the main hypothesis linking hormones and psychosis risk was the neural diathesis-stress model (Walker and Diforio, 1997). This model relies on the close relationship between the HPA axis and psychosis from previous evidence: 1) endogenous hypercortisolaemia (e.g., Cushing syndrome) and exogenous corticosteroids may induce psychotic symptoms; 2) patients with schizophrenia show HPA



Time points: T1: Onset of prodromal symptoms; T2: Psychosis onset; T3: Initial treatment; T4: Relapse (second episode); T5: Final of critical period (3-5 years)
Duration of untreated illness (DUI)= T3-T1; Duration of untreated psychosis (DUP)= T3-T2; Critical period= T5-T2

Fig. 1. The early stages of psychosis.
Abbreviations: BLIPS = Brief limited intermittent psychotic symptoms; APS = Attenuated psychosis syndrome, GRD = Genetic risk and deterioration; ROP = Recent-onset psychosis. FEP = First-episode psychosis; DUP = Duration of untreated psychosis; DUI = Duration of untreated symptoms.
The prodrome is a retrospective concept that may be defined as the period of the first noticeable symptoms (T1) to the first prominent psychotic symptoms (T2). The prodrome refers to a pre-psychotic period characterized by mental state features that represent a change from a person's premorbid functioning. To reduce the DUP, early intervention in psychosis aims to detect prodromal cases prospectively (before psychosis develops). This approach envisions the prodrome in psychosis as a syndrome that confers a heightened vulnerability to becoming psychotic but does not inevitably lead to psychosis. Three at-risk mental states or ultra-high-risk criteria for psychosis have been proposed (BLIPS, APS, GRD) in order to detect vulnerable individuals before the onset of psychosis. The second view of early intervention in psychosis is focused on the definition of a critical period (usually defined as the first 3 or 5 years of the psychotic illness), in which social deterioration may occur but an opportunity for secondary prevention is afforded. Patients with a psychotic illness in this critical period are often labelled as having recent-onset psychosis or early psychosis independently of the number of relapses.

Table 1
Longitudinal studies exploring the relationship between hypothalamic-pituitary-adrenal axis hormones or prolactin and the risk of psychosis transition in at-risk mental states.

Reference	Sample	Follow-up	Transition rate	HPA axis measures and/or prolactin[†]	Results
Walker et al. (2010)	56 ARMS	5 years	25%	3 salivary cortisol samples at the clinic (for one hour, beginning at 9:00 h) 3 follow-up times: baseline, follow-up 1 (7-10 months) and follow-up 2 (12-14 months)	Escalating cortisol in ARMS-P (at first follow-up, before the onset of the FEP): ARMS-P > ARMS-NP.
Sugranyes et al. (2012)	33 ARMS 13 HS	2 years	27.3%	Salivary cortisol at the clinic (11:30 h)	No significant differences in cortisol levels between ARMS-P and ARMS-NP
Walker et al. 2015	136 ARMS 141 HS	2 years	23.5%	3 salivary cortisol samples at the clinic (between 9:30-11:30 h)	Increased cortisol levels in ARMS-P (ARMS-P > HS; ARMS-P > ARMS in remission at follow-up)
Labad et al. (2015)	39 ARMS 44 HS	> 1 year	25.6%	Prolactin and cortisol in plasma (between 8:30 h and 9:30 h) Salivary cortisol at the clinic (between 8:30h-9:30 h) CAR at home: AUC_i and slope 0-30′ post-awakening	Increased prolactin levels in ARMS-P (ARMS-P > ARMS-NP; ARMS-P > HS). These results did not change in antipsychotic-free ARMS. Significant differences in multivariate analysis adjusted for awakening time, BMI, gender and treatments: $CAR\text{-}AUC_i$: ARMS-P > ARMS-NP Slope 0-30′ post-awakening: ARMS-P > ARMS-NP; ARMS-P > HS
Chaumette et al. (2016)	93 ARMS 52 help-seeker controls	1 year	Not reported	Salivary cortisol at the clinic (between 8:00 h and 9:00 h)	No significant differences in cortisol levels between ARMS-P and ARMS-NP
Ittig et al. (2017)	116 ARMS	5 years	19.8%	Prolactin in plasma	No significant predictive value of prolactin levels on psychosis transition in survival analysis

Abbreviations: ARMS = At-Risk Mental State; ARMS-P = At-Risk Mental State with a psychosis transition; ARMS-NP = At-Risk mental State without a psychosis transition; HS = Healthy subjects; FEP = first episode psychosis; AUC_i = Area under the curve with respect to the increase; BMI = Body mass index.
[†] All studies assessed biological measures at the baseline visit and explored associations with the risk of psychosis transition during the follow-up period. The Walker et al. (2010) study also included repeated biological measures at two follow-up visits.

axis dysregulation and reduced hippocampal volume; 3) there is a synergistic activation of the HPA axis and dopaminergic circuits that has been implicated in psychosis; and 4) prenatal factors that have been implicated in the pathogenesis of schizophrenia may contribute to HPA axis dysregulation. This theoretical hypothesis has been demonstrated by positron emission tomography studies reporting stress-induced dopamine release in ARMS and antipsychotic-naïve patients with schizophrenia (Mizrahi et al., 2012).

Few longitudinal studies have explored whether baseline abnormalities in the HPA axis in ARMS individuals differ between those who develop a psychosis or not (Table 1). The first study reported a distinct pattern of escalating cortisol secretion in morning cortisol that distinguished those ARMS individuals with a psychosis transition from those who did not develop a psychotic disorder (Walker et al., 2010). Furthermore, the cortisol increase did not appear to be induced by the psychotic episode, as significant elevations were observed before the onset of the first episode. A second larger study replicated these findings in the North American Prodrome Longitudinal Study (NAPLS) (Walker et al., 2013), reporting increased morning cortisol levels obtained at the research clinic in the ARMS group who developed psychotic symptoms compared to the levels in healthy subjects (HS) and those ARMS individuals without a progression in prodromal symptoms.

We aimed to replicate these findings with the determination of morning cortisol levels in the clinic and the assessment of the cortisol awakening response (CAR) at home. As cross-sectional studies (Day et al., 2014) had previously reported a blunted CAR in medication-free ARMS individuals when compared to that in HS, we also included this HPA axis measure in a longitudinal study that followed ARMS individuals for at least one year (Labad et al., 2015). Although morning salivary cortisol levels in the clinic in the group of ARMS individuals who developed psychosis were slightly higher than in those ARMS individuals who did not develop a psychotic disorder or in HS, these differences were not significant. This result is in accordance with other studies that also obtained one morning salivary sample at the clinic (Chaumette et al., 2016; Sugranyes et al., 2012) and previous meta-analysis (Chaumette et al., 2016) suggesting that there are no significant differences in basal cortisol levels between ARMS who develop a psychotic disorder or not. However, the examination of the CAR revealed a different pattern in cortisol secretion after awakening between groups. In the multivariate analyses adjusted for sex, body mass index, awakening time, antidepressant treatment, antipsychotic treatment and smoking, significant differences were found particularly for the cortisol slope between awakening time and 30′ post-awakening, with a great rise in ARMS individuals with a psychosis transition when compared to that in other diagnostic groups.

No other prospective studies have explored the role of the CAR in relation to psychosis transition in ARMS individuals. However, cross-sectional studies have reported mixed results: a blunted CAR has been reported in ARMS individuals (Day et al., 2014) and children with multiple antecedents of schizophrenia but not in high-risk children with a family history of illness (Cullen et al., 2014). In contrast, in people with FEP and chronic schizophrenia, a blunted CAR has been more consistently observed (Berger et al., 2016), suggesting that HPA abnormalities in ARMS individuals are more subtle than in patients with an established psychosis. Indeed, in a study from our group (Labad et al., 2018) that included both ARMS and FEP patients, a blunted CAR was associated with an FEP diagnosis after adjustments for psychopathology symptoms in multivariate analyses, although no significant differences in the CAR were found between groups in the univariate analyses. In another recent study (Nordholm et al., 2018) including ARMS individuals, FEP patients and HS, only ARMS individuals had a higher cortisol increase just after awakening compared to HS. In this study, a negative correlation between cortisol increase after awakening and symptom severity was found in ARMS individuals.

In this line, the neural diathesis-stress model of schizophrenia has been recently updated (Pruessner et al., 2017b) to underscore the

importance of the stage of the illness for explaining some differences in HPA axis indices between ARMS, FEP and chronic psychoses. Psychotic disorders show a neurodevelopmental course, and progressive brain changes are observed even before the onset of psychosis (Sun et al., 2009). A reduction in hippocampal volumes is a consistent finding in patients with FEP and schizophrenia (Adriano et al., 2012). Interestingly, hippocampal volume reductions have also been observed in ARMS individuals, although these changes might be independent of transition status (Wood et al., 2010). A meta-analysis (Walter et al., 2016) indicates that there is no reduction in hippocampal volume in ARMS individuals before transition to psychosis and that hippocampal volume cannot be used as a biomarker in ARMS individuals. However, another meta-analysis (Fusar-Poli et al., 2012b) reported a reduction in the hippocampus of ARMS individuals when compared to HS, suggesting that it is plausible that there are subtle hippocampal changes at the prodromal phase that become more prominent when the psychotic illness develops. In FEP patients, hippocampal reductions have been related with increased cortisol levels (Mondelli et al., 2010) and a blunted CAR, particularly in male patients (Pruessner et al., 2015). As the hippocampus is a key region that participates in the control of the negative feedback of the HPA axis, progressive brain changes in the hippocampus may be associated with changes in HPA axis function over time as psychosis develops.

Several studies have explored pituitary gland volumes as an indirect measure of HPA axis activity, as larger pituitary size is thought to reflect a greater activation of the HPA axis, related to an increase in the number and size of corticotroph cells (Pariante, 2008). Longitudinal studies have shown that ARMS individuals who will develop psychosis have larger baseline pituitary volumes than subjects who do not later develop psychosis (Garner et al., 2005). A meta-analysis including different diagnostic groups (ARMS, FEP, schizophrenia and HS) reported a trend of a larger pituitary volume in both ARMS individuals who transitioned to psychosis and in FEP patients compared to HS (Nordholm et al., 2013). However, no differences in pituitary volume were found in psychotic patients (combining FEP and schizophrenia) versus HS, or between ARMS (grouping those with or without psychosis transition) and HS. As acute increases in the volume of the pituitary in antipsychotic-free ARMS and FEP might involve other hormones that are activated by stress, such as prolactin (due to the increase of lactotroph cells), it is difficult to distinguish whether pituitary volume enlargements are driven by a hyperactivity of the HPA axis or by increased prolactin levels. This is particularly important because increased prolactin levels have been found in drug-naïve ARMS and FEP patients (see Section 2.3). In a recent study that assessed both HPA axis measures (CAR, diurnal cortisol) and pituitary gland volumes in ARMS individuals and FEP patients, no correlations were found between these variables (Nordholm et al., 2018). It would be interesting to know whether other HPA axis measures (e.g. corticotrophin [ACTH]) are increased in ARMS individuals prior to the onset of psychosis, but this information is lacking in longitudinal studies exploring the role of the HPA axis on psychosis transition (Table 1).

Different stages of psychotic illness might reflect different cumulative stress and allostatic load effects. In the allostatic model (McEwen, 1998), the brain coordinates behavioural and physiological adjustments to meet the demands of stressors. The active process of responding to a challenge to the body by triggering chemical mediators of adaptation (HPA, autonomic, metabolic, immune) can be adaptive in the short term (allostasis) and maladaptive in the long term (allostatic load). The prodrome phase of the psychotic illness, which typically occurs during adolescence or young adulthood, converges with a neuromaturational stage that is associated with a heightened sensitivity to stressful events (Holtzman et al., 2013, 2012). Results from our group (Gattere et al., 2016) as well as from other groups (Pruessner et al., 2011) suggest that increased perceived stress is reported in ARMS individuals when compared to that in patients with an established psychotic disorder. Furthermore, baseline increased perceived stress is also present in those ARMS individuals who develop a psychotic disorder in the future (Labad et al., 2015). In other studies from our group, we have also reported behavioural changes in dietary habits related to stressful life events (Manzanares et al., 2014). For instance, life stress was associated with a reduction in refined sugar intake in both ARMS individuals and HS but with an increased intake in patients with a psychotic disorder. In a previous study (Stojanovic et al., 2014) that found increased interleukin-6 (IL-6) levels in both ARMS and recent-onset psychosis (ROP) individuals, we reported different associations between positive psychotic symptoms and IL-6 levels in ARMS and ROP groups: a positive relationship was found in ARMS individuals, whereas a negative relationship existed for ROP patients. These findings were not attributed to confounding variables, including gender, body mass index (BMI), tobacco consumption, antipsychotic treatment or the IL6 rs1800795 SNP genotype.

Although drawing conclusions in the comparison of ARMS and psychotic patients is difficult due to the potential existence of important confounders (differences in treatment, severity of symptoms and/or metabolic comorbidities), these previous findings raise the question of whether the stage of the illness plays a role in some of the differences between ARMS and psychotic patients. In terms of the allostatic load model, those ARMS individuals who will develop a psychotic disorder may be speculated to show biological adaptative responses (e.g., increased CAR, positive associations between positive symptoms and IL-6) before the psychotic onset (lower allostatic load stage) that are later lost when the psychosis is established (higher allostatic load stage), thus revealing maladaptive responses (e.g., blunted CAR, negative associations between positive symptoms and IL-6). This allostatic load approach might explain some results of a previous meta-analysis reporting that basal cortisol levels are increased in ARMS individuals compared to HS, but that levels are not different in FEP patients from ARMS individuals or HS (Chaumette et al., 2016). Further long-term longitudinal studies exploring changes in HPA axis indices or inflammatory markers in the same cohort of patients from the prodromal phase are needed to test this hypothesis.

2.3. Prolactin

Hyperprolactinaemia is a common condition (prevalence approximately 70%) in subjects with a psychotic disorder (Montgomery et al., 2004). As dopamine from the tuberoinfundibular dopaminergic pathway, acting through the D2 receptors in lactotroph cells, is the main prolactin-inhibiting factor, hyperprolactinaemia is a common consequence of D2 receptor blockade by antipsychotic drugs (Horseman and Gregerson, 2013). However, increased prolactin levels have also been reported in drug-naïve ARMS and FEP patients (Aston et al., 2010; Garcia-Rizo et al., 2012; Riecher-Rössler et al., 2013). As no longitudinal studies had explored whether ARMS individuals who developed a psychotic disorder had increased prolactin levels at baseline, our group conducted the first prospective study to explore this hypothesis (Labad et al., 2015). In relation to baseline prolactin levels, ARMS individuals with a psychosis transition had higher prolactin than those ARMS that did not develop a psychotic disorder and a healthy control group. These results did not change after adjusting for covariates (age, sex, stressful life events) or when examined in a subsample of antipsychotic-free ARMS subjects. Although we adjusted multivariate analyses for sex in our previous article (Labad et al., 2015), a sex-stratified analysis was not conducted. However, as recent studies in antipsychotic-naïve FEP have reported a greater increase of prolactin levels in women after correcting for the normal biological variation between sexes (Ittig et al., 2017), new data regarding prolactin levels and the risk of psychosis transition by sex distribution has been included in the current review (Fig. 2). In this figure, using the same sample of a previous article by our group (Labad et al., 2015), baseline prolactin levels by sex are shown for three diagnostic groups: ARMS without a psychotic transition, ARMS with a psychotic transition and

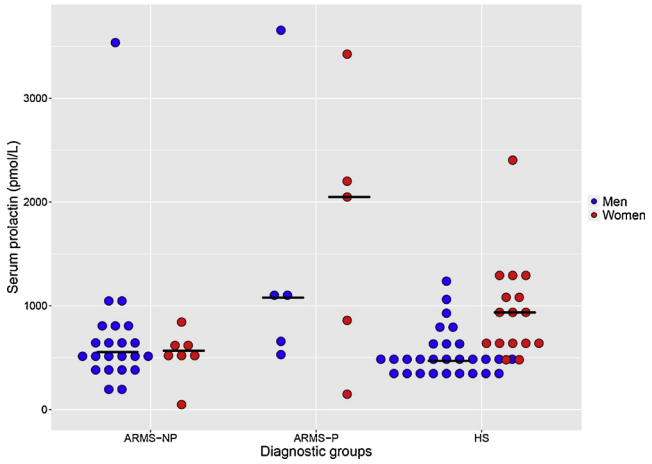


Fig. 2. Prolactin levels by diagnostic groups and sex.
Dots represent individual observations. Lines represent the median value for each subgroup.
Abbreviations: ARMS-NP = At-risk mental states without a psychosis transition; ARMS-P = At-risk mental states with a psychosis transition; HS= Healthy subjects.

HS. ARMS without a psychotic transition had similar prolactin levels than HS. In contrast, higher prolactin concentrations at baseline were observed in both male and female ARMS with a psychosis transition during the follow-up period (all ARMS were followed-up for at least one year). The comparison of log-transformed prolactin levels between groups revealed that those ARMS individuals who developed a psychotic disorder reported statistically significant higher prolactin levels than those ARMS individuals who did not develop a psychotic disorder in both men and women.

In another collaboration with Crespo-Facorro's group that included a large sample of 270 antipsychotic-naïve FEP individuals and 153 HS (Delgado-Alvarado et al., 2018), the observation of increased prolactin levels in FEP patients was also replicated. After stratification by sex and age, greater differences between FEP patients and HS were observed for young women (below 45 years). Furthermore, prolactin levels were inversely correlated with the severity of positive and disorganized symptoms only in women. Our results suggest that there are sex differences in the association between prolactin and positive psychotic symptoms, in accordance with other studies reporting sex-differences in prolactin levels in antipsychotic-naïve FEP patients (Ittig et al., 2017). However, we would have expected to find the opposite result (higher prolactin related to a greater severity of positive symptoms) considering the potential role of prolactin in the pathogenesis of the psychotic outbreak in ARMS studies (Labad et al., 2015). As mentioned before, the stage of the illness (and allostatic load status) might be an important variable when comparing people at a pre-psychotic phase (ARMS) with an established psychosis (FEP). Therefore, differences in allostatic load status may explain some differences found in the association between prolactin and the psychotic phenotype depending upon the stage of the psychotic illness.

The exact mechanisms by which prolactin levels in drug-naïve FEP patients and in those ARMS individuals who develop a psychosis are increased are not well understood. Four different non-exclusive hypotheses might be formulated (Fig. 3):

Hypothesis 1. Hyperprolactinaemia as a stress-related epiphenomenon.

As prolactin might be increased by psychosocial stress (Lennartsson and Jonsdottir, 2011), and both untreated FEP patients and ARMS individuals show increased perceived stress, increased prolactin levels may be speculated to be secondary to the heightened stress between the prodromal stage and psychosis outbreak. Some authors (Riecher-Rössler, 2017) have suggested that stress-induced hyperprolactinaemia could contribute to triggering the onset of acute psychotic symptoms via the production of dopamine as a result of a feedback loop. However, this highly speculative hypothesis is difficult to be accepted because the hyperdopaminergic hypothesis of psychosis suggests that the psychotic outbreak is driven by an increased dopamine tone in the mesolimbic pathway, which is differentially regulated from the dopamine tone in the tuberoinfundibular pathway (Demarest and Moore, 1979).

More plausibly, the increased prolactin levels are a stress-related epiphenomenon; prolactin may not directly induce psychotic symptoms, and other stress-related hormones (e.g., glucocorticoids) may have more important aetiopathogenic roles in the onset of psychosis. However, the positive association between prolactin and psychosocial stress in FEP and ARMS individuals is still a matter of debate. For

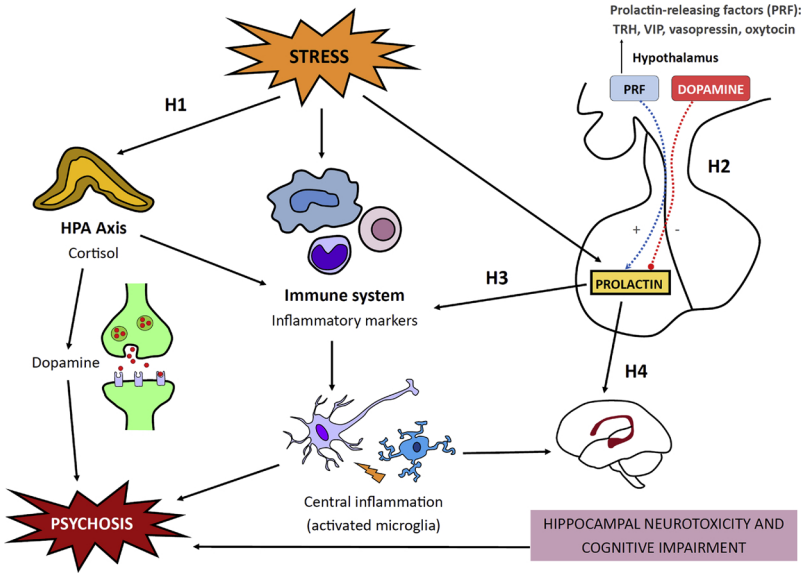


Fig. 3. Hypotheses linking prolactin with the risk of developing a psychotic disorder.
Abbreviations: HPA= Hypothalamic-pituitary-adrenal; PRF = Prolactin-releasing factors; TRH = Thyroid-releasing hormone; VIP = Vasoactive intestinal protein.
Cortisol, inflammatory markers and prolactin are increased in response to psychosocial stress. Most recognized hypotheses in the pathogenesis of psychotic disorders have involved glucocorticoids and inflammation. The neural diathesis-stress hypothesis suggests that activation of the HPA axis and glucocorticoid secretion augments dopamine activity in certain brain regions, especially the mesolimbic system, which could trigger psychosis. The inflammatory hypothesis suggests that a central inflammatory response by microglial activation may lead to excessive synaptic pruning and grey matter loss in regions such as the prefrontal cortex and hippocampus, potentially contributing to the dopaminergic dysregulation of subcortical structures. Whether prolactin plays a role in the pathogenesis of psychosis is unknown. Four complementary hypotheses may be proposed. In the first hypothesis (H1), increased prolactin in untreated psychotic patients might be a stress-related epiphenomenon, and the psychotic risk may be driven by cortisol. In a second hypothesis (H2), increased prolactin levels might be secondary to an altered regulation of the tuberoinfundibular pathway, secondary to an imbalance of prolactin-inhibiting (e.g., dopamine) and/or prolactin-releasing (e.g., thyrotropin-releasing-hormone [TRH]) factors. The third hypothesis (H3) suggests that prolactin may enhance the immune response and increase the risk of developing a psychotic disorder via an inflammatory-mediated pathway. The last hypothesis (H4) suggests that prolactin might contribute, along with other factors (cortisol and inflammation), to cognitive impairments in domains such as processing speed and executive functions, thereby increasing the risk of psychosis transition in vulnerable individuals.

instance, a recent longitudinal study (Lally et al., 2017) that examined prolactin levels in FEP patients over the course of one year did not find significant associations between prolactin levels and stress measures (perceived stress, stressful life events). Furthermore, in previous studies from our group (Labad et al., 2015), stress measures and prolactin levels in ARMS individuals were not significantly correlated.

Hypothesis 2. Hyperprolactinaemia secondary to an altered prolactin regulation.

There may also be a dysregulation of prolactin secretion at different levels of the tuberoinfundibular pathway due to an imbalance of prolactin-inhibiting (e.g., dopamine) and prolactin-releasing (e.g., thyrotropin-releasing hormone [TRH]) factors. Challenge studies of the tuberoinfundibular pathway that have compared untreated patients with schizophrenia and HS have demonstrated an altered prolactin response with dopamine antagonists (haloperidol) (Keks et al., 1992) but not with dopamine agonists (apomorphine) (Duval et al., 2003). Previous studies in drug-naïve patients with first-episode schizophrenia (Spoov et al., 2010) have shown an altered response with low doses of TRH, suggesting a "hypersensible" prolactin-stimulating system. Challenge studies in ARMS individuals are lacking. Future studies might assess this issue in ARMS to explore whether hyperprolactinaemia in those ARMS individuals at greater risk for psychosis is secondary to altered prolactin regulation.

Hypothesis 3. Hyperprolactinaemia contributes to the psychosis transition via a pro-inflammatory-mediated pathway.

Prolactin promotes pro-inflammatory immune responses via nuclear factor-kappa B and interferon regulatory factor-1 (Brand et al., 2004) and regulates monocyte/macrophage function in vitro (Carvalho-Freitas et al., 2008). The inflammatory hypothesis of schizophrenia suggests that inflammatory processes might be involved in the pathogenesis of this mental illness (Howes and McCutcheon, 2017; Soria et al., 2017) based on the observed pro-inflammatory state in FEP and chronic patients with schizophrenia compared with that in HS and increased inflammation found in patients with relapses that improves after antipsychotic treatment (Miller et al., 2011). Moreover, the major histocompatibility complex is consistently the region that is most strongly associated with schizophrenia in genome-wide association studies (Stefansson et al., 2009), which have been interpreted as strong genetic evidence supporting the immune hypothesis. A central inflammatory response by microglial activation has been suggested to lead to excessive synaptic pruning and grey matter loss in regions such as the prefrontal cortex and hippocampus, leading to negative and cognitive symptoms, and potentially contributing to the dopaminergic dysregulation of subcortical structures (Howes and McCutcheon, 2017).

As most studies have focused on FEP and schizophrenia patients rather than ARMS individuals, our group aimed to conduct the first study that explored IL-6 levels in ARMS individuals when compared to levels in ROP patients and HS (Stojanovic et al., 2014). A pro-inflammatory state was reported in both the ARMS and ROP groups. Longitudinal data in this study suggested that ARMS individuals who developed a psychotic disorder exhibited higher median IL-6 levels than those who did not transition (0.61 vs. 0.35 pg/ml). However, as the sample size was small, we were unable to detect statistically significant differences between groups. The Avon Longitudinal Study of Parents and Children (ALSPAC), a prospective general population birth cohort, has provided evidence that IL-6 levels during childhood predict the risk of suffering from psychotic experiences during young adulthood (Khandaker et al., 2014). Other longitudinal studies from our group including ARMS individuals (Labad et al., 2015) have reported lower albumin levels in those ARMS individuals who developed a psychotic disorder. Interestingly, albumin has free-radical trapping properties and is the major plasma target of oxidant stress (Roche et al., 2008), suggesting that an impaired antioxidant mechanism could play a role in the risk of developing a psychotic disorder, as oxidative stress is thought to contribute to the pathogenesis of schizophrenia (Flatow et al., 2013). In our previous study (Labad et al., 2015), serum albumin levels were negatively correlated with prolactin levels in ARMS individuals but not in HS. As both increased prolactin levels and increased inflammatory and oxidative stress markers have been reported in ARMS individuals and FEP patients (Delgado-Alvarado et al., 2018; Labad et al., 2015; Riecher-Rössler et al., 2013; Stojanovic et al., 2014), future studies need to test whether there is a connection between prolactin and the immune system in the risk of developing a psychotic disorder. However, as commented in a recent review of previous studies exploring the role of the immune system on the risk for developing a psychotic disorder, most transition studies including ARMS individuals have failed to replicate their findings probably because of small sample sizes and underpowered analyses (Khoury and Nasrallah, 2018). The largest study to date, the NAPLS project, suggest that several inflammatory markers including IL-1β, IL-7, IL-8, matrix metalloproteinase 8 (MMP-8) might be associated to the risk of psychosis transition (Perkins et al., 2015). Although in this study prolactin was not included in the final panel of 15 out of 117 baseline analytes that significantly predicted psychosis transition, given the pro-inflammatory activity of prolactin (Brand et al., 2004), more studies are needed to explore the potential prolactin-inflammation link in relation to the vulnerability to develop a psychotic disorder.

Hypothesis 4. Hyperprolactinaemia contributes to the psychosis transition via a cognitive-mediated pathway.

As both hyperprolactinaemia and cognitive alterations are present before the psychotic outbreak, and hyperprolactinaemia might contribute to cognitive performance in early psychosis (see Section 3.3. of this review), a new hypothesis can be formulated regarding cognitive impairment as a mediating factor between hyperprolactinaemia and psychosis development. This hypothesis will be discussed in Section 3.3.

3. The role of hormones in the expression of negative and cognitive symptoms

3.1. The cross-talk between negative and cognitive symptoms

Negative and cognitive symptoms might be present in the main psychotic diagnoses (schizophrenia, schizoaffective disorder, bipolar disorder), although these symptoms are more severe in patients with schizophrenia (Bora et al., 2009; Strauss et al., 2016). Negative symptoms reflect a pathological deficit, representing the absence of some normal functions, such as a reduction in emotional responsiveness, motivation, socialization, speech, and movement. They are typically defined in terms of clinical observations of behavioural features and are usually assessed in research studies with psychometric scales. In contrast, cognitive symptoms are defined in terms of performance on neuropsychological tests and include impairments in different domains including neurocognition (attention, processing speed, memory, executive functioning) and social cognition.

Both negative and cognitive symptoms are considered developmental symptoms, which might be present before the onset of psychotic symptoms, and can persist even after the remission of the psychotic symptoms (Fusar-Poli et al., 2012a; Harvey et al., 2006; Holtzman et al., 2012). The severity of negative and cognitive symptoms are correlated and are known factors of a poorer prognosis, as defined by everyday life skills and social functioning (Harvey et al., 2006). However, negative and cognitive symptoms can change independently of each other due to either treatment, or to the natural course of the illness. They also show differences in their functional relevance: cognitive performance seems to be more correlated with the ability to perform everyday living skills, while negative symptoms are more related to the likelihood of performing these skills (Harvey et al., 2006).

3.2. HPA axis

Glucocorticoid excess is thought to contribute to learning and memory problems, as cortisol can easily cross the blood-brain barrier, access the brain, and bind to glucocorticoid receptors in the prefrontal cortex, the hippocampus and the amygdala, three brain regions involved in memory processing and emotional regulation (Lupien et al., 2018). The hypothesis linking chronic exposure to stress hormones and neurotoxic effects on the brain relies on different animal and human studies that have included both non-clinical (e.g., cohorts of healthy ageing individuals) and clinical (e.g., Cushing syndrome) populations (Forget et al., 2016; Lupien et al., 2018). The life cycle model of stress suggests that the effects of chronic or repeated exposure to stress at different stages in life depend on the brain areas that are developing or declining at the time of the exposure (Lupien et al., 2018), with the hippocampus more vulnerable to stress from birth to 2 years, the amygdala during late childhood and the frontal lobe during adolescence and the transition to young adulthood. In addition to these neurotoxic effects on brain regions, prenatal stress can have programming effects on the HPA axis (Reynolds et al., 2013). The developing foetus adapts to an insult in utero with permanent changes in structure, physiology and metabolism that are initially beneficial for survival but, in later life, might be maladaptive and associated with increased disease risk including psychiatric disease risk.

In relation to psychotic disorders, the first evidence of neurotoxic effects on the hippocampus came from studies by Carmine Pariante's group. In an early longitudinal study (Mondelli et al., 2010) that included FEP patients and HS, diurnal cortisol levels were inversely correlated with left hippocampal volume in patients (but not HS) both at baseline and at follow-up. This same research group also found that both childhood trauma and stressful life events contribute to the reduction in brain-derived neurotrophic factor (BDNF) mRNA levels in FEP patient leukocytes, possibly through a stress-induced increase in IL-6 expression (Mondelli et al., 2011). The smaller left hippocampal volumes of FEP patients were associated with reduced BDNF expression, increased IL-6 expression and increased diurnal cortisol levels. Other studies have found an association between a blunted CAR and a reduced hippocampal volume in men (but not women) with an FEP (Pruessner et al., 2015) or ARMS diagnosis (Pruessner et al., 2017a). A blunted CAR has also been related to a poorer performance in processing speed and verbal memory tasks in FEP patients (Aas et al., 2011). Moreover, another study conducted among children who are at an elevated risk for developing schizophrenia also reported an association between HPA axis function abnormalities (higher diurnal cortisol levels and greater blunting of the CAR) and poorer performance on verbal memory and executive function tasks (Cullen et al., 2014). Higher afternoon cortisol levels have been associated with poorer verbal learning in men with first-episode schizophrenia (Havelka et al., 2016). In another study that assessed both cortisol and sulphate dehydroepiandrosterone (DHEAs) in FEP patients (Allott et al., 2018), DHEAs (but not cortisol) levels were associated with better baseline attention in HS and poorer attention in FEP. Change in DHEAs was associated with change in verbal learning over a 12-week follow-up period.

Other studies have found associations between HPA axis measures and cognitive abilities in patients with chronic schizophrenia. Morning salivary cortisol levels have been associated with poorer performance in explicit memory and hippocampal-related cognitive tasks (Walder et al., 2000). A negative relationship between morning plasma cortisol concentrations and processing speed performance has been also reported in men (but not women) with schizopohrenia (Halari et al., 2004). Finally post-dexamethasone cortisol levels have been related to impaired verbal learning in drug-free patients with schizophrenia (Newcomer et al., 1991).

Taking into account these previous studies, our group aimed to replicate these findings in a sample of ROP patients with an examination of three HPA axis measures: the CAR, diurnal cortisol levels and a dexamethasone suppression test (DST) using very low doses of dexamethasone (0.25 mg) (Labad et al., 2016). We also found sex differences in some associations between HPA axis measures and cognitive functioning, as women with an increased CAR demonstrated poorer processing speed and verbal memory, and those women with a more flattened diurnal cortisol slope showed poorer spatial working memory. DST non-suppression was associated with better visual memory without sex differences. Our results, as well as those from studies by other groups (Aas et al., 2011; Cullen et al., 2014), suggest that HPA axis measures influence cognitive tasks dealing with executive functions and memory processes at early stages of the psychotic illness. Interestingly, the hippocampus and prefrontal cortex are two brain regions where glucocorticoid receptors are distributed, showing a vulnerability to the neurotoxic effects of glucocorticoids (Lupien et al., 2018). Selected studies exploring the link between HPA axis hormones and cognition in ARMS and ROP patients are summarized in Table 2. As it can be seen, most studies that included HPA axis measures assessed cortisol and lacked measurement of other HPA axis hormones such as ACTH.

In an examination of negative symptoms, our group also explored the relationship between HPA axis activity and psychopathology symptoms in a study that included FEP, ARMS and HS (Labad et al., 2018) and revealed a different pattern across clinical diagnoses: in ARMS individuals, the severity of negative symptoms was associated with a more flattened diurnal cortisol slope, whereas in FEP patients, an opposite relationship was found. Negative symptoms were not associated with the CAR or the DST. These results highlight the importance of the stage of the illness when exploring the association between HPA axis measures and negative symptoms. Other studies including FEP patients have not found associations between negative symptoms and diurnal cortisol levels or the CAR (Belvederi Murri et al., 2012; Nordholm et al., 2018). In patients with chronic schizophrenia, the relationship between negative symptoms and HPA axis measures has brought mixed results (for a review, see Bradley and Dinan, 2010), with most findings related to the DST, as about half of the studies have reported an association between negative symptoms and non-suppression in cortisol levels after dexamethasone administration.

Our group also participated in a systemic review of clinical trials of drugs targeting the HPA axis that were used as potential cognitive enhancers in patients with serious mental illness including schizophrenia and bipolar disorder (Soria et al., 2018). Of all potential candidate drugs, the most promising results dealing with the HPA axis were for mifepristone or RU-486, an antagonist of glucocorticoid receptors, with positive trials in bipolar disorder patients. Verbal memory and working memory, the two cognitive domains most clearly improved by mifepristone in those positive trials, have also been found to be associated with HPA axis abnormalities in studies by our group (Labad et al., 2016) as well as from others (Aas et al., 2011; Cullen et al., 2014). However, clinical trials testing the addition of mifepristone to antipsychotic treatment in patients at early stages of psychotic illness are lacking. As HPA axis abnormalities have been associated with both cognitive and negative symptoms in patients with ROP, future clinical trials need to test whether the addition of this drug to antipsychotic treatment improves cognitive outcome in these patients. Mifepristone is a challenging drug to use in the future due to its anti-progesterone actions, requiring contraceptive measures in premenopausal women (Soria et al., 2018).

3.3. Prolactin

For many years, the most studied consequences of hyperprolactinaemia in psychotic subjects have been amenorrhoea, galactorrhoea, sexual impairment and infertility (Horseman and Gregerson, 2013). However, prolactin plays important roles as a neuropeptide and regulates neurogenesis in both the subventricular zone and the dentate gyrus of the hippocampal formation (Torner, 2016), suggesting a potential role of prolactin in the brain in aspects other than reproductive function, including cognitive abilities. The first study in humans to address this issue

Table 2
Studies exploring the relationship between hypothalamic-pituitary-adrenal axis hormones or prolactin and neurocognition in at-risk mental states or psychotic disorders at early stages of the disease.

Reference	Sample[†]	HPA axis measures or prolactin	Neurocognitive domains	Results
Aas et al. (2011)	30 FEP 26 HS	CAR (AUC_i) Salivary cortisol levels during the day (AUC_g-day: awakening, 12:00 h, 20:00 h)	SoP, VERM, VISM, WM, EF, GK	A more blunted CAR was associated with a poorer performance in VERM and SoP in FEP. No association between AUC_g-day and cognitive performance.
Cullen et al. (2014)	33 ASz 22 FHx 40 HS	CAR (AUC_i) Salivary cortisol levels during the day (AUC_g-day: awakening, 12:00 h, 20:00 h)	SoP, VERM, VISM, WM, AV, EF	CAR values were positively correlated with SoP among ASz children and with VERM in the FHx group. AUC_g-day values were negatively correlated with VERM, AV and EF in FHx children.
Montalvo et al. (2014)	55 ROP 23 ARMS 29 HS	Prolactin and cortisol in plasma (between 8:30 h and 9:30 h)	SoP, VERM, VISM, WM, EF, AV	Increased prolactin levels were associated with poorer SoP in ROP and with poorer SoP and EF in ARMS. Multivariate analyses were adjusted for cortisol levels.
Havelka et al. (2016)	23 FES (all men)	Afternoon plasma cortisol levels (16:00 h and 23:00 h) Post-dexamethasone cortisol	SoP, VERM, WM, EF, AV	Higher afternoon cortisol levels were associated with poorer VERM. No associations between post-dexamethasone cortisol levels and cognitive functioning.
Labad et al. (2016)	60 ROP 50 HS	CAR (AUC_i) Diurnal cortisol slope (between 10:00 h and 23:00 h) DSTR after administration of 0.25 mg of dexamethasone	SoP, VERM, VISM, WM, EF, AV	An increased CAR was associated with a poorer SoP and VERM in ROP women. A more flattened diurnal cortisol slope was associated with poorer WM in ROP women. DSTR was associated with better VISM in both ROP and HS, without sex differences.
Allott et al. (2018)	35 FEP 23 HS	Cortisol and DHEAs in plasma (between 9:00 h and 10:00 h) at baseline and after 12 weeks	VERM, WM, AV	DHEAs (but not cortisol) levels were associated with better baseline AV in HS and poorer baseline AV in FEP. Change in DHEAs was associated with change in VERM over a 12-week follow-up period in both groups.
Montalvo et al. (2018b)	60 ROP 50 HS	Prolactin and cortisol in plasma (between 8:30 h and 9:30 h) CAR (AUC_i) Salivary cortisol levels during the day (AUC_g-day: awakening, 30' and 60' post-awakening, 10:00 h, 23:00 h)	SoP, VERM, VISM, WM, EF, AV	There were sex differences in the relationship between prolactin levels and impaired cognition in ROP: prolactin was negatively associated with SoP tasks only in men. In women, AUC_g-day values were associated with poorer SoP and VERM.

Abbreviations: FEP = First-episode psychosis; FES = First-episode schizophrenia; ROP = Recent-onset psychosis; ARMS = At-Risk Mental States; HS = Healthy subjects; ASz = children with multiple antecedents of schizophrenia (including delays or abnormalities in speech and/or motor development; social, emotional and behavioural problems; and psychotic-like experiences); FHx = children with a family history of schizophrenia or schizoaffective disorder; CAR = Cortisol awakening response; AUC_i = Area under the curve calculated with respect to the increase; AUC_g = Area under the curve calculated with respect to the ground; DHEAs = sulphate dehydroepiandrosterone; DSTR = Dexamethasone suppression test ratio; SoP = Speed of processing; VERM = Verbal memory; VISM = Visual memory; WM = Working memory; EF = Executive functions; GK = General knowledge; AV = Attention and vigilance.

[†] All but one (Cullen et al., 2014) studies included adolescent or young adult samples.

was a prospective study (Henry and Sherwin, 2011) in women during late pregnancy and the early postpartum period that found a negative linear association between prolactin levels and executive function scores, suggesting a detrimental role of prolactin on cognition. Taking into account this study and animal studies suggesting that chronic hyperprolactinaemia induced impaired object recognition in rats (Torner et al., 2013), we aimed to conduct the first study including HS, ARMS individuals and FEP patients (Montalvo et al., 2014). Prolactin levels were negatively associated with cognitive performance in processing speed in patients with an ROP and in ARMS individuals. In the latter group, increased prolactin levels were also associated with impaired reasoning and problem solving and poorer general cognition. Notably, most ARMS individuals were not receiving antipsychotic treatment, lending support to the hypothesis that hyperprolactinaemia may affect cognitive processes independently of antipsychotic treatment. Moreover, in those early psychotic patients receiving antipsychotic treatment, increased prolactin levels mediated the negative effects of prolactin-raising antipsychotics on processing speed. In another study by our group (Montalvo et al., 2018b), we also reported sex differences in this relationship, as prolactin levels were associated with impaired processing speed in men, and this association was independent of the HPA and hypothalamic-pituitary-gonadal axes. In another study that included drug-naïve FEP patients (Delgado-Alvarado et al., 2018), negative symptoms were not associated with prolactin levels.

A methodological problem of studying the relationship between prolactin and cognition in ROP is that patients are on antipsychotic drugs that may block D2 receptors not only in the tuberoinfundibular pathway but also in the striatum or the mesocortical pathway, thus contributing to cognitive impairment. The recruitment of drug-naïve patients for exploring cognition is also not a valid approach, as cognitive performance is impaired in patients with prominent positive psychotic symptoms. An indirect way of exploring the effects of prolactin on cognition would be to study this topic in other populations not taking antipsychotic drugs. Patients with prolactinomas are a good study population, as prolactin levels have been associated with impaired cognition in this population (Bala et al., 2016). We conducted a proof-of-concept trial that was the first to demonstrate that the reduction in prolactin levels via treatment with cabergoline, a dopamine agonist, is followed by improvements in processing speed, working memory, visual learning and reasoning and problem-solving in patients with a prolactinoma (Montalvo et al., 2018a). Recent research from other groups has demonstrated a decrease in grey matter volumes in the left hippocampus, left orbitofrontal cortex, right middle frontal cortex, and right inferior frontal cortex in patients with a prolactinoma (Yao et al., 2018). In addition, patients performed worse than controls on verbal memory and executive function tasks, and this difference was significantly related to the grey matter volumes of the left hippocampus and right medial frontal cortex, respectively. Moreover, prolactin levels were inversely correlated with left hippocampus and right inferior frontal cortex volumes, suggesting a potential 'neurotoxic' effect of prolactin, although the underlying mechanism is not yet clearly understood.

Animal studies have brought mixed results regarding whether prolactin is protective or damaging for the brain. Chronic hyperprolactinaemia in male rats induced by means of transplantation of pituitary grafts was associated with impaired object recognition but not with spatial learning deficits (Torner et al., 2013). Chronic intracerebral prolactin administration inhibits restraint stress-induced neuronal activation within the CA3 and dentate gyrus of the dorsal hippocampus and reduces c-fos expression under basal conditions in the ventral hippocampus (Donner et al., 2007). However, other studies have suggested neuroprotective roles for prolactin. Intracerebral administration of prolactin in female rats protected against kainic acid-induced neurodegeneration of the hippocampus and cognitive impairment measured with the novel object recognition test (Reyes-Mendoza and Morales, 2016). Other in vitro (addition of prolactin to primary adult hippocampal cells) and in vivo (direct infusion of prolactin into the adult dentate gyrus) studies in male mice have indicated that exogenous prolactin can increase the number of hippocampal precursor cells (Walker et al., 2012).

The association between prolactin and processing speed in both ARMS and FEP patients raises the question of whether prolactin contributes to the risk of developing a psychotic disorder in vulnerable individuals. Of all cognitive domains, processing speed is the first cognitive domain to be affected in early stages of psychotic disorders and in ARMS subjects (Riecher-Rössler et al., 2009). Although both impaired processing speed (Riecher-Rössler et al., 2009) and hyperprolactinaemia (Labad et al., 2015) have been suggested to be risk factors for developing a psychotic disorder, and prolactin levels are associated with impaired processing speed in both ARMS and ROP patients (Montalvo et al., 2014), no studies have explored whether increased prolactin levels mediate the relationship between impaired processing speed and the risk of developing a psychotic disorder in vulnerable individuals.

The relationship between prolactin, cognition and psychosis may be explained by the effects of prolactin on the dopamine system. Prolactin is well known to have access to the brain, although the precise mechanisms are still unclear. Although the hypothesis that the hormone accesses the brain though prolactin receptors located in the choroid plexus has been accepted for years, recent evidence in mice with deletion of the receptor has demonstrated that these receptors are not necessary to the mechanism and that endothelial cells of brain capillaries rather than the choroid plexus might be the route of transport (Brown et al., 2016). There is also evidence in animals that prolactin might potentiate striatal dopamine release in vitro and in vivo (Chen and Ramirez, 1988), suggesting a direct role on the striatum. In fact, the presence of the receptor has been detected by immunohistochemistry in the cortex and striatum of the rat (Roky et al., 1996). Striatal D2 receptors are important for D1 receptor expression and modulate motor and cognitive processes, along with D1 and D2 receptors in the prefrontal cortex (Abi-Dargham, 2004). The dopamine hypothesis of schizophrenia suggests that there is an imbalance between the subcortical and cortical dopamine systems that may result in hypoactive subcortical mesolimbic dopamine projections (resulting in hyperstimulation of D2 receptors and positive symptoms), while the mesocortical dopamine projections to the prefrontal cortex may be hypoactive (resulting in hypostimulation of D1 receptors, negative symptoms and cognitive impairment) (Abi-Dargham, 2004). Although speculative, the potential role of prolactin on the psychosis transition could be explained by an indirect cognitive-mediated pathway, taking into account the potential effects of prolactin on dopamine at different brain regions that are important for cognitive processes.

As of now, in clinical practice, the treatment of chronic hyperprolactinaemia in patients with a psychotic disorder is restricted to those with the presence of reproductive-related symptoms, and current guidelines suggest not to treat asymptomatic hyperprolactinaemia (Melmed et al., 2011). Clinical trials are needed to explore whether the reduction in prolactin with dopamine agonists (e.g., cabergoline) or antipsychotics with partial dopamine agonist properties (e.g., aripiprazole) improves cognitive functioning in psychotic patients with hyperprolactinaemia. If so, many patients who are currently viewed as "asymptomatic" may be considered "symptomatic" if cognitive performance is considered. A potential problem in treating psychotic patients with cabergoline is the risk of worsening their psychotic symptoms or triggering a psychotic relapse due to D2 agonism in the mesolimbic pathway (Chang et al., 2008). However, a large trial (Kalkavoura et al., 2013) using different cabergoline doses (0.25, 0.5 and 1 mg/day) for 6 months suggested that cabergoline may be a safer treatment than initially thought, as no psychotic exacerbations were reported.

4. Limitations

This is a narrative review that aimed to selectively review the literature as well as to include an integrative discussion of previous studies from our group. Therefore, some limitations need to be acknowledged, including this subjective approach with a personal view of the revised literature.

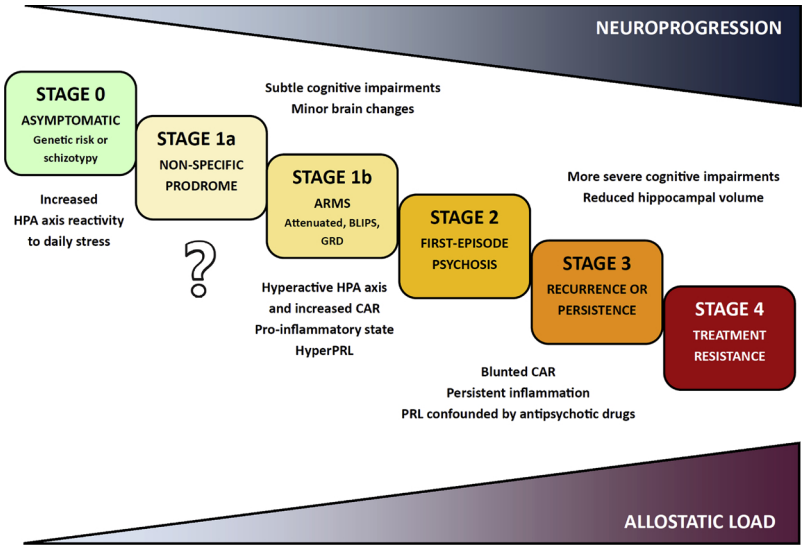


Fig. 4. The stage model of psychosis taking into account allostatic load status, stress-related biomarkers, structural brain changes and cognitive outcomes.
Abbreviations: HPA = Hypothalamic-pituitary-adrenal; ARMS = At-risk mental states; CAR = Cortisol awakening response; PRL = Prolactin.
Although cognitive and brain changes might be present before the onset of psychosis, there is a neuroprogression with a reduction in hippocampal volume and worsening in cognitive symptoms at later stages of the illness. Along with these changes, there are parallel changes in stress-related biomarkers as allostatic load increases with the progression of the illness. Studies in people at genetic risk of psychosis (Stage 0) suggest that there is increased cortisol reactivity to daily stress. In prodromal patients, most studies have focused on help-seeking ARMS individuals (Stage 1b), and studies on non-help-seeking ARMS individuals or those with non-specific prodromal symptoms (Stage 1a) are lacking. In ARMS individuals with prodromal psychotic symptoms (Stage 1b), there are subtle abnormalities of the HPA axis including increased morning cortisol levels and an increased CAR that do not seem to be shared at later stages of the illness, as FEP patients (Stage 2) show a blunted CAR and no differences in baseline cortisol levels when compared to healthy individuals. A methodological problem is that antipsychotic treatment may obscure some HPA axis findings in patients with an established psychotic disorder (Stages 2–4). Prolactin levels and inflammatory markers are similarly obscured in these patients. This methodological problem is specifically important in studies pertaining to prolactin because, although the increased prolactin levels in drug-naïve ARMS and FEP patients is a well-replicated finding, it is difficult to draw conclusions in antipsychotic-treated patients. The pro-inflammatory status that has been reported even before psychosis onset persists into later stages of the illness and might contribute, together with HPA abnormalities, to the neurotoxic effect on the hippocampus.

When exploring the role of stress hormones on the risk of psychosis transition and the cognitive outcome of psychotic disorders at early stages of the disease, most studies have been focused on the HPA axis. For a more comprehensive literature review of the role of the HPA axis in ARMS and FEP, there are excellent systematic reviews (Berger et al., 2016; Borges et al., 2013; Karanikas and Garyfallos, 2015) and meta-analyses (Chaumette et al., 2016). In terms of exploring hippocampal and pituitary volume changes at different stages of the psychotic illness, there are also specific meta-analyses (Fusar-Poli et al., 2012b; Nordholm et al., 2013; Walter et al., 2016).

A substantial part of this review has been focused on prolactin, that although has attracted less attention than the HPA axis in terms of its potential role on psychosis risk or cognitive performance, some promising findings in the last years suggest the need to continue exploring this topic.

5. Gaps and future directions

There are some problems with the current approach to the study of stress-related processes and biomarkers in people at risk for psychosis. The first problem is the definition of the 'at-risk phenotype', which is focused on positive psychotic symptoms and includes heterogeneous subgroups of vulnerable individuals (those with APS, BLIPS and GRD). An alternative approach could be the selection of vulnerable individuals using more objective clinical markers (e.g., cognitive performance) combined with either psychopathological symptoms (e.g., positive or negative symptoms) or biological markers (HPA axis measures, prolactin, inflammatory markers). A risk calculator has been recently generated in the NAPLS 2 cohort for predicting psychosis in studies on ARMS individuals (Cannon et al., 2016). This risk calculator includes a small number of demographic (age, family history of psychosis), clinical (unusual thought content and suspiciousness), neurocognitive (speed of processing, verbal learning and memory), and psychosocial (traumas, stressful life events, decline in social functioning) predictor variables. A replication test of this risk calculator in an independent sample from the Early Detection, Intervention, and Prevention of Psychosis Program has shown good discrimination (Carrión et al., 2016). Thus, future studies might take into account these predictors and select ARMS individuals at higher risk. This approach will help in the exploration of whether stress-related biomarkers differ between those ARMS individuals at greater or lower risk of developing a psychotic disorder.

As the biological underpinnings of increased prolactin levels in ARMS and FEP individuals are not well understood, this research area offers an opportunity for studying different hypotheses using longitudinal studies on ARMS individuals. The study of non-help-seeking ARMS individuals will also allow the exploration of whether prolactin is associated with attenuated psychotic experiences in individuals without increased perceived stress. Challenge studies exploring prolactin regulation in ARMS individuals are needed to explore whether the regulatory mechanisms at the tuberoinfundibular pathway are altered. Finally, the study of prolactin as a stress-related biomarker in people at risk of psychosis can be improved by the determination of prolactin levels in saliva with nanotechnology using electrochemical immunosensors (Serafín et al., 2014). The use of a non-invasive method for assessing prolactin concentrations will allow repeating testing in both laboratory and ecological conditions. For instance, some ecological approaches, such as the use of experience sampling methods, which have been used in the field of psychosis research (Collip et al., 2011), could be combined with prolactin determinations in saliva in order to explore whether there is increased prolactin secretion in daily life in people at risk for psychosis.

The research field of psychoses needs to conduct clinical trials targeting hormones systems to improve the outcome of patients at early stages of the illness. A particular important therapeutic approach would be improving cognitive symptoms, because these symptoms are closely related to psychosocial functioning (Carbon and Correll, 2014) and because pharmacological treatments targeting these symptoms are particularly lacking. Potential candidate targets for trials would include drugs targeting the HPA axis (e.g., mifepristone) and prolactin (e.g., cabergoline). Most of these drugs have not been adequately tested in patients at early stages of the psychotic illness. Moreover, as cognitive impairment is a risk factor of psychosis transition (Fusar-Poli et al., 2012a; Riecher-Rössler et al., 2009), some of these drugs could also be candidates for improving cognition in ARMS individuals, which might also reduce the risk for the development of a psychotic disorder.

Cognitive symptoms and allostatic load might fit with the stage model of psychosis (McGorry et al., 2014), as a dysregulation of stress-related biomarkers, progressive brain changes, and cognitive impairments are observed as allostatic load increases with the development of psychosis (Fig. 4). The advantage of this model is that it explicitly considers the evolution of psychopathology during the development of

the psychotic disorder and emphasizes that illness progression can be modified with appropriate interventions that target individual modifiable risk and protective factors. The stage model of psychosis has been focused on the appearance of positive psychotic symptoms. However, as suggested by some authors, examining specific neurobiological domains that cut across diagnoses (e.g., working memory, negative salience) may be more useful than using categorical distinctions (McGorry et al., 2014). Benign interventions may be applied at early stages (Stages 1a and 1b), such as N-acetylcysteine or fish oil for improving oxidative/inflammatory status or stress management or cognitive-behavioural therapy for improving HPA axis indices. Therefore, it is important to further study the neurobiological underpinnings that occur not only in ARMS individuals seeking help (Stage 1b) but also in those individuals in pre-ARMS stages when prodromal symptoms are non-specific (Stage 1a). As most prodromal studies are focused on help-seeking ARMS individuals, future studies need to combine clinical and epidemiological approaches to identify young adolescents that are at Stage 1a but do not seek help. This approach would allow the study of hormonal determinants in vulnerable individuals in order to improve psychotic and cognitive symptoms, as well as functionality.

Conflict of interest

Javier Labad has received honoraria for lectures or advisory boards from Janssen-Cilag, Otsuka or Lundbeck.

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