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Signature:

_____ _____

Daniel I. Shapiro Date

The Relationship Between Cortisol and Cognitive Functions in Individuals at Clinical High-Risk of Developing Psychosis

By

Daniel I. Shapiro
Doctor of Philosophy
Psychology

_____
Elaine F. Walker, Ph.D.
Advisor

_____
Jocelyn Bachevalier, Ph.D.
Committee Member

_____
Patricia A. Brennan, Ph.D.
Committee Member

_____
David A. Edwards, Ph.D.
Committee Member

_____
Stephan Hamann, Ph.D.
Committee Member

Accepted:

_____
Lisa A. Tedesco, Ph.D.
Dean of the James T. Laney School of Graduate Studies

_____
Date

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Daniel I. Shapiro

B.S., Indiana University, 2005
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Advisor: Elaine F. Walker, Ph.D.

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Abstract

The Relationship Between Cortisol and Cognitive Functions in Individuals at Clinical High-Risk of Developing Psychosis

By Daniel I. Shapiro

Continued research on the psychosis prodrome has been fueled by preliminary evidence that early detection and treatment can lead to better prognosis, possibly by slowing neurodevelopmental trajectories that lead to illness. Research on the hypothalamic-pituitary-adrenal (HPA) axis and cognitive function in at-risk youths are two areas that present opportunities for enhancing risk prediction. Both increased HPA activity, as indexed by elevated cortisol, and impaired cognitive function are observed in individuals at risk for psychosis. Additionally, some previous studies of healthy subjects, psychotic patients, and animals have shown that both elevated and reduced cortisol is associated with neurocognitive impairment. This suggests a possible link between the HPA axis and cognitive deficit in the premorbid or prodromal stages of illness. The current study examines this relationship in 257 adolescents at clinical high-risk (CHR) for developing psychosis and 149 controls. A quadratic association was predicted between baseline cortisol, aggregated over three measurements (AUC), and cognitive functions mediated by the hippocampus and prefrontal cortex (PFC). While a negative association was found between cortisol and putative PFC function, this association was linear and small in size. Higher cortisol and worse performance on all cognitive factors in the CHR group, relative to controls, may have led to a greater association between cortisol AUC and visuospatial abilities. Results suggest that the PFC may be more sensitive than the hippocampus to detrimental effects of cortisol in CHR youths, and that cortisol plays a modest role in the cognitive deficits seen in these individuals. Future research is needed on the longitudinal relation between changes in cortisol secretion and subsequent cognitive function.

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The biological response to stress plays a role in many conceptualizations of the pathophysiology of schizophrenia and other psychotic disorders. Many decades of research in this area have led to a diathesis-stress model of illness onset where an inherited or acquired vulnerability becomes 'activated' by stressors (Gottesman & Shield, 1967). These stressors can be environmental, biological, or psychosocial. The neural diathesis-stress model (Walker & Diforio, 1997) further suggests that the physiological response to stress, including activity of the hypothalamic-pituitary-adrenal (HPA) axis, plays a key role in this 'activation,' but may also be part of the biological substrate underlying psychotic illness. This is based on evidence that: 1) stress plays a role in the onset of psychotic illness, as well as in HPA axis function and dysregulation; 2) unmedicated patients with psychotic disorders manifest heightened cortisol secretion; 3) synthetic corticosteroids and hypercortisolemia (e g. Cushing's syndrome) are associated with increased risk for psychosis; and 4) there are plausible neural mechanisms, including augmentation of dopamine (DA) activity, linking psychotic illness and HPA axis dysregulation (Walker & Diforio, 1997; Walker et al., 2008; Bennett, 2008). Thus, research on stress-response systems in individuals at risk for developing psychosis may help elucidate their role in the pathophysiology of psychotic illness.

There is an extensive research literature documenting the effects of stress on cognitive performance (Kirshbaum et al., 1996; LeBlanc, 2009; Arnsten, 2010). This literature suggests that elevated cortisol is associated with neurocognitive impairment, which is a core feature of psychotic illness apparent in many individuals before the onset of psychotic symptoms (Keefe et al., 2006; Eastvold et al., 2007; Jahshan et al., 2010; Seidman et al., 2010; Guiliano et al., 2012). However, some research suggests that the

nature of the relationship between cortisol and neurocognitive impairment is complex and may differ in individuals with and without psychotic illness (Newcomer et al., 1998). This suggests a possible link between the HPA axis and premorbid or prodromal cognitive deficits. Although no published report has investigated the link between HPA axis and cognitive function in prodromal patients, such research holds promise for also elucidating the potential role of HPA axis dysregulation in the cognitive deficits associated with the psychosis prodrome.

The hypothalamic-pituitary-adrenal (HPA) axis and corticosteroids

The HPA axis is one of the primary modulators of the body's response to stress. After a stressful experience, corticotrophin-releasing factor (CRF) is released from the paraventricular nucleus of the hypothalamus, which stimulates secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland into the bloodstream (Jameison & Dinan, 2001). ACTH, in turn, leads to the release of catecholamines (adrenaline/epinephrine and noradrenaline/norepinephrine) and glucocorticoids (cortisol in humans, corticosterone in animals) from the adrenal glands (Lupien et al., 2007). Both are involved in the sympathetic nervous system's 'fight or flight' response (Cannon, 1929) and target receptors throughout the body. The current study concerns glucocorticoids, which cross the blood/brain barrier and bind to receptors throughout the brain, particularly in the frontal and temporal lobes (McEwen, 1998). Because of this far-reaching effect and the relative ease of measurement, cortisol levels are often used to index HPA axis activity in humans and are considered reliable means of doing so (Kiess et al., 1995; Kirschbaum & Hellhammer, 1994).

There are two types of glucocorticoid receptors in the brain—mineralocorticoid receptors (MR) and glucocorticoid receptors (GR) (Reul & de Kloet, 1985). MRs have a six- to ten-fold higher affinity for endogenous glucocorticoids (Lupien et al., 2007; de Kloet et al., 1986) and are present throughout the paralimbic system (e.g. parahippocampal gyrus, entorhinal cortex, insular cortex). They are also found widely in the hippocampus (McEwen et al., 1968; 1986; Diorio et al., 1993). GRs have a higher affinity for synthetic glucocorticoids (like dexamethasone and prednisone) and are activated by higher levels of endogenous glucocorticoids in times of stress or pharmacological challenge. They also exist throughout the hippocampus, but are primarily manifest in the dentate gyrus and CA1 and CA2 subregions (Derijk & de Kloet, 2005; Walker et al., 2008). GRs are also present in the thalamus, septum, and paraventricular nucleus, as well as broadly throughout the prefrontal cortex and other cortical areas (de Kloet et al., 1986; Diorio et al., 1993; McEwen et al., 1968; Corcoran et al., 2003). At rest, the majority of MRs are occupied, while only about 10% of GRs are bound to glucocorticoids. During stress or at the peak of the circadian cortisol rhythm (e.g. morning), MRs are saturated and increasing proportions of GRs (67-74%) become occupied (Reul & de Kloet, 1985).

Both animal and human studies suggest that the relative proportion of MR to GR activation may be an important moderating factor in multiple brain processes and may constitute an "inverted U" pattern where too much or too little activation can impair cognitive function (de Kloet et al., 1999; Lupien & McEwen, 1997). For example, mild elevations in glucocorticoids (when the MR/GR ratio is high) are thought to facilitate memory in rats (Diamond et al., 1992) and humans (Lupien et al., 2002), while more

significant elevations (high activity with lower MR/GR ratio) impair memory in humans and animals (Het et al., 2005). The relationship between cortisol and cognition will be discussed in more depth below.

In addition to their role in cognitive processes, glucocorticoid receptors in the hippocampus are involved in regulating HPA axis activity. Specifically, some of these receptors, predominantly GRs in the hippocampus, are a component of a negative feedback mechanism with the hypothalamus and pituitary gland that, in healthy individuals, inhibits further CRF and ACTH production in times of high cortisol (Corcoran et al., 2003). Thus, damage to the hippocampus or downregulation of glucocorticoid receptors therein can disrupt the HPA axis, resulting in decreased negative feedback and less suppression of subsequent cortisol release. Indeed, smaller hippocampal volume is correlated with increased basal cortisol levels in humans (Rao et al., 1989; Starkman et al., 1992; Tessner et al., 2007).

Cortisol also interacts with and modulates neurotransmitter systems in the brain, suggesting that its sequelae extend beyond cognitive functions and the sympathetic stress response (McEwen, 1999). For example, HPA axis activation, indexed by increased levels of cortisol, leads to the augmentation of DA levels in the human brain (Schatzberg et al., 1985; Wand et al., 2007). This is particularly relevant for the current study because DA, more than any other neurotransmitter system, is implicated in schizophrenia and other psychoses (Howes & Kapur, 2009). Glucocorticoid levels also affect serotonin synthesis (Belanoff et al., 2001), the uptake of norepinephrine (de Kloet, 1991), and are directly associated with levels of extracellular glutamate in the prefrontal cortex (Wolf,

2003). Glucocorticoid secretion also results in the activation of NMDA receptors in the prefrontal cortex (Bennett, 2008).

In addition to affecting brain function through the moderation of neurotransmitter levels, glucocorticoids also affect the structure of neurons and brain systems. With chronic glucocorticoid exposure, these effects tend to be deleterious. Chronic glucocorticoid elevations in rats, including those due to chronic stress, are associated with the regression of synapses and a decrease in dendritic spines in hippocampal and prefrontal neurons (as reviewed in Bennett, 2008). In the rat and primate hippocampus, elevations lead to the reduction of neuronal excitability (Joels, 2001), the impairment of synaptic plasticity (Diamond et al., 1992; Pavlides et al., 1996), and a reduction in neurogenesis in the dentate gyrus (Gould et al., 1998). Although it is debated in the literature, elevated glucocorticoid levels are also thought to *lead* to neuronal death in the hippocampus, based on findings in primates (Sapolsky et al., 1990; see Wolf, 2003 for a good review of the debate); the association in humans between decreased hippocampal volume and increased cortisol levels is not debated (Rao et al., 1989; Starkman et al., 1992; Lupien et al., 1998). In animals, corticosterone affects the levels of structural proteins in glial cells, can suppress myelination, and can affect calcium ion channels and amino acid levels in the hippocampus (Belanoff et al., 2001). All of these can result in regional volume reductions. Thus, chronic elevations in glucocorticoid levels have negative effects throughout the hippocampus and the prefrontal cortex (though the research on detrimental effects in the hippocampus is more extensive). Indeed, the effects of HPA axis dysregulation are implicated in the etiology and maintenance of numerous psychiatric conditions, including psychosis (Walker and Diforio, 1997; Walker

et al., 2008) and depression (Mannie et al., 2007; Hinkelmann et al., 2009). In fact, atypical antipsychotics are found to reduce both ACTH and cortisol secretion along with positive symptoms in patients with schizophrenia (Mann et al., 2006; Walker et al., 2008).

HPA axis function in psychosis

Cortisol and psychosis

The evidence for a relation between cortisol and psychosis was reviewed in a recent paper by Walker, Mittal and Tessner (2008). Based on their review of the literature, the authors drew several conclusions. First, there is strong evidence that nonmedicated patients with psychosis have higher baseline levels of cortisol (Garner et al., 2010; Kale et al., 2010; Venkatasubramanian et al., 2010) and ACTH (Ryan et al., 2004) than non-psychotic individuals. Second, antipsychotic medications reduce cortisol secretion and positive symptoms (Venkatasubramanian et al., 2010). Thus some studies of medicated patients do not find elevations in baseline cortisol (Jansen et al., 2000; Rao et al., 1995) or find relative reductions after stressors (van Venrooij et al., 2010). Third, psychotic patients also tend to show a more pronounced response of the HPA axis to pharmacological challenge. For example, dexamethasone is an exogenous glucocorticoid that, in the short term, leads to increased HPA axis and cortisol activity. However, in the long term, it leads to cortisol suppression by activating the negative feedback loop from the hippocampus to the HPA axis. If cortisol is not suppressed after dexamethasone administration, or "challenge," it is considered to be a marker of HPA axis dysregulation or dysfunction. This dysfunction may be one mechanism whereby chronically elevated cortisol levels are maintained (Corcoran et al., 2003). Multiple reviews and meta-

analyses have found higher rates of dexamethasone nonsuppression in schizophrenia (Corcoran et al., 2003; Sharma et al., 1988; Yeragani, 1990), as well as in psychotic versus non-psychotic depression (Nelson & Davis, 1997; Duval et al., 2000; Corcoran et al., 2003). In many, this response can be reversible with pharmacological treatment (Ceskova et al., 2006). Abnormal circadian cortisol rhythms have also been reported in patients with psychosis (Aas et al., 2010; Whalley et al., 1989), further suggesting HPA axis dysregulation (however, see Rao et al., 1995; Risch et al., 1992 for contrary findings).

In contrast to the evidence for heightened baseline cortisol in nonmedicated psychotic patients, the findings from investigations of stress-induced cortisol changes are mixed, and many of the patients in these studies are on medications that blunt the cortisol response. Many studies that attempt to induce HPA axis activity through natural psychosocial stressors, like public speaking or exercise, tend to find that psychotic patients show *less* cortisol increase after stress (Gispen-de Wied, 2000), both on (Jansen et al., 2000) and off (van Venrooij et al., 2010) antipsychotic medications. Similarly, blunted cortisol responses to pharmacologic challenge are also found in individuals with SPD (Mitropoulou et al., 2004) and in non-affected siblings of individuals with schizophrenia (Brunelin et al., 2008), suggesting that HPA axis dysregulation may be heritable and associated with risk for psychosis. The absence of a stress- or challenge-induced increase in cortisol, despite evidence for elevated baseline levels, has also been observed in depression (Martin et al., 2000), and may reflect ceiling effects on cortisol increments beyond the elevated baseline level (Crowley et al., 1993).

Other lines of research also suggest that HPA axis dysregulation and/or higher baseline cortisol levels may be part of the vulnerability for psychosis (Walker and Diforio, 1997). In his review, Bennett (2008) discusses the neural mechanisms through which early stressful experiences can alter the 'set point' of the HPA axis. The conclusion is that these premorbid factors can lead to dysregulation, structural changes, and chronically higher glucocorticoid activity, which may, in turn, increase the risk for subsequent psychosis. This may be one reason that early environmental stressors, like stressful living situations, are associated with higher basal cortisol levels later in life (Lupien et al., 2000; Flinn and England, 1997; reviewed in Jessop & Turner-Cobb, 2008). Stressors associated with low familial SES during childhood may also be associated with cortisol levels later in life, though findings in this area are not consistent (Dowd et al., 2009), despite early positive findings. Regardless, HPA 'set point,' as well as basal cortisol levels, are moderately heritable (as reviewed in Walker et al., 2008; Walker, 2002), and are impacted by early environmental factors like prenatal maternal stress (Walker et al., 2008; Maccari et al., 2003). Thus, while some results are mixed, there is sufficient evidence to conclude that environmental and heritable factors can affect later HPA axis function, which may play a role in risk for psychosis.

Factors like HPA 'set point' also appear to affect the clinical picture in psychosis, after illness develops. Symptom severity in individuals with psychotic disorders is positively related to circulating cortisol levels. This has been shown for positive symptoms (Garner et al., 2010; Keshevan et al., 1989; Rybakowski et al., 1991; Walder et al., 2000), negative symptoms (Newcomer et al., 1991; Tandon et al., 1991; Garner et al., 2010), and disorganized symptoms (Walder et al., 2000). Moreover, as noted,

medications that lead to a reduction in symptom severity, like clozapine or risperdone, also lead to lower cortisol levels (Mondelli et al., 2010a; Hatzimanolis et al., 1998; Markianos et al., 1999; Walker et al., 2008).

Similar relations are found in individuals who have elevated cortisol levels, but no previous diagnosis of psychotic illness. In fact, hypercortisolemia induced by exogenous corticosteroids can trigger psychotic symptoms in high doses (Warrington & Bostwick, 2006; Buchman, 2001). Symptoms of hypercortisolemia-induced psychosis include pressured speech, hallucinations, delusions, and disorganized thought (Wada et al., 2001; Lewis & Smith, 1983; Ling et al., 1981), and in many cases meet criteria for a psychotic disorder. Further, disorders characterized by hypercortisolemia often involve psychotic symptoms. For example, Cushing's syndrome is an endocrine disorder with sustained hypercortisolemia. In some cases, it is also associated with psychotic symptoms that remit with the successful treatment of abnormally high glucocorticoid levels (van der Lely et al., 1991; Chu et al., 2001; Corcoran et al., 2003). Cortisol levels in Cushing's syndrome are also inversely correlated with hippocampal volume (Starkman et al., 1992); this association has been found in schizophrenia (Mondelli et al., 2010b). This relation between cortisol and psychotic symptoms further suggests a link between HPA axis dysregulation, as indexed by cortisol levels, and the onset of psychosis.

Retrospective studies also add support to this link. Psychosocial stressors of sufficient intensity reliably lead to elevations in cortisol (Linden et al., 1998). As summarized in Walker and colleagues' recent review (2008), there is no evidence for more stressors in the lives of patients with schizophrenia and other psychoses (Megna et al., 2005; Phillips et al., 2006). However, schizophrenia patients have been found to

report greater *subjective* stress (Norman & Malla, 1993) and more stressful daily 'hassles' (Thompson et al., 2007) than non-psychotic controls. Also, there appears to be an increase in the rate of stressful life events in the weeks or months immediately preceding an acute psychotic episode (Mondelli et al., 2010a; Malla et al., 1990; Hultman et al., 1997; Corcoran et al., 2003), suggesting that these events may be involved in 'triggering' these episodes. Similarly, the expressed emotion literature suggests that stressful home environments are associated with a greater number of subsequent relapses (Brown et al., 1962; Vaughn & Leff, 1976).

In summary, many different lines of research find links between HPA axis function and psychosis. Included are findings of heightened baseline cortisol levels and HPA axis dysregulation in many patients with psychosis after both psychosocial and pharmacological challenge. Also included is research suggesting that adverse early life factors that can influence the development of the HPA axis are associated with both increased risk for psychosis and severity of post-onset clinical course. The fact that hypercortisolemia can induce psychotic symptoms in patients with no history of psychosis further implicates the HPA axis. The following section will address some possible mechanisms underlying this link.

Cortisol, dopamine, and the hippocampus; relevance for psychosis

A reduction in hippocampal volume is among the most consistent neurological finding in schizophrenia (Steen et al., 2006; Geuze et al., 2005; Wright et al., 2000). While it is not clear exactly what role this reduction plays in the illness, it is thought to reflect aberrant brain development (Weinberger et al., 1987) and to affect the connectivity of the hippocampus with other brain regions (Eisenberg & Berman, 2010).

As noted above, chronic glucocorticoid elevations have been found in animal studies to be associated with hippocampal volume reductions. In rats, these reductions in volume can occur as a result of experimentally induced glucocorticoid elevations (as reviewed in Walker et al., 2008; Sapolsky et al., 1985; 1986). While such studies cannot be conducted with human subjects, the link between increased basal cortisol and smaller hippocampal volumes is well established (Knoops et al., 2010; Sapolsky et al., 1986; Lupien et al., 1998). Further, twin studies suggest that the environmental contribution to such reductions is significant (van Erp et al., 2004), suggesting that external factors that influence HPA axis activity, like stress, could play a role in increasing the diathesis for illness, possibly by contributing to decreased hippocampal volumes.

In their meta-analysis, Belanoff and colleagues (2001) discuss some of the mechanisms by which glucocorticoids may result in the reduction of hippocampal volume. They suggest that inhibition of glucose transport into neurons and glia, which has been shown in humans (De Loen et al., 1997), and atrophy of dendritic spines may mediate the relationship. Post-mortem studies have found abnormalities in dendritic spines in the hippocampi of schizophrenia patients (Corcoran et al., 2003; Rosoklija et al., 2000), possibly as a result of these mechanisms. Belanoff and co-authors also note that corticosteroids can reduce levels of brain derived neurotrophic factor (BDNF) and neurotrophin 3 (NT-3), each of which is implicated in the regulation of neuronal cell preservation. Consistent with this suggestion, a recent study by Issa and colleagues (2010) found an inverse relationship between cortisol and BDNF levels in post-mortem brains of schizophrenia patients. In a review paper by Bennett (2008), NMDA receptors, important in controlling the structure and proliferation of dendritic spines, are also cited

as affected by excess glucocorticoid levels. In rats, Sapolsky and co-authors (1986) also implicate excitatory amino acids in the atrophy of apical dendrites in CA3 pyramidal cells.

Although the molecular mechanisms continue to be the subject of investigation, these authors agree that animal studies, particularly those conducted in rats, are fairly consistent in showing that the result of chronic corticosterone elevations is depletion of hippocampal glucocorticoid receptors. To explain this finding, Sapolsky and colleagues proposed the "Glucocorticoid Cascade Hypothesis (Sapolsky et al., 1986)." This theory suggests that elevations in glucocorticoids serve to down-regulate glucocorticoid receptors and inhibit negative feedback to the HPA axis, which results in the maintenance of elevated glucocorticoid levels. While this model has more recently met with some resistance, given some contradictory findings in the animal literature (see Belanoff et al., 2001 for a review), it remains the predominant model. Alternative theories, like de Kloet's corticosteroid balance theory (de Kloet et al., 1998), have attempted to modify Sapolsky's model to account for findings of changes in ratios of MR v. GR receptors in some animals, as opposed to downregulation of all glucocorticoid receptors (Kudielka et al., 2009).

Another mechanism through which the HPA axis may be involved in psychosis is its interaction with DA. DA dysregulation, particularly in the cortex and limbic system, is implicated in psychotic processes (Howes & Kapur, 2009). As previously mentioned, HPA axis activation (and cortisol release) leads to an increase in DA levels in the human brain (Schatzberg et al., 1985; Wand et al., 2007; Dallman et al., 2004; Arnsten et al., 2010), particularly in the mesolimbic system (Marinelli et al., 2006; Walker et al., 2008).

Additionally, substances that increase DA activity also lead to an increase in cortisol levels (Philippi et al., 2000). Conversely, in rats, the suppression of glucocorticoids results in a reduction in DA release (Piazza et al., 1996), though the mechanisms underlying this synergistic relationship are not well understood (Walker et al., 2008).

In summary, there is evidence for differences in cortisol levels and HPA axis activity between individuals with and without psychotic disorders. Further, hypercortisolemia is often associated with psychotic symptoms in individuals with no previous history of psychosis. One possible mechanism for this relationship is the facilitating effect cortisol has on DA levels. Finally, hippocampal volume reductions are associated with HPA axis dysregulation, as well as psychotic disorders. Together, these findings suggest that cortisol release triggers a cascade of events, including increased DA activity which, in those vulnerable to psychosis, leads to the onset of illness (Walker & Diforio, 1997). To investigate the relation of HPA activity with psychosis onset, researchers have increasingly focused on the psychosis prodrome.

The psychosis prodrome

While the clinical onset of schizophrenia and other psychoses is typically in the early 20's, most individuals who are subsequently diagnosed with a psychotic disorder, especially schizophrenia, experience a period of prodromal symptoms that begins in late adolescence/early adulthood, and lasts from 6 months to two years (McGorry et al., 1995; Cornblatt et al., 2003). Both retrospective and prospective studies have been conducted on this period and suggest that it entails functional decline and gradual onset of attenuated positive symptoms, as well as negative, affective, and 'non-specific' symptoms (Cornblatt et al., 2003; Yung & McGorry, 1996), and often diagnosable

depression (Lee et al., 2008). As discussed below, cognitive deficits in a variety of domains are also frequently detectable.

Within the past decade, researchers have developed standardized diagnostic interview procedures for diagnosing prodromal syndromes and rating the severity of various symptom dimensions (ex: Bonn Scale for the Assessment of Basic Symptoms (BSABS): Klosterkotter et al., 2001; Structured Interview for Prodromal Syndromes (SIPS): McGlashan et al., 2001; Comprehensive Assessment of At-Risk Mental States (CAARMS): Yung et al., 2005). Individuals who meet criteria for a prodromal syndrome, based on these measures, are considered at "clinical high-risk" (CHR) for developing Axis I psychosis and show a rate of conversion that varies from 25 to 40% (Yung et al., 2003), though some studies have reported rates up to 50% (Miller et al., 2003; Yung et al., 2003; Lemos et al., 2006; Cannon et al., 2008). Conversely, retrospective studies suggest that up to 91% of first-episode patients showed characteristic prodromal signs before illness onset (Klosterkotter et al., 2001). While these conversion rates mean that many individuals labeled as having a prodromal syndrome will not go on to develop a psychotic illness, the convention in the literature is to refer to them as either 'prodromal' or CHR.

Given that HPA axis dysregulation is implicated as both a diathesis and trigger for psychotic illness, it would be expected that prodromal individuals would also show HPA axis dysregulation. Very little research has investigated this hypothesis. The following sections briefly summarize this research, as well as neuroimaging studies that support it. Subsequent sections will address the relation between this hypothesized dysregulation and cognition in the prodromal period.

Structural neuroimaging and the prodrome

The structural neuroimaging literature in the psychosis prodrome is relatively small, especially when compared to the literature on first-episode and more chronic populations. Broadly, there is evidence for structural abnormalities that are similar to, but less extensive than, those found in the adult psychosis literature. Some of these are associated with illness processes, some are present in all CHR groups.

A few studies have found reductions in hippocampal volume in high-risk groups identified based on familial (Lawrie et al., 1999; Seidman et al., 2002) and clinical factors (Hurlemann et al., 2008). However, reviews of this literature suggest that hippocampal structural abnormalities should be seen as markers of the early stages of psychotic illness, as opposed to premorbid risk factors for illness (Pantelis et al., 2007). For example, the most recent review, conducted by Witthaus and co-authors (2010), concluded that evidence for hippocampal volume reductions in CHR patients is equivocal, though no subregions of the hippocampus have been investigated. In the studies where differences were apparent, they did not predict conversion to psychosis—a finding that has been replicated elsewhere (Wood et al., 2010). There is some suggestion that premorbid structural abnormalities in the hippocampus may be more pronounced in those who eventually develop schizophrenia, versus other psychotic disorders (Seidman et al., 2002; 2003).

Results tend to be more consistent with respect to prefrontal pathology in prodromal and CHR patients. For example, Wood et al. (2008) recently reviewed the structural imaging studies of CHR youths and reported consistent evidence for reduced cortical thickness of the anterior cingulate cortex, an area that, along with the prefrontal

cortex, is implicated in executive functions (e.g. cognitive control). There are also reports of reduced gray matter density across multiple prefrontal regions (Pantelis et al., 2003; Takahashi et al., 2009). The most recent meta-analysis of this area found that gray matter reductions in prefrontal, cingulate, insular, and cerebellar regions are small to medium in effect size in CHR subjects who subsequently develop a psychotic disorder (Smieskova et al., 2010).

Other imaging studies have revealed that increased pituitary volumes are frequently found in true prodromal cases, relative to controls (Pantelis et al., 2007). These finding suggests that structural abnormalities in the HPA axis and prefrontal cortex may lead to dysregulation of the stress-response system and possibly to hippocampal pathology in the early prodromal phase of illness.

Cortisol and the HPA axis in the prodrome

To date, only four studies have directly investigated cortisol and HPA axis functioning in CHR youths and one has studied individuals deemed at genetic risk for psychosis. In preliminary analyses, Thompson and colleagues (2007a) conducted a combined dexamethasone/CRH test in 12 CHR patients, three of whom converted during a two year follow-up period. In this test, dexamethasone was administered and, after a delay during which HPA axis activity was naturally suppressed, CRH was administered. As mentioned, non-suppression of the HPA axis response is considered abnormal. While the sample size did not allow for any statistical analyses, the authors found that blood cortisol levels were similar in the 3 converters and 9 non-converters at baseline. However, after the test, non-converters had *higher* cortisol levels which peaked 60 minutes after the administration of CRH. Further, non-converters reported more

depression, anxiety, lifetime stressful events, and daily hassles than converters. This is contrary to past reports that typically find more severe stress, anxiety and depression among those who later convert (Hambrecht et al., 2002; Yung et al., 2003). In addition to its small sample size, this study was limited by three major methodological factors: 1) the samples were so small that there were no statistical analyses; 2) only one measurement was used to index baseline cortisol; 3) blood draws rather than less invasive methods were used to measure cortisol. Blood draws have the potential to induce an HPA axis response that may confound baseline measurement (Jessop & Turner-Cobb, 2008).

In another report, the same research group studied 23 unmedicated CHR participants and found that baseline cortisol levels were positively correlated with the experience of daily hassles, but not with lifetime stressful events (Thompson et al., 2007b). They were also positively correlated with levels of depression and anxiety, but were not correlated with psychotic symptomology, global psychopathology, or current global functioning. The authors also conducted structural MRI scans and found no correlations between serum cortisol levels and pituitary or hippocampal volumes. While the sample size in this study did not allow for the differentiation of converters from non-converters, it did suggest a lack of association between CHR cortisol levels and psychotic symptom severity. Again, measuring cortisol via blood draw is not optimal for indexing baseline cortisol and a single cortisol measurement is often considered an unreliable metric of basal cortisol levels (Dowd et al., 2009)

A more recent study of a larger sample of 56 CHR subjects found that those who subsequently developed a psychotic disorder (n = 14) had higher baseline salivary cortisol levels 6-months after baseline, trend-level elevations at one year, and greater area

under the curve (AUC), when all data points were considered (Walker, et al, 2010). In contrast to previous reports, this study utilized multiple measures of cortisol at each time point. Further, cortisol was measured in saliva, rather than blood, thus reducing the confound of stress-induction through blood draw. Following these procedures in a different CHR sample, some of which is included in the current analyses, Shapiro and colleagues (October, 2010, *unpublished data*) found that a group of 22 CHR young adults showed higher basal salivary cortisol than 18 age-matched controls in lab samples. However, they also found that time of day is an important factor to account for when analyzing cortisol data and did not take medication status into account.

Corcoran and colleagues (2012) also attempted to replicate these findings, but did not report on a healthy comparison group. They identified 31 CHR individuals based on modified SIPS criteria and obtained one morning saliva sample. They found that females demonstrated higher baseline cortisol levels than males and that individuals on antidepressants had trend-level elevations in cortisol while antipsychotic use was not related to cortisol levels. Similar to the findings reported by Thompson et al. (2007b), these authors also found positive associations between cortisol levels and suspiciousness, anxiety, and impaired stress tolerance. They did not find an association between cortisol and negative symptoms or overall positive symptoms.

Collip and colleagues (2011) investigated stress, psychotic experiences, negative affect, and cortisol in 60 discordant siblings of psychosis patients. They used an experience sampling method in which probands and healthy controls were asked to complete survey forms and take a saliva sample at 10 random times per day over 6 days. The authors found that siblings had higher cortisol levels than controls and that this

difference persisted throughout the day over the course of an expected diurnal decline in cortisol secretion. While the two groups did not report different frequencies or intensities of daily stressors, siblings had a larger cortisol increase following unpleasant events, even after controlling for group differences in negative affect. Showing further evidence of HPA axis dysregulation and sensitivity, siblings also showed increased cortisol responses to "momentary psychotic experiences" and increases in negative affect, while the control group did not.

Finally, a recent investigation of baseline cortisol levels in the North American Prodrome Longitudinal Study (NAPLS), from which the present sample is drawn, reported significantly higher salivary cortisol levels in CHR subjects than healthy controls matched on age and sex (Walker, et al., *manuscript submitted for publication*). Cortisol levels were also positively correlated with ratings of positive, negative, disorganized, and general prodromal symptoms, with associations of r = .10 to .13. As described below, the NAPLS project has ascertained the largest sample of prospectively assessed CHR subjects to date.

Cortisol and cognition

Cortisol levels have been shown to be associated with a number of cognitive processes, some of which may be mediated by the effects of glucocorticoids on the hippocampus. Other processes likely involve glucocorticoid receptors in the frontal lobe (discussed below). Here, too, there is overlap in the relation between cortisol and cognition in non-psychotic individuals and the cognitive deficits seen in many patients with psychotic disorders. In addition, antipsychotic medications that reduce both heightened cortisol levels and positive symptoms also lead to improvements in

hippocampal- and frontal-mediated cognitive functions (Meltzer & McGurk, 1999; Harvey et al., 2005). The following sections will briefly describe a number of cognitive functions that are impacted by cortisol and HPA axis activity.

Cortisol and hippocampal-dependant memory

The hippocampus is of seminal importance in declarative memory (Manns & Eichenbaum, 2008; Squire, 1992), the recollection of facts and events, and in the process by which these memories become consolidated for long-term storage and recall (Squire and Zola-Morgan, 1991). The prefrontal cortex also plays a role in the organization and encoding of declarative memory (Lesh et al., 2011; Cirillo & Seidman, 2003). These processes are affected by glucocorticoids. Evidence for the involvement of cortisol in normal human declarative memory function comes from two well established lines of research. The first is the use of lesion studies. The best known example of hippocampal lesion is the famous patient, H.M., who had intact short-term and non-declarative memory, but impaired long term declarative memory (Scoville & Milner, 1957). While his surgical lesion also extended beyond the hippocampus to other parts of the medial temporal lobe, the anterograde amnesia he demonstrated has been confirmed in subsequent decades of research as due to hippocampal damage (Schmolck et al., 2002; Bechara et al., 1995; Reed & Squire, 1998;). In other words, hippocampal lesions lead to the inability to form and encode new declarative memories, suggesting a seminal role of this formation in the development of declarative memories. A second line of evidence comes from imaging studies. For example, activation of the intact hippocampus is reliably found in healthy individuals performing tasks that require the encoding and

retrieval of declarative facts (Wais, 2008). Performance on these tasks is also inversely related to hippocampal volume (Lencz et al., 1992; Starkman et al., 1992).

Cortisol plays an important role in declarative memory, likely through the effects of glucocorticoid receptors in the hippocampus and frontal lobe. However, it appears that the relation of cortisol with cognitive functions is nonlinear, and that both reductions and elevations are linked with deficits. This is evidenced by rat studies showing that pharmacologically-induced *reductions* in cortisol lead to impaired retrieval of declarative memories (Belanoff et al., 2001; Zorawski et al., 2006), though these studies are rare in the human literature. Only one study has induced reductions in cortisol in humans and tested their effects on short-term memory; none have investigated effects on executive functions. Lupien and colleagues (2002) decreased cortisol levels by administering metyrapone, an inhibitor of cortisol synthesis, then restored baseline cortisol levels and tested memory recall at each stage. The authors found that inhibiting cortisol synthesis did not impact immediate memory, but did lead to declarative memory impairments 20 minutes after learning a word list. Subsequent studies using metyrapone after longer delays indicate that these results are likely due to the effects of cortisol at retrieval, rather than learning (e.g., Rimmele et al., 2010).

Studies showing that *elevated* levels of cortisol selectively impair declarative memory performance in humans are abundant (Het et al., 2005; Aleman et al., 1999; Sauro et al., 2003). For example, Newcomer and colleagues have conducted a number of experiments in which they modulate HPA axis activity through the administration of exogenous glucocorticoids. They have found that verbal declarative memory performance, but not performance on non-hippocampal-dependant memory, decreases

after days of repeated exposure to dexamethasone (Newcomer et al., 1994) and hydrocortisone (Newcomer et al., 1999). Studies from other research groups have found similar results (Wolfowitz et al., 1990; Schmidt et al., 1999; Het et al., 2005) and this decrease is reversible with correction of cortisol levels (Newcomer et al., 1999; Corcoran et al., 2003; Lupien et al., 2002). Psychosocial stressors, which putatively result in increased cortisol levels, are also associated with poorer performance on declarative memory tests (Kirshbaum et al., 1996). Similarly, naturalistic studies have found that, in the long term, chronic elevations in cortisol are associated with both memory impairment and hippocampal volume reductions (Lupien et al., 2007; Lupien et al., 1998; Lee et al., 2007).

The hippocampus is also integral in long-term potentiation (LTP), the process by which declarative memories are consolidated for long-term storage and subsequent retrieval (McGaugh, 2000). This process involves interaction between the hippocampus and prefrontal cortex (among others) that results in 'storage' of a memory throughout broad cortical networks, then the re-involvement of the hippocampus at retrieval (Eichenbaum & Cohen, 2001; Nader, 2003). Thus, both the hippocampus and prefrontal cortices are involved in the encoding and retrieval of declarative memories; both of these structures contain cortisol receptors and are implicated in the pathophysiology of psychotic disorders. This suggests that if the prodromal period of psychotic illness is marked by increased cortisol levels, there is likely to be decreased performance on declarative memory tasks during this period. Indeed, heightened glucocorticoid levels are associated with the attenuation of both LTP in rats (Foy et al., 1987; Pavlides et al., 1993) and subsequent memory retrieval in humans (de Quervain, 2000; 2003; Lupien et

al., 2007). However, there is a great deal of heterogeneity in the levels of cortisol associated with memory deficits (e.g. Vedhara et al., 2000), with the overall picture suggesting a dose-dependant effect (Jameison & Dinan, 2001), possibly due to differential occupation of MRs and GRs (Sapolsky, 2003; de Kloet et al., 1999).

One predominant model of cortisol's role in hippocampal-dependant memory is the aforementioned "inverted U" model (Lupien & McEwen, 1997; Lupien et al., 2007; Diamond et al., 1992). This model suggests that optimal levels of cortisol are important for normal declarative memory functions, but that too much or too little leads to impairment, with excess cortisol contributing to long-term destabilization of the HPA axis. Thus, HPA axis dysfunction, hippocampal volume reductions, and/or the subjective experience of stress likely contribute to declarative memory function. Again, evidence for the presence of all three of these factors in prodromal psychosis suggests that declarative memory may be particularly affected in this early phase of illness.

Frontal cortex, working memory, and executive function

Working memory involves the ability to cognitively maintain and manipulate information in the short term. In addition to playing an important role in declarative memory consolidation, storage, and recall, the frontal lobe, particularly the prefrontal cortex, is integral for working memory function and other executive processes (Smith & Jonides, 1999). Evidence for this role comes from research showing that frontal lobe damage leads to changes in both behavior and cognition (e.g., executive processes, planning, decision making, behavior inhibition)(Sapolsky, 2004). Further evidence is provided by many imaging studies which support the differential involvement of the frontal, as well as parietal and parahippocampal lobes (Glabus et al., 2003) in human

working memory (Wager & Smith, 2003; Smith & Jonides, 1998; Fletcher & Henson, 2001). These studies implicate different areas within the frontal lobe in different components of working memory (e.g., storage v. manipulation v. rehearsal, verbal v. nonverbal), and suggest that frontal regions work in concert with other areas of the brain. Further, imaging studies that use working memory tasks of progressive difficulty typically find an "inverted U" relationship between DA levels or prefrontal activation on one axis and performance on the other (Williams & Castner, 2006). Thus, the frontal lobe is necessary for successful working memory function and over or under-activation can affect performance. As will be discussed below, cortisol receptors in the frontal lobe can also affect performance on working memory tasks, suggesting that these may be particularly affected by changes in HPA axis activity in the prodromal phase of psychotic illness.

Executive function tasks involve the ability to plan and think abstractly, selectively attend to important cues, inhibit inappropriate action, and adjust performance in response to dynamic environmental demands (Barch et al., 2009). Aspects of processing speed are also reflective of executive functions. These abilities rely heavily on the involvement of the frontal lobe, along with other regions (Carpenter et al., 2000; Robbins, 1997), though slightly different cortical areas are involved, depending on the type of executive function being assessed (Robbins, 1996). Working memory is often considered to be a component executive function process (Brocki et al., 2008; Duncan & Owen, 2000), as well. Support for the role of frontal circuits in executive function comes from studies that show working memory impairments, but intact non-executive functions, in patients with frontal lobe lesions (as reviewed in Royall et al., 2002). Support is also

garnered by imaging studies that show preferential activation of prefrontal areas during executive function tasks (Carter et al., 1999; Carpenter et al., 2000; Wager & Smith, 2003).

Cortisol and executive functioning

There is evidence that cortisol levels affect performance on working memory and executive function tasks, partly due to the presence of GR glucocorticoid receptors in the frontal lobe—particularly in the prefrontal cortex (Jameison & Dinan, 2001). In the area of working memory, the majority of studies fall into two categories: those that either induce varying levels of cortisol with psychosocial stressors or pharmacological challenge (Lupien et al., 1999; Kirshbaum et al., 1993; Porcelli et al., 2008), and those that study naturalistic groups with elevated cortisol levels, like Cushing's syndrome (Martignoni et al., 1992). Both lines suggest impairments with high levels of cortisol.

A number of studies have investigated the effects of exogenous glucocorticoid administration on cognition. Lupien and co-authors (2007) recently published a comprehensive review on the topic. They concluded that both declarative and working memory are adversely affected by high levels of circulating glucocorticoids in humans and animals, but suggested that it may take higher levels of circulating cortisol to affect declarative memory than working memory. A study by Lupien and colleagues (1999) illustrates this conclusion. These authors administered hydrocortisone to a healthy control sample and found impairments on a working memory task. Interestingly, however, there were no decrements in declarative memory performance and low doses of hydrocortisone, as opposed to high doses, actually improved working memory performance. Young et al. (1999) found similar results. In their study, 10 days of

hydrocortisone treatment led to impairments in visuospatial working memory, but improved reaction times on a pattern and spatial recognition test (declarative memory). However, as previously mentioned, higher levels of cortisol reliably impair performance on declarative memory tasks.

Less invasive experiments have studied the effects of psychosocial stressors, and presumably elevations in cortisol, on cognitive processes. In two recent reviews, LeBlanc (2009) and Arnsten (2010) concluded that elevated stress impairs performance on tasks that require executive processes like divided attention, working memory, set shifting, and decision making, as well as declarative memory. Typical laboratory stressors that yield executive function impairments include such tasks as public speaking using the Trier Social Stress Test (Hoffman & al'Absi, 2004; Kirshbaum et al., 1993), viewing aversive photos (Qin et al., 2009), and cold water hand emersion (Porcelli et al., 2008). Though they are less common, some studies have also found inverse associations between basal cortisol levels and performance on executive function tasks (Lee et al., 2007).

Cushing's syndrome is a disorder that involves hypercortisolemia, and in many patients, is also characterized by executive function impairments. Martignoni and co-authors (1992) investigated cognitive functions in Cushing's patients and found impairments on two tasks that tap verbal and non-verbal working memory. In support of the effect of cortisol on hippocampal-dependent memory, these patients also showed impairments on declarative memory tasks that improved after surgical treatment to ameliorate hypercortisolemia. In a different Cushing's sample, Forget and colleagues (2000) found impairments in attention, reasoning, and spatial information processing, all

considered ‘executive processes.’ Mauri et al. (1993) reported similar findings. Together, these studies provide cogent support for an adverse effect of increased levels of cortisol on declarative and working memory, as well as other executive functions. As mentioned, this suggests that these areas may be affected in the prodromal phase of psychosis, given the cognitive deficits (discussed below) seen in this period.

Cortisol and cognition in the psychosis spectrum

Cognitive impairment is often considered a core feature of schizophrenia and other psychotic disorders (Heinrichs, 2005; Lewis, 2004; Wilk et al., 2005), and is among the most extensively studied facets of psychosis. Many recent meta-analyses (Dickinson et al. 2007; Fioravanti et al. 2005; Heinrichs and Zakzanis 1998; Mesholam-Gately et al. 2009; Piskulic et al., 2007; Wang et al., 2009; Bora et al., 2010) and qualitative reviews on the topic are available (Palmer et al., 2009; Keefe, 2007; Lewis, 2004; Joyce & Roiser, 2007; Flashman & Green, 2004; Reichenberg & Harvey, 2007), with generally consistent findings: Despite substantial heterogeneity within and between subjects (Palmer et al., 2009), impairment on tests of verbal memory and fluency (e.g., Gur et al., 2007), executive functions and working memory (e.g., Silver et al., 2003; Barch, 2005), and particularly sustained attention (e.g., Birkett et al., 2007), are consistently found in groups of individuals with psychosis. Decrements in overall cognitive abilities are also generally reported (e.g., Allen et al., 2001; Reichenberg et al., 2006; Ott et al., 1998). As noted, these ‘core’ deficits overlap with the cognitive functions affected by HPA axis dysregulation. Further support for this connection comes from evidence that, in addition to suppressing cortisol elevations, antipsychotic medications also lead to improvements in cognitive function in many but not all psychotic patients (Mishara & Goldberg, 2004).

Few studies have directly investigated the link between the HPA axis and cognition in patients with psychotic disorders. In two separate studies, Newcomer and colleagues assessed cognitive function and serum cortisol levels before and after extended periods of dexamethasone administration. In their first study, the authors administered dexamethasone to 21 inpatients with a diagnosis of schizophrenia, then administered a short neuropsychological test battery the following day (Newcomer et al., 1991). All participants had been off medications for at least 14 days. The authors found that higher serum cortisol levels the morning after dexamethasone administration were associated with poorer performance on tests tapping verbal and visual declarative memory (Benton Visual Retention Test, Rey Auditory Verbal Learning Test) and executive functioning (Wechsler Adult Intelligence Scale-Revised digit symbol, digit span, and picture arrangement), as well as non-verbal performance IQ, which also taps executive processes. This inverse correlation was not significant when afternoon cortisol levels were examined, likely due to the cumulative effects of daytime food/beverage consumption. Typical decreases in circulating cortisol in the afternoon (Het et al., 2005) may also have contributed to the lack of significance.

In a second study, the same research group administered four days of dexamethasone (n = 11) or placebo (n = 8) to a group of inpatients with schizophrenia, many of whom were on concurrent antipsychotic medications (Newcomer et al., 1998). They found that dexamethasone treatment did not result in poorer performance on any cognitive tests, as it had in a previous experiment with normal controls (Newcomer et al., 1994). However, the authors did find an inverse association between cortisol levels and verbal declarative memory (Wechsler memory Scale verbal memory) before drug

treatment in the schizophrenia group. No correlations were found between baseline cortisol levels and performance on a brief visual discrimination (Benton line orientation) task, or non-normed tasks assessing vigilance or working memory. These results suggest that the presence of psychosis may moderate the relationship between cortisol and cognition. This may be due to ceiling effects in the psychosis group, resulting from baseline cortisol elevations. It is also possible that the use of non-normed and poorly validated neuropsychological tests impacted the results of this study or that medications affected results by reducing levels of circulating glucocorticoids.

In a slightly different study design, Walder and co-authors (2000) also investigated the association between baseline cortisol levels and cognition in adults with psychosis. They compared a group of 18 outpatients with psychosis with a group of 7 non-psychotic psychiatric patients and a healthy control group (n = 15). These authors measured salivary cortisol and collected three to five hourly samples from each participant. They found that, as expected in the overall sample, cortisol levels were inversely correlated with performance on declarative memory (Wechsler Memory Scale-Revised Logical memory I and II, Verbal Paired Associates, I and II) and executive function (Continuous Performance Test, Modified Wisconsin Card Sorting Test) tasks. None of these associations were significant in the psychosis group alone, though the authors note that relationships were in the same direction as those in the overall sample and statistical power was low for detecting smaller effect sizes. Furthermore, 15 of the psychosis patients were on antipsychotic medications at the time of cortisol sampling. Given that antipsychotics dampen cortisol levels (Walker et al., 2008), this may have affected the nature of the relationship observed between cortisol and cognition.

In a different study, Silver et al. (2005) measured blood cortisol levels in a group of 26 inpatients with either schizophrenia or schizoaffective disorder. After blood draw, they administered five tests of both intellectual (Abstraction, Inhibition, and Working memory task, Penn Face Memory Test, Visual Object Learning Test, Wechsler Memory Scale verbal memory subtest) and social cognitive (Identification of Facial Emotions) function. The authors reported no significant associations between baseline cortisol levels and performance on any of the tests administered. All patients in this sample were treated with antipsychotic medications. Finally, one study has investigated the association between cortisol and cognition in first episode psychosis patients (Aas et al., 2010); nearly all patients in this study were also on antipsychotic medications. The authors found that patients performed worse than controls across all cognitive domains measured and that a blunted cortisol awakening response in patients was associated with verbal (declarative) memory and processing speed deficits. However, trend level elevations in whole-day cortisol were not correlated with cognitive function.

Other studies have indirectly assessed the relationship between glucocorticoids and cognitive function in psychosis by investigating the effects of Dehydroepiandrosterone and Dehydroepiandrosterone sulfate (DHEA/S) on cognitive function. Briefly, DHEA and its sulfate are the most abundant steroid hormones in both sexes (Baulieu & Robel, 1996) and have been extensively studied because they are often sold in health food stores as natural cognitive enhancers (Huppert & Van Niekerk, 2006). Importantly, DHEA/S are known to covary with and actively suppress glucocorticoid levels in humans (Blauer, 1991; Kimonides, 1999; van Broekhoven & Verkes, 2002), though they also affect other neurotransmitter systems implicated in psychotic disorders,

including glutamate (Debonnel, 1996) and GABA (Majewska, 1995). Reports of baseline DHEA/S levels in schizophrenia have been mixed, with increased, decreased, and normal levels of the hormone reported (as reviewed in Ritsner & Strous, 2010; Strous et al., 2007; Silver et al., 2005). Nonetheless, a number of studies have investigated the association between baseline DHEA/S and cognition, as well as the effect of DHEA administration on cognition in this population. Results are mixed: Harris et al. (2001) reported a positive correlation between baseline DHEA levels and performance on attention, declarative memory, and working memory tests, while Silver and colleagues (2005) found that the relationship was only significant for executive function tasks and not declarative memory. These results are consistent with the view that higher levels of glucocorticoids are associated with decrements in cognitive function, though all patients in both studies were again concurrently treated with antipsychotic medications.

In pharmacological studies with psychotic patients (who are generally medicated), the administration of DHEA has been associated with improvements in declarative memory and executive function (Ritsner & Strous, 2010), as well as in sustained attention (Ritsner et al., 2006). Conversely, Strous et al., (2007) found no change in cognitive function after DHEA administration. If psychosis patients are hypothesized to have excess circulating cortisol, which impairs cognitive function, then one would expect DHEA, which attenuates glucocorticoid levels, to lead to an improvement in these functions. While there are some inconsistencies, these studies suggest this may be the case. However, these studies, as well, may be confounded by the effects of medications.

In summary, preliminary evidence in patients with psychosis suggests an association between increased cortisol levels and declarative memory and executive

functioning deficits. While this relationship is also found in healthy controls, preliminary evidence suggests that this association may be moderated by the presence of psychotic illness. However, the neuropsychological tests used vary among these studies, patients are typically being treated with antipsychotic medications, and in many cases, power is insufficient for detecting small to moderate effects.

Cognitive Functioning in the Prodrome and CHR Syndrome

To date, a number of studies have investigated cognitive function in the psychosis prodrome. Many others have studied cognition in groups believed to be at clinical high-risk for developing psychosis, based on the presence of the symptom syndromes identified by clinical indices like the SIPS/SOPS, CAARMS, and BSABS. Broadly, these lines of research yield similar results.

In a recent meta-analysis, Guiliano and colleagues (2012) summarized the literature on cognition in individuals deemed CHR based on the CAARMS and SIPS (14 studies, n = 1215). They also examined longitudinal studies in which CHR individuals subsequently developed a psychotic disorder (7 studies, n = 175). These authors concluded that individuals identified prospectively as at-risk for psychosis, based on diagnostic interview procedures, tend to have impairments in cognitive function across all domains (with the exception of motor skills) that are small-to-medium in size (Cohen's d = -.26 to -.67), when compared with healthy controls. In these domains, true prodromal cases tend to have more pronounced deficits than CHR cases who do not develop psychosis over the follow-up period (Cohen's d = -.35 to -.84), but less severe deficits than first-episode patients. In order of magnitude (larger to smaller) particular deficits were seen in olfaction, general cognitive ability, language functions, immediate verbal

memory, attention/processing speed, visual-spatial abilities, attention/vigilance, working memory, executive functioning measured with the Wisconsin Card Sorting Task, nonverbal memory, and delayed verbal memory. There was considerable variability in effect sizes across studies, as well as in which specific tasks predicted conversion to psychosis. A number of the studies included in the meta-analysis found particularly pronounced deficits in the working memory and executive functioning domains (e.g., Keefe et al., 2006; Eastvold et al., 2007; Jahshan et al., 2010; Seidman et al., 2010), as well as in declarative memory (e.g., Seidman et al., 2010; Niendam et al., 2006; Simon et al., 2007).

Other studies of cognition in the prodrome rely solely on the 'basic symptoms' approach to identifying risk for psychosis (Klosterkotter, et al., 2001). While the Guiliano et al. (2012) meta-analysis did not include studies using this operationalization of psychosis risk, findings converge. For example, Hambrecht and colleagues (2002) defined risk as the presence of at least two of nine subthreshold 'basic' psychotic symptoms. They found that their sample of 51 CHR patients performed significantly worse on tests of attention, verbal memory/recall, and verbal fluency than a sample of control patients. As expected, this group performed significantly better than a sample of schizophrenia patients in all domains tested. Using the identical basic-symptom identification approach in a new sample, the same group (Schultze-Lutter et al., 2007a) found that CHR participants, divided based on the duration of prodromal symptoms (early prodrome, n = 33; late prodrome, n = 69), were impaired on tests of verbal memory, sustained attention, and processing speed, but not on some other tests of working memory or executive function. Two other studies (Hawkins et al., 2008;

Schultze-Lutter et al., 2007b) investigated cognition at different points in the prodrome, but did not include comparison groups.

Finally, many studies have investigated cognitive dysfunction in schizotypal personality disorder (SPD). Individuals with SPD have been shown to be at high risk for developing a psychotic disorder based on the high rate with which they develop psychosis (Mittal et al., 2008; Asarnow, 2005), the high rate of SPD in families of schizophrenia patients (Kendler et al., 1981; Webb & Levinson, 1993), the high rate with which individuals with SPD meet CHR syndrome criteria on measures like the SIPS (Woods et al., 2009; Shapiro et al., 2011), and the assumption that SPD and schizophrenia share some genetic and environmental determinants (Kendler et al., 1995). In accord with findings in other at-risk groups, SPD samples tend to show impaired performance on verbal and episodic declarative memory/learning (Bergman et al., 1998; Voglmaier et al., 2000; McClure et al., 2007; Mitropoulou et al., 2002), working memory and executive function (Diforio et al., 2000; McClure et al., 2008; Trestman et al., 1995), and attention/concentration (Cadenhead et al., 1999; Moriearty, 2003). Further, as in the previously described literature, studies that include a healthy comparison group typically find that the performance of individuals with SPD is intermediate to that of control and psychosis groups.

In summary, studies of cognition in the psychosis prodrome and CHR groups (including SPD) find general decrements in cognitive abilities, with specific deficits seen in the areas of verbal (declarative) learning and memory; attention, working memory, and other executive functions; and processing speed. These areas are also affected both in schizophrenia and by excess levels of circulating glucocorticoids. Further, those who

subsequently convert to psychosis tend to show more pronounced impairments, as well as a decline in cognitive function over time (Keefe et al., 2006). One question to be addressed is whether cognitive functions, or their decline, are related to basal cortisol levels in the CHR period.

Summary

As noted, no study has yet investigated the relationship between cortisol and cognitive function in the prodromal phase of psychotic illness. However, stress and the HPA axis are implicated in the onset and maintenance of psychotic symptoms. They also play a role in declarative memory, working memory, and executive functions. In healthy controls and animals, previous studies show an "inverted U" shape to this association, such that deficits in performance are associated with both elevated and attenuated cortisol levels. To date, however, nonlinear relations between cortisol levels and cognition have not been examined in psychotic patients. Although numerous studies of psychotic patients have shown deficits across all domains of cognitive function, the few studies that have examined the relation of cognition with cortisol reveal a less consistent linear association than that seen in controls. Further, given that nearly all participants in these studies were on antipsychotic medications, which can reduce basal cortisol levels, these findings highlight the importance of examining the relationship between cortisol and cognition in nonmedicated subjects in the psychosis spectrum. Moreover, while deficits in cognitive function are apparent in the prodromal phase of psychotic illness, there are no reports on the association between cortisol secretion and cognition in CHR subjects.

It has been suggested that heightened glucocorticoid release may contribute to deficits in both cognitive performance and brain function in several major psychiatric

disorders, including mood disorders and psychosis (Sheline et al., 1999; Brown et al., 1999). If this notion receives empirical support, it suggests a neural mechanism to explain the decline in cognitive function that appears to be associated with the emergence of psychosis. Moreover, it would suggest potential approaches for the prevention of cognitive decline, and provide a theoretical basis for research on preventive intervention aimed at dampening HPA activity, especially in those at risk.

The chief goals of the present study are to determine whether there is evidence of a linear or nonlinear (e g., inverted 'U') relation between cortisol levels and cognitive performance in youth at clinical high risk for psychosis. It does so by focusing on a CHR sample with limited exposure to psychotropic medication and by using multiple cortisol measurements.

Cortisol and cognition in the prodrome; Hypotheses and Research Questions

Hypothesis 1: Based on past research and theories concerning the effects of glucocorticoids on the hippocampus and frontal cortex, it is hypothesized that cortisol levels will be associated with performance on declarative memory, working memory, and executive function tasks in a non-linear fashion. Specifically, investigations in human and animal subjects suggest faciliatory effects of cortisol levels varying between low and moderate, but adverse effects of higher cortisol levels on these cognitive functions. Thus, it is hypothesized that the nature of the association between cortisol and measures of these cognitive functions will be a nonlinear, quadratic, "inverted U" shape.

Hypothesis 2: Previous research has suggested elevated baseline cortisol levels in individuals with established psychotic disorders. A small number of reports also

suggest that such elevations are present in those at clinical high risk for illness. This includes findings of increased baseline cortisol in the current sample (Walker et al., *manuscript in preparation*). Thus, it is hypothesized that control and CHR groups will be at different places along the "inverted U" relationship between cortisol and cognition. This could manifest as a direct relationship (left arm) in the control group and either no relationship (top of the U) or an inverse relationship (right arm) in the CHR group. Alternatively, it may be that both groups are on the right arm of the "inverted U," with the CHR group showing a stronger negative association between cortisol and cognition.

Research Question 1: While findings are not consistent, some studies have found that cortisol levels at baseline (Corcoran et al., 2012; Kajantie & Phillips, 2006) and in response to stress (Kudielka & Kirschbaum, 2005) differ between the sexes. This may be related to sexual dimorphisms in HPA axis development, which include differences in pituitary volume (MacMaster et al., 2007). Thus, sex will be investigated as a possible moderator of the relationship between cortisol and cognitive function.

Method

Participants and Recruitment

Participants for the current study were drawn from the larger North American Prodrome Longitudinal Study (NAPLS), an NIMH-funded longitudinal study designed to investigate factors that precede and are associated with the development of psychosis. This study is ongoing and involves eight different research sites across North America (University of Calgary, UCSD, UCLA, Zucker Hillside Hospital, UNC, Harvard

University, Emory University, Yale University). Participants in the present study were 506 individuals. The age range was 12 to 35 with a mean of 19.03. This included 328 individuals who met criteria for a CHR syndrome (192 (58.5%) male; mean age = 19.01) and 178 healthy controls (100 (56.2%) male; mean age = 19.06).

CHR Subjects

Diagnostic criteria for CHR syndromes are based on the Criteria of Prodromal Syndromes (COPS) criteria (Woods et al., 2001; Miller et al., 2003), derived from the Structured Interview for Prodromal Symptoms (SIPS), which is described below. CHR participants were also included if they met criteria for the Youth and Schizotypy Syndrome, defined as the presence of DSM-IV schizotypal personality disorder in adolescents below the age of 19, or the Genetic Risk and Deterioration Prodromal Syndrome (GRD). Criteria for GRD are presence of a first-degree relative with a psychotic disorder accompanied by a significant drop in overall functioning (represented by a 30% in Global Assessment of Function score) over the past year.

Participants were included in the CHR group if they were between 12 and 30 years of age and met criteria for a CHR syndrome. Exclusion criteria were current or lifetime Axis I psychotic disorder, IQ below 70, past or current history of a clinically significant central nervous system disorder or closed head injury, or substance dependence in the past 6 months. Participants treated with antipsychotic medications were only included if it could be shown that antipsychotics were prescribed for prodromal or non-psychotic symptoms (this was only the case in a small subset of participants). Non-psychotic Axis I disorders were not considered exclusionary unless they clearly better accounted for what appeared to be diagnostic prodromal symptoms.

Control Participants

Inclusion and exclusion criteria were the same for the healthy comparison group, with two exceptions: control participants could not meet criteria for any CHR syndrome, current Axis I disorder, or Axis II cluster A personality disorder; and controls could not have a family history, in first- or second-degree relatives, of any psychotic disorder.

Procedures

Potential CHR subjects were ascertained through referrals from health care providers and educators, as well as self-referred in response to announcements and newspaper advertisements. Control participants were recruited through community outreach and public announcements. All potential participants were first screened over the phone. Those likely to meet criteria for the study were then scheduled for an in-person evaluation at which they were informed about study procedures and provided informed consent. When participants were younger than 18, parental written informed consent was also obtained. All consent/assent and study procedures have been approved by the IRBs of Emory University and the other NAPLS sites. After consent, the SIPS and the Structured Clinical Interview for DSM-IV (SCID) were administered to determine whether individuals met criteria for a CHR syndrome and to diagnose Axis I disorders. Information about demographics, family history of mental illness, treatment history, social and vocational/academic function, and history of head injury was also collected at this screening interview. Participants were then discussed on a weekly clinical conference call with investigators from all eight sites and admitted to the study if consensus was achieved.

Three lab cortisol samples were collected every hour during a lab visit in which diagnostic interviews and self-report measures were administered. In all cases, attempts were made to collect the first hourly sample between 9:30 and 11:00 am; a timer-alarm was used to signal subsequent collection times. All samples were provided in a plastic specimen tube labeled with participant's ID, sample number, and collection times. While the term "baseline" is typically used to refer to the measurement of cortisol in the absence of stress-induction, it is assumed that for at least some individuals the experience of participating in a clinical research assessment is sufficiently novel and/or stressful to induce an elevation in cortisol above basal levels Thus, although the term "baseline" is used here, it is acknowledged that cortisol is not being measured in a natural setting.

Diet (Kirschbaum et al., 1997; Benedict et al., 2005), alcohol (Beresfold et al., 2006; Adinoff et al., 2003), caffeine (Kudielka et al., 2009), and tobacco (Hansen et al., 2008) affect short-term cortisol readings. Thus, participants were asked to fast and abstain from these substances after 7:00 pm on the evening before saliva sampling. They were also asked to fast on the morning of sampling in order to further reduce measurement confounds. Food, liquid, tobacco, and medication consumption the evening before and morning of sampling was recorded.

Participants completed a neuropsychological test battery comprised of tasks designed to tap the various cognitive domains that are affected in schizophrenia (described below). Due to the length of both the clinical lab visit and this neuropsychological battery, most participants completed these assessments on different days.

Measures

Structured Interview for Prodromal Syndromes (SIPS)

The SIPS (McGlashan et al., 2001) is a semi-structured diagnostic interview designed to assess and diagnose the severity of prodromal symptoms of psychosis. It is composed of 19 symptom-items, each comprised of a number of questions, and rated on a 0-6 scale. Scores between 3 and 5 are considered to be within the prodromal range while a score of 6 is considered to be at the psychotic level. The 19 symptom-items are grouped into the positive, negative, disorganized, and general symptom scales.

The positive symptom scale consists of items that assess unusual thought content and delusional ideas, suspiciousness and persecutory ideas, grandiosity, perceptual abnormalities and hallucinations, and disorganized communication. The negative symptom scale includes items that assess social anhedonia, avolition, reduced expression of emotion, decreased experience of emotion and self, ideational richness, and deterioration of role functioning. Items on the disorganized symptom scale assess odd behavior or appearance, bizarre thinking, trouble with focus and attention, and impairment in personal hygiene. Finally, the general symptom scale contains items that assess sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance to stress.

Scores on these symptom dimensions are used to determine whether subjects meet criteria for the APS or BIPS CHR syndromes. The APS is characterized by the presence of at least one subthreshold positive symptom and no psychotic level positive symptoms. In BIPS, an individual experiences at least one psychotic level positive symptom for, on average, at least several minutes per day once per month, but not occurring more than 4 days per week. This symptom must have developed or increased to psychotic intensity

within the past three months. In addition to these CHR syndromes, the SIPS can also classify individuals as meeting criteria for Presence of Psychotic Syndrome (POPS). Criteria for POPS are similar to those of APS except that individuals have at least one positive symptoms rated as 'psychotic.'

Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive neuropsychological battery (MATRICS)

The MATRICS battery of neuropsychological tests (Nuechterlein et al., 2008) was designed to target cognitive domains that are often impaired in schizophrenia. It is a compendium of neuropsychological tasks developed, under NIMH contract, through the consensus of many of the leading researchers in the field of cognition in schizophrenia (e.g., Green & Nuechterlein, 2004; Geyer & Heinssen, 2005). Most of the tasks chosen for this compendium were developed and commonly used prior to the MATRICS battery (Nuechterlein & Green, 2006). From a preliminary battery of 36 candidate tasks, empirical testing resulted in the identification of 7 cognitive domains with one to three tests per domain. While social and non-social cognitive abilities tend to show moderate sized correlations in schizophrenia (Ventura et al., 2011), these domains are generally conceptualized as being distinct from one another (Fanning et al., 2012). Thus, only the speed of processing (executive function), attention/vigilance (executive function), working memory, verbal learning (declarative memory), visual learning (declarative memory), and reasoning and problem solving (executive function) domains are included in the present study.

The MATRICS battery includes two declarative memory domains. The *Hopkins Verbal Learning Test—Revised* (HVLT-R; Brandt & Benedict, 2001) comprises the

Verbal Learning domain. The HVLT-R is a verbal list-learning task in which examinees are orally presented with a list of 12 words and asked to immediately recall them. Learning occurs over three presentations of the list. The HVLT-R yields a total correct raw score, computed by summing the number of words correctly recalled over all three trials. Age- and sex-based norms can also be used to calculate a total correct t-score and total correct percentile. The *Brief Visuospatial Memory Test—Revised* (BVMT-R; Benedict, 1997) comprises the visual learning domain. In this task, examinees are presented for ten seconds with an array of six figures, then asked to immediately reproduce the form and placement of these figures from memory. Learning occurs over three presentations of the array. Each reproduced figure is scored based on correct form (1 point) and correct location in the array (1 point), resulting in 12 possible points per presentation. The BVMT-R total raw score can then be converted to a total correct t-score and total correct percentile.

The working memory domain is assessed with two MATRICS tasks. The *Wechsler Memory Scale—Third Edition: Spatial Span* task (WMS-3-SS; Wechsler, 1997) taps nonverbal working memory skills, while the *University of Maryland Letter-Number Span* (LNS; Gold et al., 1997) taps more verbal working memory skills. In the former, examinees are asked to remember up to 16 sequences of blocks to which the administrator points (WMS-3-SS forward). Working memory is further exercised when examinees are asked to reproduce up to 16 sequences in reverse order (WMS-3-SS backward). The WMS-SS yields a WMS-SS Forward raw score and a WMS-SS Backward raw score. Age- and sex-based norms are available for use in computing t-scores and percentile scores for the WMS-SS Total score. The LNS task requires

examinees to mentally reorder and reproduce an orally presented list of intermixed letters and numbers of increasing length. They are administered up to 24 trials, resulting in the LNS raw, t, and percentile scores.

Additional tasks from the MATRICS battery that tap broader executive functions are also included. As mentioned, there is likely some overlap in the skills necessary for these tasks and those utilized in the WMS-SS and LNS tasks. Specifically, participants complete the speed of processing, attention/vigilance, and reasoning/problem solving modules of the MATRICS battery. The speed of processing module includes the *Brief Assessment of Cognition in Schizophrenia: Symbol Coding* task (BACS-SC; Keefe, 1999), the *Animal Category Fluency* task (Category Fluency; Spreen & Strouss, 1998), and the *Trail Making Test: Part A* task (TMT; "Army Individual Test Battery: Manual of Directions and Scoring," 1944). In the BACS-SC task, which involves both memory and visuomotor speed, participants are given 90 seconds to quickly write numbers that correspond with nonsense symbols on an answer key. Animal naming, which taps verbal speed of processing skills, requires the examinee to name as many animals as possible in one minute. For both of these tasks, a Total raw score is recorded and a resultant Total t-score and Total percentile can be computed. Finally, the TMT task involves quickly locating and connecting numbers on a page in sequential order. Visual scanning, visuomotor tracking, and processing speed are necessary skills for this task. The length of time needed to correctly connect all numbers is recorded, then can be used to compute a TMT t-score and percentile.

To assess attention/vigilance, the MATRICS *Continuous Performance Test—Identical Pairs* (CPT-IP; Cornblatt et al., 1988) was administered, while the

Neuropsychological Assessment Battery—Mazes task (Mazes; White & Stern, 2003) was included to assess reasoning/problem solving skills. The CPT-IP is a computerized measure of sustained, focused attention/vigilance in which participants monitor a series of quickly presented numbers and respond each time two identical stimuli appear in a row. Blocks of 150 2-, 3-, and 4-digit numbers are presented and scored separately. For each block, total number of hits and false alarms are used to compute a D prime score (2-Digit D', 3-Digit D', 4-Digit D'). An average D prime score (CPT-IP Ave) is also calculated and can be used to derive a t-score and percentile score. The Mazes task assesses foresight, planning, and impulse control by asking examinees to complete a set of increasingly complex maps with pen and paper. Time needed to correctly complete each maze is used to generate a Mazes Total raw score (0-24). Mazes t and percentile scores are also available.

Seidman Auditory CPT

The NAPLS neuropsychological test battery includes a number of non-MATRICS tasks that also tap cognitive domains of interest. The *Seidman Auditory CPT* task *(*Auditory CPT; see Seidman et al., 1998) is similar to the CPT-IP. It is comprised of three separate tasks that also tap sustained, focused attention/vigilance skills, but taps working memory skills, as well. In all three tasks, participants are presented with an audio recorded list of numbers and asked to respond by tapping a pencil when they hear a correct response. In the first two tasks, they tap when they hear an A either immediately after a Q (QA task) or 4 letters after a Q (Q3A-MEM task). In a third task, the 4-letter Q→A sequences overlap, requiring examinees to keep track of multiple sequences at the same time (Q3A-INT task). For each task, hits, misses, and false alarms are tallied and

used to compute the percent of correct hits. Thus, the Auditory CPT has three summary variables: QA % Hits, Q3A-MEM % Hits, and Q3-INT % Hits.

Wide Range Achievement Test—4th Edition (WRAT-4) Reading

The WRAT-4 reading task (Wilkinson et al., 1993) is a word recognition reading test that taps reading ability. It is often used as an estimate of premorbid verbal IQ. Individuals are asked to read a list of 42 words out loud and are scored on whether or not they pronounce each word correctly. The test yields a Total raw score and an age- and sex-normed standard score.

Wechsler Abbreviated Scale of Intelligence (WASI)

The WASI (PsychCorp, 1999) was designed to provide a short and reliable estimate of overall intellectual abilities. The current study uses the *Vocabulary* (WASI-V) and *Block Design* (WASI-BD) subtests. The Vocabulary subtest, which assesses expressive vocabulary, verbal knowledge, and fund of information, requires participants to provide definitions for up to 42 orally and visually presented words. In the *Block Design* task, which taps spatial visualization, visual-motor coordination, and abstract conceptualization skills, participants use two-color cubes to replicate up to 13 visually presented patterns. These tasks yield raw scores, age- and sex-normed standard scores, and an estimate of IQ.

Babble Task

The babble task (see Hoffman et al., 2007) was designed to be a "simulation of disordered speech perception," based on the premise that auditory hallucinations derive from deficits in speech perception abilities, which involve working memory and other executive functions (Hoffman et al., 1995). In the babble task, participants listen to an

audio recording of many people speaking at the same time and are asked to repeat any words or phrases they hear. The total number of words and the length of the longest phrase repeated are recorded. Longest phrase heard is used as a summary variable based on previous findings showing its utility in predicting conversion to psychosis in non-medicated CHR individuals (Hoffman et al., 2007).

Cannon Episodic Memory Task (PAM)

The PAM task is a paired-associate memory test designed to assess the ability to remember stimuli in their original spatiotemporal context. This ability taps declarative memory skills and has been associated with activation of the hippocampus (Langston et al., 2010). Participants are shown pairs of stimuli, presented as both written words and pictures. In the retrieval phase, one item is presented and participants are asked to state whether this stimulus was paired with one of two options, or whether it is new. Mean reaction time for correct responses is used as the summary variable.

University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT (Doty, 1995) is an olfactory test that assesses one's ability to identify smells. Olfactory processing is thought to be mediated by frontal and temporolimbic brain regions (Nguyen et al., 2010). It is included in the current study because it has reliably been found to be impaired in individuals with schizophrenia (Moberg et al., 1999), shows promise as a clinical high risk marker (Giuliano et al., 2012; Turetsky et al., 2012), and because of the potential impact cortisol may have on the frontal lobe. Participants are presented with booklets that contain 40 smell strips which release odor when scratched. They are then asked to match their smell experience with one of 4 multiple choice options. A total raw score out of 40 is used as a summary variable.

Cortisol Assay

After collection, saliva samples were immediately frozen and stored in lab freezers at -20C, a temperature at which salivary cortisol is considered stable (Hansen et al., 2008). For salivary cortisol assay, the Salimetrics (Salimetrics, LLC, College Park, Pa) High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit was used. This assay captures the full range of salivary cortisol levels (0.003 to 3.0μg/dL), requiring only 25 uL of saliva per test.

On the day of assay, samples were thawed, vortexed, and centrifuged at 1500 x g (@3000 rpm) for 15 minutes. Pipetted clear samples were then placed in wells before a microtitre plate was coated with monoclonal antibodies to cortisol. After incubation, unbound components were washed away and bound cortisol peroxidase was measured by the reaction of the peroxidase enzyme on the substrate tetramethylbenzidine (TMB). This procedure has been shown to provide a reliable measure of salivary cortisol: Salimetrics reports a correlation of r = .91 with serum cortisol and a minimum concentration of cortisol that can be distinguished from 0 of <.003 μg/dL (Salimetrics Enzyme Immunoassay Kit Manual, 2011).

Statistical Analyses

Neuropsychological Data Imputation

Neuropsychological data were collected on 501 participants (CHR n = 325; control n = 176) across 19 subtests. Distribution statistics for these tasks are included in Table 1. Many of the neuropsychological tasks overlap in the cognitive domains they tap, suggesting that an empirical approach to identifying working memory and executive function components may be the optimal approach to deriving measures of these

functions. Given that the neuropsychological battery was selected to tap specific latent constructs with multiple tasks, a factor analytic approach was selected. This was preferable to a principal component analysis because factor analysis (FA) utilizes only shared variance to extract factors. Other methods that do not discriminate between shared and unshared variance (like principal components analysis) can inflate estimates of variance accounted for when the variables of interest are intercorrelated (Costello & Osborne, 2005). Fabrigar and colleagues (1999) suggest that maximum likelihood is an optimal factor analytic strategy when variables are significantly intercorrelated and when the assumption of multivariate normality is not "severely violated." Significant intercorrelations are shown in Table 2. Skewness statistics (see Table 1) and distribution Tables suggested that only the TMT, Mazes, and Auditory CPT QA and CPTQ3-MEM tasks deviated significantly from normality. Data transformations were conducted to attempt to normalize these distributions.

32.9% of all cases were missing PAM data (n = 165) as a result of changes to the task during its development. No other variable had missing data for more than 29 cases (3.99%), suggesting a need to either impute PAM data or eliminate it from FA to avoid limiting the sample size. In order to determine whether performance on the neuropsychological battery could be used to impute PAM data, PAM scores were regressed independently on each of the other cognitive variables and variance accounted for was computed (see Table 3). Finally, multiple imputation was conducted using all cognitive data. Prodromal diagnostic status, education, maternal education, paternal education, race, and age were also included in the imputation model as predictors to better impute PAM values given variability across these other variables. Because no

systematic pattern of missing data was apparent, a Fully Conditional Specification iterative Markov Chain Monte Carlo (MCMC) method of imputation was utilized over 5 iterations. The MCMC method uses all other variables in the imputation model as predictors for each missing data point, then repeats the process for each iteration. Descriptive statistics after imputation are listed in Table 4.

Exploratory Factor Analysis

The same factor analysis procedure was run on data generated during each iteration of the data imputation to determine whether or not imputation changed the nature of the neuropsychological test variables. The procedure was also run on data with age effects regressed out. Both scree plots and Eigenvalues were examined to determine the optimal number of factors. The traditional cutoff of Eigenvalue = 1 was used as a guideline, though not a strict cutoff, for this determination. Subsequently, a varimax rotation with Kaiser normalization was utilized. A goodness-of-fit χ^2 /df between 1.0 and 2.0 for the resultant factor structure is typically considered to indicate a good fit to the initial data.

Guidelines discussed by Costello & Osborne (2005) were used in the further interpretation of the factor analysis. These authors suggest that an interpretable factor structure has items that load on factors at a minimum of .32 or above, with few cross-loadings, and no factors with fewer than three items (though 5 or greater is preferred). A minimum loading threshold of .4 is more typically used for interpretation while items that load at .5 or above are considered to load "strongly." The authors also suggest that communalities be "low to moderate" (.40 to .70) or "high" (.8 or greater). When items do not load on extracted factors, crossload, have communalities less than .40, or are

freestanding, the authors recommend re-running the analysis without these items to see if the factor structure changes.

Cortisol Aggregation

Cortisol data were available from 411 individuals (CHR n = 260, control n = 151), though not all participants provided 3 samples (control n = 150, 147, 136; CHR n = 257, 255, 221 for time 1, 2, and 3, respectively). Cortisol values by group and sample are listed in Table 5. In order to maximize reliability of cortisol values, the three lab measures were aggregated in two different ways. First, the mean of all available lab samples from each individual was computed. Second, Area Under the Curve (AUC) was computed. AUC is often used in cortisol and other endocrinological studies to investigate the association between multiple hormone measurements and other variables (Preussner et al., 2003; Walker et al., 2010). Because total baseline cortisol levels are of principal interest in the proposed analyses, as opposed to changes over time, AUC with respect to ground (AUC_g) was used, as opposed to AUC with respect to increase (AUC_i)(Fekedulegn et al., 2007). The formula for AUC_g is:

$$AUC_G = \sum_{i=1}^{n-1} \frac{(m_{(i+1)} + m_i) \cdot t_i}{2}$$

where m_i denotes a given cortisol measurement and t_i denotes the length of time between m_i and $m_{(i+1)}$ (Preussner et al., 2003).

Computation of AUC_g requires at least three data points. Data for all three lab cortisol samples were available for 132 control (87.42%) and 217 CHR (83.46%) participants. Thus, multiple imputation was again conducted to maximize the power of statistical analyses, including all participants who provided at least one cortisol sample.

All three cortisol variables were imputed with age and diagnostic group also included in the imputation model as predictors. Because no systematic pattern of missing data was apparent, a Fully Conditional Specification iterative Markov Chain Monte Carlo (MCMC) method of imputation was again utilized over 5 iterations. Resultant descriptive statistics are shown in Table 5. These data were examined for outliers outside the potential normal or clinical range for salivary cortisol values.

Potential Confounds of cortisol values

Cortisol values were regressed on time of sampling to determine whether there was a significant effect of collection time on cortisol. Since samples were reliably collected at 60 minute intervals in the lab, the time of sample 1 was used. t-tests were used to investigate whether cortisol values differed between individuals who did or did not consume alcohol, dairy, caffeine, or tobacco after 7 pm the night before saliva sampling. T-tests were also run to investigate the effects of current antipsychotic, antidepressant, or stimulant use on cortisol values. Significant results led to the inclusion of confounding variables as covariates in subsequent analyses.

Age Effects in Cortisol and Cognitive Data

As described below, age was found to be associated with increases in both cognitive scores and cortisol, suggesting a need to account for age differences in analyses. The relation of age with cortisol is assumed to at least partially reflect neuromaturational processes, whereas the relation of age with cognition is assumed to reflect both neuromaturation and learning. The current study hypothesizes that cortisol will also be associated with changes in cognitive performance, in part due to the effects of cortisol on brain function. As illustrated in Figure 1, there is assumed to be a direct

relationship between age and cognitive function, as well as an indirect relationship that is mediated by cortisol. Thus covarying for age in analyses including both cortisol and cognition may obscure the relationship between variables. Therefore, the effects of age were independently regressed out of cortisol and cognitive scores before their relationship was examined. The current study hypothesizes that increases in cortisol, that are partially age determined, will have both faciliatory and adverse effects on cognitive process, consistent with an inverted 'U' relation. Thus analyses were also rerun without regressing age out of cortisol.

Regression analyses

Both linear and quadratic ("inverted U") regression models were evaluated to test the hypotheses. The curve estimation procedure in PASW 18 was used as an alternative to the standard linear regression model because it assesses whether various curvilinear relationships better predict the value of a dependant variable, given change in an independent variable. Linear and quadratic models were run separately for AUC_g and each of the cognitive factor scores, both in the whole sample (hypothesis 1), and within each diagnostic group (hypothesis 2). Because the linear association in these relationship for the CHR group was predicted to be negative, one-tailed p values were used. When the quadratic component was significant, the "inverted U" shape was investigated by conducting a median-split on residualized cortisol AUC_g values and performing linear regression analyses separately below and above the median. A positive association was expected below the median (the left arm of the "inverted U"), while a negative association was expected above the median (the right arm of the "inverted U"). Thus, one-tailed p-values were again used. Fisher's r to z transformations and z-tests (Preacher,

2002) were conducted to determine whether relationships differed significantly between diagnostic groups.

Finally, the research question concerning the potential moderating effects of sex on the relationship between cortisol and cognition was assessed by rerunning the curve estimation procedure on males and females, separately. Sex was considered a moderator if the nature of the relationship between cortisol and cognitive factors differed between the sexes. Because there were no directional a priori hypotheses, two-tailed p values were used.

Results

Cognitive Data

Table 6 shows group means and group contrasts (t-tests) on each of the cognitive measures. In cases where variances differed significantly between groups, the t-test for unequal variances was performed (Ruxton, 2006). As shown, the control group performed significantly better than the CHR group on all cognitive tasks except for the babble task, with effect sizes in the small to moderate range for all comparisons except Mazes, which fell below the "small" threshold of .2

Data Transformation and Imputation

Skewness statistics (see Table 1) were greater than |1| for the Babble task, Auditory CPT QA % Hits, Auditory CPT Q3A-MEM % Hits, TMT, Mazes, and the UPSIT. While Kolmogorov-Smirnov tests indicated that the distribution of Babble ($Z = 4.338$, $p < .001$) and UPSIT ($Z = 3.217$, $p < .001$) data deviated from normality, visual inspection of frequency histograms suggested that they were roughly normal in shape with large kurtoses (with a slight negative skew in the UPSIT distribution). The

remaining four variables all demonstrated significant skew (positive for TMT, negative for Mazes, Auditory CPT QA % Hits, and Auditory CPT Q3A-MEM % Hits), suggesting that data transformations might normalize their distributions. The TMT task is the only task in the current study's neuropsychological battery in which higher scores denote poorer performance. An inverse transform performed better at normalizing TMT scores (skewness = .559; Kolmogorov-Smirnov Z = 1.369, p = .047) than either a square root or logarithmic transform and also changed the direction of scoring. In the remainder of these tasks, neither a square root nor logarithmic transform succeeded in reducing skewness statistics (square root = -1.686, -3.309, -1.502; logarithmic = -2.841, -3.720, -1.907 for mazes, Auditory CPT QA % Hit, and Auditory CPT QA-MEM % Hit, respectively). Further, neither led to a non-significant Kolmogorov-Smirnov test (square root: Z = 3.446, p < .001 ; Z = 5.998, p < .001 ; Z = 3.555, p < .001; logarithmic: Z = 4.350, p < .001, Z = 6.212, p < .001, Z = 3.855, p < .001 for mazes, Auditory CPT QA % Hit, and Auditory CPT QA-MEM % Hit, respectively). Because Auditory CPT QA and Auditory CPT QA-MEM scores are less than one, square root and logarithmic transforms adding a constant were also examined. These transforms also failed to yield smaller skewness statistics (QA square root = -1.496, Q3A-MEM square root = -3.304, logarithmic QA = -3.708, logarithmic Q3A-MEM = -1.892) and did not lead to non-significant Kolmogorov-Smirnov tests (square root: Z = 5.996, p < .001; Z = 3.553, p < .001; logarithmic: Z = 6.206, p < .001; Z = 3.844, p < .001 for the QA and Q3A-MEM tasks, respectively). Thus, only the TMT task score was transformed before imputation and factor analysis.

As shown in Table 3, all cognitive variables, except babble and trails, accounted for significant variance in PAM scores, suggesting that performance on other tasks in the neuropsychological battery can be used to predict performance on the PAM task in an imputation. Descriptive statistics for imputed cognitive variables (after 5 imputation iterations) are shown in Table 4 and are comparable to those for non-imputed variables (Table 1), suggesting that imputation did not change the distribution of these variables.

Factor Analysis

As shown in Table 2, performance on the 19 cognitive tasks was highly intercorrelated, supporting maximum likelihood as an optimal factor analytic approach. The only task that did not correlate highly with nearly all other tasks was the babble task, which only correlated significantly with 4 of the tests in the neuropsychological battery. For all 6 versions of the factor analysis (raw data and each of the 5 imputation iterations), 5 factors had Eigenvalues > 1. A 5 factor solution also coincided with a plateau in the scree plots. Further, while extracting a sixth factor resulted in a model that accounted for an additional 4.652% of the variance in cognitive performance (total variance accounted for = 64.614%), the 6^{th} factor had only 2 tasks load positively and the model yielded only one fewer crossloading than the 5 factor model. As seen in Table 7, Eigenvalues in the 5 factor model appear roughly the same before and after imputation. Further, the 5 factor structure accounts for roughly the same amount of variance in raw cognitive variables before and after imputation. Similarly, Table 8 shows that communalities (the amount of variance in each variable accounted for by the 5 factor structure) are roughly the same before and after data imputation; the largest differences were .023 for Auditory CPT Q3A-INT % Hits, with the post-imputation solution accounting for 2.3% more variance

in scores, and .017 for PAM, with the pre-imputation solution accounting for 1.7% more variance. Finally, Table 9 shows that, while factors 1 and 2 switch order before and after imputation in the rotated factors, the magnitude with which each item loads onto respective factors remains relatively unchanged by imputation.

Because the factor structure was relatively unchanged by data imputation, only the factor analysis including imputed data was interpreted. Bartlett's test of sphericity was significant ($p < .001$) and the Kaiser-Meyer-Olkin test value of .905 suggests an adequate sample size. As stated, Eigenvalues (Table 7) and the scree plot suggested that 5 factors be retained. Table 8 indicates communalities above .4 in the 5 factor structure for all variables except the Babble task, the UPSIT, the three Auditory CPT tasks, and the PAM task. However, given this low communality for the Babble task, as well as negligible loadings on all 5 rotated factors (Table 9), the factor analysis was rerun excluding the Babble task.

In the final factor analysis, 4 factors had Eigenvalues greater than 1 (see Table 7), and this again coincided with a plateau in the scree plot. Bartlett's test of sphericity was significant ($p < .001$). The Kaiser-Meyer-Olkin test value of .908 suggests an adequate sample size and that a large proportion of variance in the original variables might be caused by underlying factors. This 4 factor model accounted for 57.144% of the variance in cognitive scores, indicating that eliminating the Babble task resulted in a 2.818 decrease in variance accounted for by the model. As shown in Table 8, the same tasks had communalities below .4 (UPSIT, the three Auditory CPT tasks, PAM) in addition to the WMS-3-SS Forward, Category Fluency, and TMT. The remainder of the tasks had communalities above .4. This includes communalities for tasks thought to tap declarative

memory (HVLT-R, BVMT), working memory (WMS-3-SS Backward), and other executive functions (BACS-SC, Mazes, CPT-IP), suggesting that the factor structure incorporates significant variance in tasks designed to assess these domains.

Table 9 shows factor loadings after Varimax rotation with Kaiser normalization. Using a cutoff of .4, only 3 tasks crossloaded (WASI-Block Design, LNS, CPT-IP), in contrast to 5 in the 5 factor solution. 6 tasks loaded onto the first factor (WASI-BD, Mazes, WMS-3-SS Backward, WMS-3-SS Forward, TMT, Auditory CPT Q3A-INT), with the BVMT-R also nearing threshold (factor loading = .393). Of these, WASI-Block Design, Mazes, and both WMS-3-SS tasks loaded most strongly, suggesting that Factor 1 was dominated by tasks requiring visuospatial abilities. 5 tasks loaded onto the second factor (Auditory CPT Q3A-MEM, BACS-SC, CPT-IP, Auditory CPT QA, LNS) with the third Auditory CPT Q3A-INT task nearing threshold (loading = .380). On this factor, the Auditory CPT Q3A-MEM task and BACS-SC loaded most strongly, suggesting that the factor is tapping attention and working memory abilities. 4 tasks loaded onto the third factor (WRAT-4, WASI-Vocabulary, CPT-IP, Auditory CPT QA), with LNS nearing the threshold (loading = .394). Both WRAT-4 and WASI-Vocabulary loaded strongly, suggesting that Factor 3 is dominated by tasks requiring verbal abilities. The fourth factor had four tasks with significant factor loadings (HVLT-R, PAM, BVMT-R, LNS); all but LNS can be considered strong loaders. All tasks loading on Factor 4 tap declarative memory abilities. Based on this pattern of results, the four factors will be referred to as the Visuospatial Abilities Factor (Factor 1), the Attention and Working Memory Factor (Factor 2), the Verbal Abilities Factor (Factor 3) and the Declarative Memory Factor (Factor 4) in subsequent sections.

The four factors showed a statistically significant but minimal level of intercorrelation, as would be expected after the varimax rotation. The Visuospatial Factor correlated significantly with the Attention and Working Memory ($r = .110$, $p = .027$) and Declarative Memory ($r = .103$, $p = .039$) factors, but not the Verbal Abilities factor ($r = .073$, $p = .142$). The Attention and Working Memory factor also correlated with the Verbal Abilities Factor ($r = .160$, $p = .001$) and Declarative Memory Factor ($r = .145$, $p = .003$), which was significantly correlated with the Verbal Abilities Factor ($r = .100$, $p = .043$).

The factor analysis was re-run using data from 18 cognitive tasks after the effects of age were regressed out. While the order in which factors were extracted differed, the amount of variance in cognitive tasks accounted for (55.77%) was roughly the same. The age-regressed factors were as follows: Visuospatial Abilities, Declarative Memory, Attention and Working Memory, Verbal Ability. Further, significant factor loadings differed for only two tasks: the auditory CPT Q3A-INT loaded significant at .402 on the Attention and Working Memory Factor, whereas the CPT-IP no longer significantly loaded (.341) on the Verbal Abilities factor. Thus, age did not significantly affect the cognitive factor structure.

Cortisol

Imputation

Only one individual had cortisol values that fell in the clinical range (Salimetrics Enzyme Immunoassay Kit Manual, 2011), though all cases were within the range of possible values. This individual's score was more than 4 SDs above the mean, so analyses were run with and without this case to investigate its influence. Descriptive

statistics for cortisol samples (before and after 5 imputation iterations) are shown in Table 5 and are comparable to those for non-imputed variables, suggesting that imputation did not change the distribution of these variables. After imputation, 3 participants had negative values for sample 2, 6 had negative values for sample 3, and 3 had negative AUC_g values. A pearson correlation indicated that AUC_g was highly correlated with mean cortisol values calculated from the non-imputed data ($r = .986$, $p < .001$; without potential outlier: $r = .978$, $p < .001$). Given this high correlation, hypothesis tests were conducted using only AUC_g to reduce the risk of Type I error.

Final Sample

A total of 406 individuals had complete data. Demographic characteristics of this final sample are shown in Table 10. The diagnostic groups did not differ in age ($t(404) = -.146$, $p = .884$), education ($t(245.350) = 1.361$, $p = .175$), or with respect to sex ratio ($\chi^2(1) = 1$, $p = .976$) or race ($\chi^2(5) = 2.184$, $p = .823$). Parental education was used as a proxy for socio-economic status, though these data were not available for all cases. The diagnostic groups did not differ in paternal education ($\chi^2(7) = 11.89$, $p = .104$), but did differ in maternal education ($\chi^2(7) = 30.026$, $p < .001$). The control group (Median = completed college/technical school/undergraduate) reported higher maternal education than the CHR group (Median = some college/technical school/undergraduate). This pattern of results did not change when the potential outlier was removed.

Do participants with complete data differ from those excluded due to incomplete data?

Significant comparisons between diagnostic groups (Table 6) on all individual cognitive tests except the Mazes task remain significant in the final sample. The Mazes

task was still marginally significant, in the same direction, both with ($t(404) = 1.871$, $p = .062$), and without ($t(403) = 1.836$, $p = .067$) the potential outlier.

Those with and without cortisol data did not differ in the proportion of CHR participants (Kolmogorov-Smirnov $Z = .726$, $p = .667$) or on cognitive function on the Visuospatial Abilities Factor ($t(499) = -1.484$, $p = .138$) or the Verbal Abilities Factor ($t(499) = .130$, $p = .896$). However, individuals with no cortisol data were younger ($M = 17.989$, $SD = 3.563$) than those with cortisol data ($M = 19.305$, $SD = 4.519$)($t(172.450) = -3.069$, $p = .002$) and also had higher scores on the Attention and Working Memory Factor ($t(499) = -2.591$, $p = .010$) and the Declarative Memory Factor ($t(122.825) = -3.976$, $p < .001$). Differences in the factor scores remained significant when age differences were accounted for using ANCOVA (Attention and Working Memory Factor: $F(1,498) = 4.080$, $p = .044$; Declarative Memory Factor: ($F(1,498) = 19.578$, $p < .001$). These results did not change when the potential outlier was excluded from analyses.

Potential Confounds of Cortisol Values

At the time of saliva collection, 44 participants (10.8%) reported taking prescribed antipsychotics, 68 (16.7%) were taking prescribed antidepressants, and 14 (3.4%) reported taking prescribed stimulants. 304 participants (74.9%) reported not being on any of these psychotropic medications at the time of saliva collection, while 5 participants did not provide information on current medications. Cortisol values did not differ between individuals on versus off antipsychotics ($t(395) = .297$, $p = .766$), stimulants ($t(395) = -.283$, $p = .777$), or antidepressants ($t(395) = -1.584$, $p = .114$). This pattern remained when the potential outlier was removed.

31 individuals (7.6%) reported consuming tobacco after 7 pm the night before saliva collection. These individuals had higher cortisol AUC_g values (No tobacco: M = .3423, SD = .324; Tobacco use: M = .494, SD = .092) both with (t(381) = -2.361, p = .019) and without the potential outlier (t(31.150) = -3.250, p = .087). 20 participants (4.9%) reported consuming alcohol before saliva sampling. No differences in cortisol values due to alcohol use were found when the potential outlier was included in analyses, but a difference was found (No alcohol: M = .334, SD = .268; Alcohol use: M = .469, SD = .228) when this participant was removed (t(403) = -2.210, p = .028). Neither caffeine nor dairy use was associated with differences in average cortisol values with or without the potential outlier included in analyses. 106 individuals (26.1%) reported consuming dairy, 74 (18%) reported consuming caffeine

Time of sample 1 was a significant predictor of average cortisol values both with (β = -.144, t = -2.855, p = .005) and without the potential outlier (β = -.231, t = -4.641, p < .001). The negative regression coefficient indicates that earlier saliva collection was associated with higher cortisol values, reflecting the expected diurnal decline in cortisol levels. In subsequent analyses (e.g., curve estimation), mean substitution was used for the minority of cases that did not have data on covariates. This involved 23 cases without tobacco or alcohol use data and 20 cases for which no sampling time was recorded.

Age as a Moderator of Cortisol and Cognitive Function

Age accounted for a significant amount of variance in cortisol values, (R^2 = .043, F(1,404) = 18.254, p < .001), with a positive regression coefficient (β = .208, t = 4.272, p < .001) indicating an association between higher cortisol and older age. This result did

not change when the potential outlier was removed and alcohol use was included in the model.

Age also accounted for significant variance in cognitive performance on the Attention and Working Memory Factor (R^2 = .047, F(1, 404) = 20.064, p < .001), with a positive regression coefficient indicating better performance with increasing age (β = .218, t = 4.479, p < .001). Similar results were found for the Verbal Abilities Factor (R^2 = .176, F(1, 404) = 86.509, p < .001; β = .420, t = 9.301, p < .001). Age did not account for a significant amount of variance in cognitive scores on the Visuospatial Abilities Factor or the Declarative Memory Factor. This pattern of results was unchanged when the potential outlier was removed.

Summary

In participants with both cortisol and cognitive data, diagnostic groups did not differ with respect to demographics, except for slightly higher maternal education in the control group. In this final sample, both methods of aggregating cortisol data—AUC_g and mean cortisol—were highly correlated, so only AUC_g was used. One case had a mean cortisol value that was potentially an outlier statistically, but not clinically, so analyses were done both with and without this case. Under both circumstances, earlier time of saliva sampling and tobacco use were associated with higher cortisol values, but cortisol did not differ based on medication status or based on consumption of caffeine or dairy after 7 pm the day before saliva collection. The majority of participants were not on any psychotropic medications at the time of saliva sampling. Alcohol use the night before sampling only affected cortisol values when the potential outlier was removed (alcohol use = higher cortisol AUC_g). Higher age was associated with higher aggregated

cortisol values, as well as better performance on the Attention and Working Memory and Verbal Abilities Factors.

Cortisol and Cognition

Group Comparisons

After regressing out the effects of significant covariates, the CHR group (raw scores: M = .3770, SD = .392) had higher cortisol AUC_g scores than the control group (raw: M = .306, SD = .208) using a t-test for unequal variances (t(400.538) = -2.149, one-tailed p = .016), with a Cohen's d effect size of .214. Cognitive factor scores by diagnostic group are shown in Figure 2. As shown, the control group had higher scores on all 4 factors, after regressing out the effects of age on the Attention and Working Memory and Verbal Abilities Factors. Cohen's d values for these contrasts were .283, .501, .264, and .286 for the Visuospatial Abilities, Attention and Working Memory, Verbal Abilities, and Declarative Memory Factors, respectively. Group contrasts did not change when the potential outlier was removed.

Curve Estimation and Hypothesis 1

Curve estimation procedures were run both with and without the potential outlier. Regression coefficients are shown in Table 11. On the Visuospatial Abilities, Attention and Working Memory, and Declarative Memory Factors, excluding the potential outlier did not change the nature, direction, or shape of the association between cortisol and cognitive function—it only affected the level of significance. In contrast to what is shown in Table 11, excluding the potential outlier resulted in a significant positive linear component for the Verbal Abilities Factor in the overall sample (β = .085, t = 1.708, one-tailed p = .044) and in the CHR group (β = .106, t = 1.701, one-tailed p = .045), as well as

a non-significant negative quadratic component in the overall sample (β = -.158, t = -2.13, one-tailed p = .088) and CHR group (β = -.201, t = -1.973, one-tailed p = .105). However, as seen in Figure 3, the high cortisol case appears to fall roughly along the same curvilinear interpolation line as the rest of the cases in both the overall sample and the CHR group. Thus, it appears not to change the nature of the association between aggregated cortisol and cognition and was included in the hypothesis testing analyses. Similarly, rerunning the curve estimation procedure without regressing age effects out of AUC_g values did not result in different results in either the overall sample or in the separate diagnostic groups (Appendix 1).

Figures 4 through 7 show the relationship between aggregated cortisol and cognitive factors, after the effects of age (cortisol and the Attention and Working Memory and Verbal Abilities Factors) and significant moderators of cortisol AUC_g were regressed out. Linear and quadratic components are also shown. For both, given the sample size, power of .58 and .94 for detecting a small and moderate effect sizes (β = .02, .15, respectively) was achieved. In the overall sample, a linear relation was not significant for the Verbal Abilities of Declarative Memory Factors, but was significant for the Visuospatial Abilities and Attention and Working Memory Factors. Negative regression coefficients indicate that higher cortisol values were associated with poorer cognitive function on these significant factors. Aggregated cortisol accounted for 8% of variance in Visuospatial Abilities Factor scores (R^2 = .008, F(1, 404) = 3.280, one-tailed p = .036), and 1% of the variance in Attention and Working Memory Factor scores (R^2 = .01, F(1,404) = 4.096, one-tailed p = .022).

Contrary to prediction, there was little evidence for a significant quadratic component to the relationship between cortisol and cognitive function in the overall sample. Only the Verbal Abilities Factor had a significant quadratic component, where aggregated cortisol accounted for 1.4% of the variance in cognitive scores (R^2 = .014, F(2,403) = 2.823, one-tailed p = .031), with a negative regression coefficient indicating a parabola or "inverted U" shape to the relationship. After a median-split in cortisol values, those below the median showed a positive linear association between aggregated cortisol and the Verbal Abilities Factor (β = .148, t = 2.129, one-tailed p = .017), while those above the median showed a non-significant negative linear association (β = -.024, t = -.336, one-tailed p = .369).

Hypothesis 2

As noted above, significant relationships between cortisol and cognitive function were found in the overall sample on all but the Declarative Memory Factor. Given the sample sizes, power was sufficient in both groups for detecting a medium effect size (.82 and .89 for the control and CHR groups, respectively), but low for detecting a small effect size (.55 and .56, respectively). The linear association on the Visuospatial Abilities Factor was significant in the CHR group, where cortisol accounted for 1.6% of the variance in factor scores (R^2 = .016, F(1,255) = 4.122, one-tailed p = .022). A negative regression coefficient indicated decreasing cognitive performance with increasing cortisol. In the control group, this association was positive, but not significant. The negative linear association found for the Attention and Working Memory Factor in the overall sample was negative and significant in the control group, but negative and not significant in the CHR group. In the control group, cortisol accounted for 2.3% of the

variance in Attention and Working Memory scores (R^2 = .023, F(1, 147) = 3.501, one-tailed p = .032). On the Verbal Abilities Factor, the quadratic component that was significant in the overall sample was significant in the CHR group, accounting for 1.9% variance in factor scores (R^2 = .019, F(2,254) = 2.402, one-tailed p = .047), but not significant in the control group. CHR participants below a cortisol AUC_g median-split showed a non-significant positive relationship between cortisol and Verbal Abilities Factor scores (β = .069, t = .781, one-tailed p = .218). Those above the median-split showed a non-significant negative relationship (β = -.049, t = -.547, one-tailed p = .293).

Using curve estimation alone, it appeared that the linear component differed between diagnostic groups on the Visuospatial Abilities and Attention and Working Memory Factors, while the quadratic component differed on the Verbal Abilities Factor. After performing Fisher's r to z transforms (control z = .073, -.154, -.126; CHR z = -.127, -.065, -.137 for factors 1, 2, and 3, respectively), the relationship between cortisol and cognition differed significantly by diagnostic group on the Visuospatial Abilities Factor (Z = 1.924, one-tailed p = .027), but not on Attention and Working Memory Factor (Z = .858, one-tailed p = .195) or Verbal Abilities Factor (Z = .108, one-tailed p = .457). Thus the relation between cortisol and Visuospatial Abilities Factor scores was more pronounced for the CHR group than for the control group. Power was low (.68) for detecting a small effect size (Z = .1), but sufficient (.93) for detecting a medium effect size (Z = .3).

Post-hoc analyses were also performed in the Verbal Abilities Factor. First, the median split analyses were performed in the control group. Controls below the AUC_g median showed a positive relationship between cortisol and Verbal Abilities Factor

scores (β = .221, t = 2.053, one-tailed p = .022), but no relationship was seen above the median-split (β = .045, t = .360, one-tailed p = .360). Fisher's r to z test determined that the regression below the median did not differ between the control and CHR groups (Z = 1.093, one-tailed p = .137).

Research Question 1

Males and females did not differ on residualized cortisol AUC_g or Attention and Working Memory Factor scores, but did differ on residualized Visuospatial Abilities (t(404) = 3.324, p = .001), Verbal Abilities (t(404) = 2.146, p = .032), and Declarative Memory (t(404) = -4.413, p < .001) Factor scores. Males performed better on the Visuospatial and Verbal Abilities Factors, while females performed better on the Declarative Memory Factor (see Table 13). Linear and quadratic regression coefficients for the relationship between cortisol AUC_g and cognitive factors in males and females are shown in Table 12, means and standard deviations are in Table 13. The results did not differ between the sexes on the Verbal or Declarative Memory Factors. In contrast, there was a sex difference in the relationship between cortisol and cognition on the Visuospatial Abilities Factor, where it was characterized by a significant negative quadratic component in males and a significant negative linear component in females. The quadratic component accounted for a marginally significant 2.1% of the variance in Visuospatial Abilities Factor scores in males (R^2 = .021, F(2,231) = 2.462, p = .087) and the linear component accounted for a marginally significant 1.8% of the variance in females (R^2 = .018, F(1, 170) = 3.046, p = .083). There was no significant linear or quadratic component to the relationship between aggregated cortisol and Attention and Working Memory Factor scores in males, but there was a significant negative linear

component in females. This linear component accounted for a marginally significant 2.1% of the variance in Attention and Working Memory Factor scores in females (R^2 = .021, F(1,170) = 3.678, p = .057). A post-hoc Fisher's z-test determined that the strength of the linear association on Attention and Working Memory Factor did not differ between males and females (Z = .79, p = .430).

Discussion

Neuropsychological Data

Factor Structure

Using all available subjects to maximize power, analyses revealed a factor structure consisting of four latent cognitive factors. The validity of this factor structure is supported both empirically and theoretically. Empirical strengths of the results are that all but two tasks load on a derived factor at .4 or greater (with the remaining two nearing .4), only 3 tasks cross-load, and the final four factor model accounts for a majority of the variance in the 18 cognitive tests on which it was conducted. Further, at least four individual tests load significantly on all derived factors, indicating no "method factors," which are often found in factor analytic studies of cognition in the psychosis spectrum (Dickinson et al., 2010). Alternative analyses forcing 5 or 6 factor models did result in such "method factors." Rerunning the factor analysis using age-regressed cognitive scores also did not significantly change the resultant factor structure.

The four derived factors are consistent with the results of previous factor analytic studies in controls and the psychosis spectrum (Dickinson et al., 2010). For example, prior to constructing the MATRICS battery, Nuechterlein and colleagues (2004) summarized the literature on separable cognitive factors in schizophrenia. Their

quantitative review concluded that visual learning (Visuospatial Abilities Factor), attention/vigilance and working memory (Attention and Working Memory Factor), verbal comprehension (Verbal Abilities Factor), and verbal and visual learning (Declarative Memory Factor) were all reliable separate factors. However, these authors chose to exclude tests of verbal abilities from the MATRICS battery because such skills are "overlearned" and "resistant to change." The fact that re-inclusion of such tasks (e.g., WASI-Vocabulary, WRAT Reading) in the current neuropsychological battery yielded a separable verbal abilities factor adds further support to the validity of these results.

Finally, these results have face validity—the latent factors identified in the current analyses appear to match the cognitive domains of the MATRICS battery. For example, tasks comprising the verbal learning (HVLT-R) and visual learning (BVMT-R) domains load strongly together onto the Declarative Memory Factor, along with the PAM task, which was designed to tap associative declarative memory. Similarly, the MATRICS attention domain (CPT-IP) loaded moderately strongly on the Attention and Working Memory Factor, along with two of the three auditory CPT tasks, which were designed to assess the same domain (Seidman et al., 1998). This factor also appears to be tapping broader executive functions; tests from the MATRICS speed of processing (BACS-SC) and working memory (LNS) domains also load onto it. Finally, the Visuospatial Abilities Factor is comprised of multiple MATRICS executive function domains (visual reasoning and problem solving, nonverbal working memory, one test of the speed of processing domain), as well as the WASI-BD task, which taps spatial visualization and problem solving (PsychCorp, 1999).

Hippocampal- and Cortical-Dependant Cognition in Extracted Factors

Hypotheses in the current study focus on executive functions and declarative memory with respect to associations with cortisol. The Attention and Working Memory and Declarative Memory Factors most directly tap these functions, though functions tapped by the Visuospatial Abilities Factor are also relevant.

All tasks loading strongly onto the Declarative Memory Factor (HVLT-R, PAM, BVMT-R, LNS) assess either verbal or non-verbal declarative memory, supporting it as a unitary factor. As previously mentioned, these processes reliably activate hippocampal brain regions, and to a lesser extent, prefrontal regions.

Similarly, each of the tasks loading significantly onto the Attention and Working Memory Factor (Auditory CPT, BACS-SC, CPT-IP, and LNS) require sustained attention and working memory skills. As previously discussed, these abilities rely heavily on activity of the prefrontal cortex, a region with large numbers of glucocorticoid receptors. However, this cortical region also likely plays a role in performance on the Visuospatial Abilities Factor. Tasks that load heavily onto this factor (WASI-Block Design, Mazes, WMS-Spatial Span, TMT, and Auditory CPT) all require visuospatial processing. A large functional neuroimaging and transcranial magnetic stimulation literature suggests that visuospatial processing/attention relies primarily on the activity of the posterior parietal lobe (Nobre et al., 1997; Kessels et al., 2000). However, more anterior/frontal cortical areas are recruited during these tasks, as well (Sack et al., 2007). This is particularly true when the visuospatial tasks include an aspect of working memory (Kwon et al., 2002) or planning (Basso et al., 2006), both of which are executive processes tapped by the tasks on the Visuospatial Abilities Factor.

The Verbal Abilities Factor

No studies have been published showing an association between cortisol levels and verbal abilities. The Verbal Abilities Factor in the current study is dominated by strong loadings of the WRAT-Reading subtest and the WAIS-3-Vocabulary subtest. These tasks are thought to measure more crystallized cognitive abilities that are learned over time and are due to diffuse neural networks that include broad cortical, temporal, parietal, and cerebellar structures (Gernsbacher & Kaschak, 2003; Highnam & Bleile, 2011). These abilities are typically viewed as more stable over time and are often used as proxy measures of overall or 'premorbid' cognitive ability, given their strong correlations with measures of IQ (Tulsky, 2003). Thus, the Verbal Abilities Factor may be tapping overall cognitive ability.

'g' and Fluid Intelligence

IQ, or general cognitive ability, is often referred to as 'g' by cognitive scientists and is assumed to influence performance on most cognitive measures. In factor analytic studies of multiple cognitive tests, the first extracted factor often includes an aspect of 'g' and accounts for the largest proportion of covariance among measures, even when Maximum Likelihood factor analytic procedures that rely only on unshared variance are used. Consistent with this, the first factor extracted in the present factor analysis accounted for the largest proportion of the variance, and this remained after the Varimax rotation. Factor 1 scores also correlated significantly with all factors except the Verbal Abilities Factor, consistent with the notion that an aspect of overall cognitive ability, including those measured by the Attention and Working Memory and Declarative Memory Factors, were captured by this factor. In contrast, as discussed above, the Verbal Abilities Factor may represent a dissociable crystallized aspect of cognitive ability

influenced by education and other environmental factors. This crystallized intelligence may also play a role in performance on the Declarative Memory and Attention and Working Memory Factors, which were correlated with the Verbal Abilities Factor.

Group Comparisons on Cognitive Factors

The CHR group performed more poorly than the control group on all four cognitive factors. This finding is consistent with a large body of literature that finds cognitive deficits in the prodrome and CHR groups across nearly all cognitive domains, including all of the factors examined in the current study. Effect sizes for these comparisons were small to medium in size, which is also consistent with previous findings. Specifically, in the most thorough quantitative review to-date, Guiliano and colleagues (2012) calculated the average effect sizes across studies of cognitive deficits in CHR groups, relative to controls. They identified 4 studies examining visuo-spatial abilities (Visuospatial Abilities Factor) and found an average effect size of .42. This effect size is slightly larger than that found in the current study (.283), but still small-to-moderate in size. Similarly, CHR individuals performed .39 standard deviations below controls across 7 studies on attention-working memory and .40 SDs below on attention-vigilance across 8 studies. This is comparable to the medium effect size of .501 found for the Attention and Working Memory Factor in the current study. Findings were also consistent with respect to Verbal Abilities Factor (Cohen's d = .264), where 8 previous studies examining language (verbal) function found average mean differences of .51. Finally, Guiliano and co-authors identified 8 previous studies of immediate verbal memory and 5 of non-verbal memory. These studies employed tasks comparable to those on the Declarative Memory Factor in the current study. Average effect sizes of .51 and

.35, respectively, are again comparable to, but slightly larger than the standardized mean difference of .286 found in the current study. None of these previous studies used a factor analytic strategy to assess the cognitive domains of interest. The current study adds to this literature by doing so.

Cortisol and Cognition

As shown in Table 11, the amount of variance in cognitive scores accounted for by significant associations with cortisol was small (1.6% to 1.9% in the CHR group and 2.3% in the control group), in contrast to a previous report on the relationship between *baseline* cortisol and verbal memory in patients with psychosis (Newcomer et al., 1997). R^2 values in that study were much higher (.287). This is to be expected, given that only a subgroup of the CHR group will subsequently be diagnosed with a psychotic disorder. Thus their level of cognitive impairment and cortisol elevations would not be as great as those in a patient sample.

Hypothesis 1; Cortisol and Cognitive Functions

Hypothesis 1, that hippocampal- and prefrontal-mediated cognitive functions would be negatively associated with cortisol, was partially supported. As shown in Figures 4, 5, and 7 the Visuospatial Abilities and Attention and Working Memory Factors were negatively associated with AUC_g, but the Declarative Memory Factor was not. Further, it was predicted that these relationships would be in the form of a quadratic, "inverted U" shape. This was only true for the Verbal Abilities Factor (Figure 6). Thus, increased baseline cortisol was associated with performance decrements on cognitive tasks mediated by the frontal lobe, but not on tasks more heavily dependent on hippocampal functioning. These findings are discussed in turn.

As predicted, a negative association was found between cortisol and executive functions tapped by the Visuospatial and Attention and Working Memory Factors; the association was linear and not quadratic. These results are consistent with a large literature demonstrating negative linear associations between cortisol and executive functions in humans (LeBlanc, 2009; Arnsten, 2010; Lee et al., 2007). None of these studies directly tested a non-linear component. It may be that laboratory stressor studies and naturalistic studies, like the current investigation, are identifying the relationship between cortisol and executive functions on the right arm of the "inverted U" and that experimental manipulations are needed to assess the effects of low cortisol (left arm) on cognitive functions. Indeed, Figures 4 through 7 show possible floor effects at low cortisol values. Testing participants during the low point of the diurnal cortisol rhythm (e.g., in the evening) may be one way to assess the left arm of the cortisol/cognition relationship in future studies. Similarly, indexing cognitive function soon after the administration of a compound that inhibits subsequent glucocorticoid production, like Metyrapone, may be another way. Two such studies have been informative. In the first, Lupien and colleagues (2002) used a hormone removal-replacement protocol and showed that pharmacologically blocking the production of glucocorticoids led to a reduction in memory recall function, but only 20 minutes after encoding. Rimmele et al. (2010) found similar results by using the same compound to block the normative rise in cortisol that occurs throughout the day. No study has investigated working memory or other executive functions using these types of paradigms.

The lack of an association between cortisol and the Declarative Memory Factor may be explained by previous studies that have assessed the effects of manipulating

glucocorticoid levels in humans. The administration of exogenous glucocorticoids can reliably lead to decrements in declarative memory abilities (Het et al., 2005). However, at least two studies have found that experimentally-manipulated cortisol increases lead only to decrements in executive functions and not to poorer declarative memory performance (Young et al., 1999; Lupien et al., 1999), suggesting that it may take higher levels of cortisol to impair declarative memory than executive functions (Lupien et al., 2007). Since the current study examined levels of circulating cortisol at baseline, as opposed to levels following a pharmacological or psychosocial stressor, elevated cortisol levels may not have been sufficient enough to affect declarative memory. It is also possible that the lack of association between cortisol and declarative memory is due to the type of test stimuli used in the current study.

Lupien and colleagues (2007) reviewed findings on stress, cortisol, and cognition in studies that either examined naturally circulating baseline levels of cortisol or stress-induced increases in cortisol. They found that the affective valence of stimuli to-be-remembered is important. For example, when individuals are being asked to remember stimuli with a negative emotional valence, increased levels of cortisol are actually associated with *better* declarative memory. Conversely, in studies of memory for non-emotionally valenced stimuli, the majority of studies find no relationship between cortisol and cognition when cortisol is not manipulated externally. Thus, using emotionally valenced stimuli in future studies may be a way to better investigate the relationship between cortisol and declarative memory when experimental stressors are not used.

Alternatively, it may be the case that the lack of association between cortisol and the Declarative Memory Factor is due to differences in the effects of glucocorticoids on

the hippocampus and frontal lobe. As stated, neuroimaging studies investigating hippocampal volume reductions in CHR samples have resulted in equivocal findings (Witthaus et al., 2010), though studies in individuals with established psychotic disorders reliably find volume reductions (Steen et al., 2006; Wright et al., 2000). This suggests that hippocampal structural abnormalities may only be reliably detectable in the early stages of psychotic illness (Pantelis, 2007). Studies using clinical methods of identifying prodromal youth, like the current study, suggest a conversion rate of 25% - 40% (Yung et al., 2003, Cannon et al., 2008). This means that 303 to 341 of the current study's 406 participants would *not* be expected to be in the early stages of psychotic illness and thus would be less likely to manifest hippocampal abnormalities. Since it is hypothesized that overactivity or dysregulation of the HPA axis is involved in early psychotic processes, and that these are associated with deficits in hippocampal-mediated cognitive function, a strong association between baseline cortisol and declarative memory may only be seen in those who later develop psychosis. Future studies with longitudinal follow-ups should explore differential relationships at baseline in those who subsequently develop a psychotic disorder. Conversely, prefrontal structural abnormalities are more consistently found in CHR individuals regardless of whether they subsequently develop a psychotic disorder (Wood et al., 2008; Smieskova et al., 2010; Takahashi et al., 2009). This supports the associations found in the current study. Group differences in the association between cortisol and cognitive functions are addressed in hypothesis 2.

Given the lack of association between cortisol and verbal functions found in the literature on diagnosed schizophrenia patients (e.g., Newcomer et al., 1994; 1998), it is unlikely that the "inverted U" association found between the Verbal Abilities Factor and

cortisol in the current study is due to the direct effects of glucocorticoids on verbal skills. Rather, the verbal factor may be tapping overall crystallized cognitive abilities, which are impaired in the psychosis prodrome (Guiliano et al., 2012). There is some preliminary evidence that such global impairments are associated with glucocorticoid levels (Jameison et al., 2001), suggesting that this may be an alternative explanation for the pattern of findings on Verbal Abilities Factor.

Another possible explanation concerns the role of motivation in performance on Verbal Abilities Factor tasks. Post-hoc analyses indicate that the relationship with cortisol in the overall sample is driven by a strong positive association in individuals with lower cortisol, but no association in those with high cortisol. This relationship in individuals with low cortisol did not differ between diagnostic groups (but was only significant in the control group). This positive association at low cortisol levels may be an artifact of motivation or alertness, which likely varies with increasing low levels of cortisol. In other words, motivation, which is associated with performance on tests of broad intelligence and verbal ability (Duckworth et al., 2011), may be lacking in individuals who show very low levels of cortisol in the lab. Indeed, three of the four tasks that load heavily onto the Verbal Abilities Factor (WRAT-4, WASI-V, and WASI-BD) have performance-related discontinue points. Thus, individuals who are more motivated to continue trying hard on these tasks when confronted with difficult test items may be more likely to score higher. Feeling stressed in the face of difficult questions, or being more sensitive to the effects of stress under such conditions, may be motivating. In contrast, individuals who are less motivated are more likely to hit a discontinue point.

Individuals who are less reactive to stress may not feel the same motivation to try hard when confronted with difficult test questions.

Hypothesis 2; Diagnostic Group Differences

Hypothesis 2, that the relationship between cortisol and cognitive functions are different in the control and CHR groups, was partially supported. No differences were observed on the Declarative Memory Factor, where neither group showed an association with cortisol. In contrast, the CHR group showed a stronger significant relation between Visuospatial Abilities Factor performance and cortisol elevations. While only one diagnostic group showed a significant association with cortisol on the Attention and Working Memory (control group) and Verbal Abilities (CHR group) Factor, the magnitude of associations did not differ between groups on these factors. These findings will be discussed, in turn.

The Visuospatial Abilities Factor shows the predicted difference between the diagnostic groups, with no significant association with cortisol in the control group, but a significant negative linear component in the CHR group. Given that the CHR group showed elevated cortisol values, this difference in association supports the hypothesis that the CHR group is further along the "inverted U" relationship than the control group. In other words, the relationship in controls between cortisol and visuospatial abilities comprises the top of the "inverted U," while the relationship in CHR participants comprises the right arm of the "inverted U." This accords well with studies showing that laboratory induced elevations in cortisol also lead to a negative association (like that seen in the CHR group) between cortisol and executive functions in healthy controls (Lupien et al., 2007; Kirshbaum et al., 1993; Porcelli et al., 2008).

This finding also replicates the results of a series of studies conducted by Newcomer and colleagues in adults with schizophrenia (1994; 1998). These authors found a differential pattern of association between cortisol and cognition (declarative memory) both before and after 4 days of dexamethasone administration. Patients failed to show a negative association after treatment that was seen in healthy controls, presumably due to ceiling effects on already elevated cortisol. In contrast, patients showed an inverse association between cortisol and memory before treatment that was not seen in controls. The authors suggested that these differences were due to increased sensitivity to glucocorticoid-induced cognitive effects in the psychosis spectrum. The current investigation is the first to show these effects in CHR youths, extending the findings to a different cognitive domain.

In controls, the Visuospatial Abilities Factor shows the opposite pattern of results as the Attention and Working Memory Factor, in that there was a negative linear association between cortisol and the Attention and Working Memory Factor. As previously discussed, there is likely some overlap in the brain regions activated by the visuospatial abilities tapped on the Visuospatial Abilities Factor and the attention and working memory abilities tapped by Attention and Working Memory Factor (Glabus et al., 2003). However, performance on visuospatial tasks is also heavily reliant on the posterior parietal lobe (Nobre et al., 1997; Kessels et al., 2000), which is not a primary area of localization for glucocorticoid receptors (de Kloet et al., 1986; McEwen, 1998). This difference in activated brain regions may explain the different pattern of results. Given the large number of glucocorticoid receptors located in frontal areas (de Kloet et al., 1986; McEwen, 1998), it is likely that neuropsychological tasks that depend more

exclusively on this region are more sensitive to the effects of glucocorticoids. This explains the significant negative association in controls on the Attention and Working Memory Factor but not on the Visuospatial Abilities Factor. The association with cortisol did not differ between control and CHR groups on the Attention and Working Memory Factor.

Sex Differences

Study results, parsed by sex, are shown in Figure 12. There was no evidence for sex differences in the relationship between cortisol and the Verbal Abilities or Declarative Memory Factors. While only women showed a significant negative linear relationship between cortisol and Attention and Working Memory Factor scores, the strength of this relationship did not differ between men and women. However, a difference was found for the Visuospatial Abilities Factor, where there was a significant negative linear association with cortisol in females and a significant negative quadratic association with cortisol in males. There was more variability between sexes in cognitive scores (males had higher Visuospatial Abilities Factor scores) than in cortisol values, which did not differ. Thus, sex differences in the relationships between cortisol and cognition are likely due to either differences between males and females in cognitive performance, which are commonly found, or in stress reactivity (Kudielka & Kirschbaum, 2005; Kajantie & Phillips, 2006). However, sex and developmental period (e.g., age) were comparable between diagnostic groups, suggesting that these differences are not likely to significantly affect the results of the study's hypotheses.

Strengths and Limitations

Finally, a few limitations of the current study are important to note. First, a goal of the present study was to assess the effects of cortisol on the function of focal brain regions. However, neuropsychological measures are limited in their capacity to tap specific, dissociable cognitive functions. Furthermore, although certain cognitive functions are more dependant on certain brain regions, most, including declarative memory and executive functions, are subserved by multiple areas and circuits. Thus, each of the cognitive tasks and cognitive factors in the current study likely index multiple cognitive processes which would not be expected to map onto highly focal or non-overlapping brain regions. Adding a functional neuroimaging component to future studies will be necessary to make inferences about how regional brain activation is affected by varying levels of cortisol.

Second, the true psychiatric outcome of CHR subjects is not yet known. Thus, the question of whether certain patterns of association between cortisol and cognition discriminate true prodromal cases from individuals who will not develop psychosis will have to be addressed in future studies.

Third, the measurement of cortisol was focused on basal, rather than stress-induced or pharmacologically-reduced levels. Thus, the variability in cortisol levels may not have been sufficient to thoroughly test the "inverted U" hypothesis. The current results may also not generalize to stress-induced measures of cortisol. Future studies assessing a broader range of cortisol variability will be important.

Despite these limitations, the current study contributes meaningfully to the field, given its many strengths. Principle among these is the very large sample that resulted in sufficient power to detect medium effect sizes in both hypotheses. The large sample also

supported the use of multivariate analyses and data aggregation. This, combined with multiple tests tapping each cognitive domain of interest also allowed for the measurement of latent constructs. Aggregating across multiple cortisol measurements also resulted in a more reliable index of basal cortisol than most studies in the psychosis spectrum. Finally, the current study improves upon previous reports by accounting for psychotropic medication use and relying on CHR and control samples that are well-matched and primarily medication-naïve.

Summary and Study Conclusions

Factor analysis on a broad range of neuropsychological tasks resulted in the extraction of Visuospatial Abilities, Attention and Working Memory, Verbal Abilities, and Declarative Memory Factors. These factors are consistent with those found in previous studies of individuals at-risk for psychosis. Subsequent analyses finding small-to-moderate sized cognitive performance deficits in CHR subjects, relative to controls, replicate the results of previous reports.

Partial support was found for the hypothesized relations between cortisol and cognition. Although the quadratic components of these relations were only observed in some analyses, they were not pronounced in the hypothesized cognitive domains. In contrast, the linear components were more pronounced in the overall sample and supported an inverse relation between cortisol and cognitive functions, most likely mediated by the prefrontal cortex. No relationship was found between cortisol and declarative memory abilities. Future studies using stress tests will help determine whether higher levels of glucocorticoids are necessary to adversely affect declarative

memory abilities, as has been found, and whether the nature of these effects differ in CHR and healthy individuals.

Linear and not quadratic relationships with cortisol were found for frontal-mediated cognitive functions in the CHR and control groups, separately. While this relationship did not differ between groups on attention and working memory abilities, the CHR group showed a greater adverse impact of cortisol on visuospatial abilities, consistent with an "inverted U." Future research testing the relationship between various cognitive domains and both higher and lower levels of cortisol will also be important to further test the "inverted U" hypothesis. It may be that cortisol differentially affects some executive functions in the prodrome more than others. Similarly, despite elevated baseline cortisol in the CHR group, no relationship with deficits in declarative memory abilities was found, suggesting that the effects of cortisol on putative hippocampal function may occur in only true prodromal cases or later in the progression of psychotic illness. Future research using longitudinal designs may help better understand the time course of the effects of the HPA axis on the onset and development of psychosis.

Finally, in both the CHR and control groups, variability in cortisol only accounted for about 2% of the variance in cognitive functions versus a previous report of roughly 29% in schizophrenia. This is in contrast to cognitive deficits in the CHR group that had Cohen's d effect sizes of roughly .26 to .5. Thus, cortisol appears to be playing a much smaller role in the cognitive deficits seen in CHR individuals than in established psychotic disorders, where cognitive deficits tend to be larger. It may be that the effects of HPA dysregulation on cognition in psychosis are cumulative, developing over time, rather than predating the onset of sub-clinical psychotic symptoms. It will be important

for future research to determine whether the size of this relationship differs in CHR youths who do and do not eventually develop a psychotic disorder. Such research has the potential to improve the positive predictive power of algorithms that predict subsequent psychoses. This has powerful implications for targeted preventive intervention.

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Table 1

Descriptive Statistics

Task	n	Min	Max	M	SD	Skewness
WRAT-4	500	31	70	58.91	7.150	-.966
WASI-V	501	23	77	56.52	9.968	-.235
WASI-BL	501	3	71	46.60	15.555	-.704
Babble	491	0	16	2.79	1.719	1.384
Auditory CPT QA % Hits	491	50.00	100.00	95.7376	6.68662	-2.970
Auditory CPT Q3A-MEM % Hits	490	29.17	100.00	84.4752	13.01447	-1.187
Auditory CPT Q3A-INT % Hits	489	8.00	100.00	57.0675	20.87144	-.126
TMT	501	11.25	85.00	28.3356	11.00277	1.704
BACS-SC	500	24	100	60.27	12.997	.215
HVLT-R	501	9	36	26.26	4.757	-.530
WMS-3-SS forward	501	3	14	8.87	2.001	-.059
WMS-3-SS backward	499	2	15	8.19	1.958	-.381
LNS	500	1	24	15.39	3.722	-.317
Mazes	501	2	26	20.45	4.855	-1.072
BVMT	499	3	36	26.32	5.994	-.801
Category Fluency	500	6	45	24.23	5.911	.263
CPT-IP Average	490	.11	4.24	2.5770	.78429	-.412
UPSIT	472	11	40	33.72	4.083	-1.698
PAM	336	.00	1.00	.6330	.20771	-.513

Note. 307 cases had valid data for all neuropsychological variables

Table 1: Descriptive statistics for each of the raw neuropsychological tasks are listed. More cases were missing PAM data because the task was revised during its development and the current version was introduced after the study began.

Table 2

Correlations among cognitive tasks

Task	WASI-V	WASI-BD	Babble	Auditory CPT QA % Hits	CPT Q3A-MEM % Hits	Auditory CPT Q3A-INT % Hits	BACS-SC	HVLT-R	WMS-3-SS Forward	WMS-3-SS Backward	LNS	Mazes	BVMT-R	Category Fluency	CPT-IP Average	UPSIT	PAM	TMT
WRAT-4	.713***	.468***	.007	.337***	.324***	.354***	.358***	.290***	.206***	.269***	.547***	.232***	.303***	.246***	.544***	.274***	.257***	.247***
n	500	500	491	491	490	489	499	500	500	498	499	500	498	499	489	471	336	500
WASI-V		.531***	0.07	.343***	.342***	.333***	.381***	.364***	.194***	.322***	.561***	.288***	.380***	.392***	.545***	.349***	.253***	.322***
n		501	491	491	490	489	500	501	501	499	500	501	499	500	490	472	336	501
WASI-BD			.056	.249***	.232***	.427***	.366***	.210***	.404***	.502***	.414***	.525***	.473***	.264***	.360***	.288***	.216***	.374***
n			491	491	490	489	500	501	501	499	500	501	499	500	490	472	336	501
Babble				.009	-0.039	.075	.031	.014	.016	.056	.088*	.123**	-.029	.093*	-.004	.078	.001	.098*
n				487	486	485	490	491	491	489	490	491	489	490	481	465	333	491
Auditory CPT QA % Hits					.423***	.349***	.318***	.231***	.183***	.254***	.358***	.223***	.278***	.275***	.370***	.219***	.222***	.220***
n					490	489	490	491	491	490	490	491	489	490	481	465	333	491
Auditory CPT Q3A-MEM % Hits						.347***	.383***	.275***	.175***	.255***	.420***	.162***	.268***	.292***	.399***	.199***	.159**	.266***
n						488	489	490	490	489	489	490	488	489	480	464	333	490
Auditory CPT Q3A-INT % Hits							.368***	.214***	.281***	.346***	.403***	.327***	.250***	.244***	.363***	.187***	.193***	.310***
n							488	489	489	488	488	489	487	488	479	464	332	489
BACS-SC								.354***	.359***	.381***	.420***	.360***	.375***	.359***	.427***	.313***	.294***	.394***
n								500	500	498	499	500	498	499	489	471	335	500
HVLT-R									.131**	.232***	.445***	.109*	.385***	.395***	.269***	.299***	.434***	.176***
n									501	499	500	501	499	500	490	472	336	501
WMS-3-SS forward										.510***	.374***	.294***	.351***	.159***	.278***	.148**	.124*	.312***
n										499	500	501	499	500	490	472	336	501
WMS-3-SS backward											.408***	.380***	.407***	.217***	.334***	.240***	.228***	.339***
n											498	499	497	498	488	470	335	499
LNS												.211***	.440***	.372***	.534***	.298***	.325***	.256***
n												500	498	499	489	471	336	500
Mazes													.306***	.289***	.237***	.184***	.164**	.409***
n													499	500	490	472	336	501
BVMT-R														.293***	.304***	.286***	.408***	.168***
n														498	488	470	334	499
Category Fluency															.287***	.251***	.249***	.290***
n															489	471	336	500
CPT-IP Average																.280***	.316***	.277***
n																464	333	490
UPSIT																	.256***	.168***
n																	317	472
PAM																		.047
n																		336

Note. Pearson r values are shown. * p ≤.05; ** p < .01; *** p < .001

Table 2: All cognitive tasks except the Babble task were highly intercorrelated in the overall sample.

Table 3

Do Cognitive Variables Account for Significant Variance in PAM Scores?

Task	r	R^2	F Change	df1	df2	p
WRAT-4	.257	.066	23.577	1	334	.000
WASI-V	.253	.064	22.808	1	334	.000
WASI-BD	.216	.047	16.348	1	334	.000
Babble	.001	.000	.000	1	331	.984
Auditory CPT QA % Hits	.222	.049	17.086	1	331	.000
Auditory CPT Q3A-MEM % Hits	.159	.025	8.636	1	331	.004
Auditory CPT Q3A-INT % Hits	.193	.037	12.744	1	330	.000
TMT	.072	.005	1.752	1	334	.187
BACS-SC	.294	.086	31.462	1	333	.000
HVLT-R	.434	.189	77.703	1	334	.000
WMS-3-SS forward	.124	.015	5.190	1	334	.023
WMS-3-SS backward	.228	.052	18.197	1	333	.000
LNS	.325	.106	39.580	1	334	.000
Mazes	.164	.027	9.185	1	334	.003
BVMT-r	.408	.166	66.114	1	332	.000
Category Fluency	.249	.062	22.101	1	334	.000
UPSIT	.256	.066	22.087	1	315	.000

Table 3: Results of linear regression models are shown in which PAM scores were regressed on each cognitive task, separately. R^2 values represent the proportion of variance in PAM scores accounted for by each cognitive task, while the F statistic and p values indicate the significance of each model. The table shows that performance on all tasks in the neuropsychological battery, except Babble and TMT, significantly predicts PAM scores.

Table 4

Descriptive Statistics for Cognitive Data After Imputation

Task	n	Cases Imputed	Min	Max	M	SD	Skewness
WRAT-4	501	1	31	70	58.90	7.146	-.962
WASI-V	501	0	23	77	56.52	9.968	-.235
WASI-BD	501	0	3	71	46.60	15.555	-.704
Babble	501	10	-2	16	2.81	1.730	1.294
Auditory CPT QA % Hits	501	10	50.00	103.89	95.641	6.719	-2.861
Auditory CPT Q3A-MEM % Hits	501	11	29.17	100.00	84.292	13.019	-1.141
Auditory CPT Q3A-INT % Hits	501	12	-26.63	100.00	56.677	21.235	-0.217
BACS-SC	501	1	24	100	60.35	13.082	.235
HVLT-R	501	0	9	36	26.26	4.757	-.530
WMS-3-SS Forward	501	0	3	14	8.87	2.001	-.059
WMS-3-SS Backward	501	2	2	15	8.20	1.957	-.382
LNS	501	1	1	24	15.40	3.719	-.320
Mazes	501	0	2	26	20.45	4.855	-1.072
BVMT-R	501	2	3	36	26.32	5.993	-.798
Category Fluency	501	1	6	45	24.23	5.906	.264
CPT-IP Average	501	11	.11	4.24	2.576	0.782	-0.398
UPSIT	501	29	11	42	33.675	4.056	-1.605
PAM	501	165	.00	1.18	0.633	0.212	-0.444
TMT (inverse)	501	0	.01	.09	0.040	0.013	0.559

Table 4: Results of a Fully Conditional Specification iterative Markov Chain Monte Carlo (MCMC) data imputation are shown. Descriptive statistics are comparable to those before imputation (shown in Table 1).

Table 5

Cortisol Values by Group Before and After Imputation

	Control					CHR				
Cortisol	n	Min	Max	M	SD	n	Min	Max	M	SD
					Before Imputation					
Lab 1	150	.020	.757	0.209	0.169	257	0.015	2.338	0.236	0.223
Lab 2	147	.012	.750	0.142	0.106	255	0.010	2.516	0.172	0.220
Lab 3	136	.010	.650	0.120	0.099	221	0.010	0.950	0.153	0.130
M	151	.030	.563	0.159	0.105	260	0.013	2.427	0.194	0.205
					After Imputation					
Lab Cortisol 1	151	0.020	0.757	0.210	0.169	260	0.015	2.338	0.234	0.223
Lab Cortisol 2	151	-0.168	0.750	0.138	0.109	260	-0.027	2.516	0.173	0.219
Lab Cortisol 3	151	-0.154	0.650	0.124	0.110	260	-0.110	1.639	0.171	0.182
AUC_g	151	-0.127	1.170	0.305	0.207	260	-0.025	4.505	0.376	0.390
					Final Sample					
Lab Cortisol 1	149	.020	.757	0.210	0.170	257	.015	2.338	0.235	0.224
Lab Cortisol 2	149	-.168	.750	0.139	0.109	257	-.027	2.516	0.174	0.220
Lab Cortisol 3	149	-.154	.650	0.124	0.110	257	-.110	1.639	0.172	0.183
AUC_g	149	-.13	1.17	0.306	0.208	257	-.03	4.505	0.377	0.392

Note. Values in micrograms/deciliter

Table 5: Cortisol values, both aggregated and by individual sample, are shown. Statistics both before and after a Fully Conditional Specification iterative Markov Chain Monte Carlo (MCMC) data imputation are listed. The Final sample includes only those participants with both cortisol and neuropsychological data.

Table 6

Decscriptive Statistics and Diagnostic Group Contrasts

Statistic	WASI Vocabulary	BACS Symbol Coding	Letter-Number Sequencing	Auditory CPT QA % Hits*	Auditory CPT Q3A-MEM % Hits*	CPT-IP Average d'	Auditory CPT Q3A-INT % Hits	WMS-3 Spatial Span Forward	Category Fluency	HVLT-R Total*	WMS-3 Spatial Span Backwards	BVMT-R	WRAT Reading	PAM	WASI Block Design	Trails A	UPSIT	NAB Mazes	Babble*
Control Group																			
n	176	176	176	175	174	171	175	176	176	176	175	176	176	107	176	176	170	176	175
M	59.16	63.69	16.34	97.25	87.73	2.77	61.33	9.27	25.39	27.15	8.54	27.34	60.03	0.67	48.76	26.85	34.24	20.92	2.75
SD	9.12	13.06	3.41	3.91	10.71	0.76	20.83	1.99	5.86	4.24	1.85	5.71	6.58	0.20	14.95	10.60	3.76	4.50	1.44
CHR Group																			
n	325	324	324	316	316	319	314	325	324	325	324	323	324	229	325	325	302	325	316
M	55.09	58.42	14.88	94.90	82.68	2.47	54.69	8.65	23.60	25.77	8.00	25.77	58.30	0.62	45.44	29.14	33.43	20.20	2.82
SD	10.13	12.60	3.79	7.69	13.81	0.78	20.55	1.98	5.85	4.95	1.99	6.08	7.38	0.21	15.77	11.15	4.23	5.02	1.86
Group Comparisons																			
t	4.45	4.42	4.27	4.49	4.49	4.14	3.40	3.38	3.27	3.28	2.96	2.82	2.60	2.08	2.29	-2.24	2.09	1.59	-0.47
df	499	498	498	485.99	434.70	488	487	499	498	408.61	497	497	498	334	499	499	470	499	437.24
p	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.01	0.04	0.02	0.03	0.04	0.11	0.64
Cohen's d	0.42	0.41	0.41	0.41	0.41	0.39	0.32	0.32	0.31	0.30	0.28	0.27	0.25	0.25	0.22	-0.21	0.20	0.15	-0.04

Note. *t-test for unequal variances

Table 6: Descriptive statistics for each cognitive task, parsed by diagnostic group, are listed. Results of independent samples t-tests are also shown. Where Levene's test of heterogeneity of variance was significant, the t-test for unequal variances was used. The CHR group performed more poorly than the control group on all tasks except NAB Mazes and the Babble task.

Table 7

Eigenvalues and Variance Accounted for

	Factor Analysis without Data imputation			Factor Analysis with Data Imputation			Final Factor Analysis		
Factor	Eigenvalue	% of Variance Explained	Cumulative % Variance Explained	Eigenvalue	% of Variance Explained	Cumulative % Variance Explained	Eigenvalue	% of Variance Explained	Cumulative % Variance Explained
1	6.467	34.038	34.038	6.505	34.235	34.235	6.500	36.110	36.110
2	1.545	8.134	42.172	1.556	8.189	42.424	1.546	8.588	44.699
3	1.212	6.377	48.549	1.188	6.254	48.678	1.188	6.601	51.299
4	1.112	5.854	54.403	1.106	5.821	54.499	1.052	5.844	57.144
5	1.035	5.446	59.849	1.038	5.464	59.962	.955	5.304	62.448
6	.869	4.573	64.422	.884	4.652	64.614	.786	4.368	66.816
7	.794	4.179	68.601	.784	4.125	68.739	.754	4.189	71.005
8	.769	4.048	72.649	.754	3.968	72.707	.692	3.846	74.851
9	.681	3.586	76.235	.691	3.636	76.343	.633	3.516	78.366
10	.633	3.330	79.565	.626	3.294	79.637	.586	3.257	81.623
11	.578	3.040	82.605	.580	3.055	82.692	.559	3.105	84.728
12	.562	2.958	85.563	.556	2.927	85.618	.497	2.761	87.489
13	.516	2.716	88.279	.494	2.602	88.220	.466	2.587	90.076
14	.465	2.446	90.726	.465	2.448	90.668	.434	2.413	92.489
15	.431	2.270	92.996	.434	2.286	92.954	.426	2.366	94.855
16	.409	2.151	95.147	.424	2.230	95.185	.363	2.019	96.875
17	.359	1.892	97.039	.354	1.864	97.049	.317	1.760	98.635
18	.316	1.661	98.699	.317	1.667	98.716	.246	1.365	100.000
19	.247	1.301	100.000	.244	1.284	100.000			

Table 7: Results of maximum likelihood factor analysis, performed both before and after data imputation, are shown. In both, a 5 factor model was optimal and accounted for roughly the same amount of variance in raw cognitive scores. The Babble task was excluded for the final factor analysis, where a 4 factor model was optimal, but accounted for roughly 2% less variance in the original cognitive scores.

Table 8

Communalities for Factor Analyses: Before and After Data Imputation

Task	Before Imputation	After Imputation	Final Factor Analysis
WRAT-4	.708	.720	.717
WASI-V	.761	.749	.722
WASI-BD	.706	.716	.747
Auditory CPT QA % Hits	.297	.306	.315
Auditory CPT Q3A-MEM % Hits	.386	.384	.395
Auditory CPT Q3A-INT % Hits	.343	.366	.374
BACS-SC	.466	.464	.464
HVLT-R	.515	.496	.456
WMS-3-SS Forward	.487	.491	.354
WMS-3-SS Backward	.510	.512	.461
LNS	.607	.601	.562
Mazes	.512	.506	.417
BVMT-R	.524	.521	.514
Category Fluency	.401	.419	.284
CPT-IP Average	.513	.521	.497
UPSIT	.221	.224	.217
PAM	.372	.355	.372
TMT (inverse)	.424	.439	.371
Babble	.034	.027	

Table 8: Communality values are shown. These indicate the proportion of variance in each cognitive task accounted for by factors in factor analyses performed before and after data imputation, as well as in the final 4 factor model excluding the Babble task. Communalities of .40, .70, and .80 are considered to be low, moderate, and high, respectively.

Table 9

Rotated Factor Loadings Before and After Data Imputation

	Factors Before Imputation					Factors After Imputation					Factors Without Babble			
Task	1	2	3	4	5	1	2	3	4	5	1	2	3	4
WRAT-4	.759*	.135	.174	.281	.063	.134	.763*	.201	.278	.045	.150	.261	.763*	.212
WASI-V	.744*	.106	.293	.241	.229	.108	.725*	.310	.256	.224	.224	.267	.721*	.285
WASI-BD	.445*	.572*	.183	-.007	.382	.577*	.454*	.215	-.037	.360	.722*	-.007	.419*	.224
Babble	.012	-.001	.009	.016	.183	.002	.005	.011	.020	.163				
Auditory CPT QA % Hits	.200	.140	.199	.429*	.117	.160	.204	.212	.420*	.131	.181	.445*	.204	.207
Auditory CPT Q3A-MEM % Hits	.172	.118	.193	.546*	.088	.127	.173	.184	.536*	.130	.152	.559*	.179	.168
Auditory CPT Q3A-INT % Hits	.219	.323*	.112	.361	.219	.359	.237	.104	.354	.212	.409*	.380	.223	.107
BACS-SC	.134	.298	.312	.442*	.257	.308	.136	.298	.436*	.268	.365	.476*	.133	.294
HVLT-R	.127	.023	.662*	.238	.055	.019	.096	.629*	.288	.087	.037	.302	.121	.591*
WMS-3-SS Forward	.045	.650*	.074	.235	.037	.655*	.041	.078	.231	.030	.529*	.223	.013	.155
WMS-3-SS Backward	.129	.623*	.195	.212	.150	.627*	.123	.188	.215	.149	.585*	.237	.088	.236
LNS	.420*	.299	.389*	.435*	-.027	.297	.398*	.386	.453*	-.009	.230	.432*	.394	.409*
Mazes	.118	.408*	.101	.070	.562*	.420*	.142	.093	.037	.548*	.617*	.121	.126	.070
BVMT-R	.188	.441*	.536*	.058	.063	.426*	.158	.549*	.079	.080	.393	.108	.128	.576*
Category Fluency	.120	.019	.420*	.299	.347	.020	.102	.399*	.319	.383	.189	.354	.139	.322
CPT-IP Average	.454*	.211	.206	.467*	.038	.229	.454*	.195	.473*	.027	.195	.458*	.447*	.224
UPSIT	.209	.122	.346	.144	.149	.130	.195	.357	.145	.142	.174	.166	.195	.348
PAM	.114	.138	.573*	.104	-.028	.110	.162	.557*	.069	-.050	.051	.070	.157	.583*
TMT (inverse)	.111	.264	.012	.337	.478*	.281	.130	-.027	.326	.486*	.463*	.368	.136	-.050

Note. * Factor loadings greater than .40

Table 9: Factor loadings by analysis are shown. A loading threshold of .4 is typically used for interpretation while items that load at .5 are considered 'strong' loaders.

Table 10

Sample Demographics by Diagnostic Group

	Control Group (n = 149)		CHR Group (n=257)	
Demographic	n (%)	M (SD)	n (%)	M (SD)
Sex				
male	86 (57.7)		148 (57.6)	
female	63 (42.3)		109 (42.4)	
Age		19.25 (4.78)		19.32 (4.38)
Education		12.17 (3.52)		11.72 (2.64)
Race				
Interracial	17 (11.4)		36 (14)	
Asian	14 (9.4)		18 (7)	
Black	23 (15.4)		37 (14.4)	
Central/S. American	5 (3.4)		14 (5.4)	
White	86 (57.7)		146 (56.8)	
Other	4 (2.7)		6 (2.3)	
Paternal Education (median)	Some College		Some College	
Maternal Education (median)	Completed College		Some College	
Prodromal Syndrome Criteria				
APS			231 (89.9)	
BIPS			7 (2.7)	
GRD			47 (18.3)	
Youth & Schizotypy			35 (13.6)	

Table 10: Demographics, parsed by diagnostic group, are shown. Diagnostic groups only differed significantly on maternal education.

Table 11

Curve Fit: Relationship of Cortisol with Cognitive Factors

	Visuospatial Abilities (Factor 1)				Attention & Working Memory (Factor 2)				Verbal Abilities (Factor 3)				Declarative Memory (Factor 4)			
Component	R^2	β			R^2	β			R^2	β			R^2	β		
Whole Sample (n=406)																
Linear	.008	-0.09	-1.811	.036*	.010	-0.1	-2.024	.022*	.003	0.052	1.048	.148	.001	0.035	0.706	.240
Quadratic	.090	0.01	0.134	.447	.010	0.024	0.322	.374	.014	-0.158	-2.13	.017*	.002	0.036	0.486	.314
Control Group (n=149)																
Linear	.005	0.073	0.882	.190	.023	-0.153	-1.871	.032*	.008	0.088	1.077	.142	.000	-0.009	-0.107	.458
Quadratic	.007	0.048	0.523	.301	.035	-0.124	-1.353	.089	.016	-0.098	-1.067	.144	.000	0.018	0.189	.425
CHR Group (n=257)																
Linear	.016	-0.126	-2.03	.022*	.004	-0.065	-1.045	.149	.004	0.059	0.949	.172	.004	0.065	1.034	.151
Quadratic	.018	0.076	0.748	.228	.004	-0.12	-0.12	.453	.019	-0.201	-1.973	.025*	.004	0.026	0.249	.402

Note. One-tailed p-values used. * $p < .05$

Table 11: Results of the curve estimation procedure, performed on both the overall sample and separately on each diagnostic group, are summarized. R^2 values indicate the proportion of variance in factor scores accounted for by cortisol AUC_g in each model. β values indicate the regression coefficient for each linear or quadratic model, while t statistics and p values indicate the significance of these coefficients.

Table 12

Curve fit: Relationship of cortisol with cognitive functions parsed by sex

	Visuospatial Abilities (Factor 1)				Attention & Working Memory (Factor 2)				Verbal Abilities (Factor 3)				Declarative Memory (Factor 4)			
Component	R^2	β			R^2	β			R^2	β			R^2	β		
Whole sample (n=406)																
Linear	.008	-0.09	-1.811	.036*	.010	-0.1	-2.024	.022*	.003	0.052	1.048	.148	.001	0.035	0.706	.240
Quadratic	.090	0.01	0.134	.447	.010	0.024	0.322	.374	.014	-0.158	-2.13	.017*	.002	0.036	0.486	.314
Males (n=234)																
Linear	.002	-0.041	-0.624	.267	.004	-0.067	-1.024	.154	.000	-0.01	-0.15	.441	.000	-0.022	-0.329	.372
Quadratic	.021	-0.193	-2.128	.017*	.011	0.11	1.206	.115	.015	-0.167	-1.838	.034*	.001	0.023	0.253	.401
Females (n=172)																
Linear	.018	-0.133	-1.745	.042*	.021	-0.146	-1.918	.029*	.013	0.115	1.503	.068	.006	0.077	1.007	.158
Quadratic	.029	0.194	1.38	.085	.021	0.02	0.144	.443	.059	-0.396	-2.859	.003*	.007	-0.047	-0.333	.370

Note. One-tailed p values used. * $p < .05$

Table 12: Results of curve estimation procedure, performed on both the overall sample and separately by sex, are summarized. R^2 values indicate the proportion of variance in factor scores accounted for by cortisol AUC_g in each model. β values indicate the regression coefficient for each linear or quadratic model, while t statistics and p values indicate the significance of these coefficients.

Table 13

Independent and Dependant Variables by Sex

Dependant Variable	M	SD
Male (n = 234)		
Raw Visuospatial Abilities (Factor 1)	0.150	0.878
Raw Attention and Working Memory (Factor 2)	0.016	0.833
Raw Verbal Abilities (Factor 3)	0.072	0.856
Raw Declarative Memory (Factor 4)	-0.058	0.735
Raw AUC_g	0.341	0.267
Female (n = 172)		
Raw Visuospatial Abilities (Factor 1)	-0.137	0.833
Raw Attention and Working Memory (Factor 2)	0.083	0.732
Raw Verbal Abilities (Factor 3)	-0.104	0.885
Raw Declarative Memory (Factor 4)	0.263	0.711
Raw AUC_g	0.364	0.416

Figure 13: Mean Factor and Cortisol AUC_g scores are shown by sex. After regressing out significant effects of age, males had higher Visuospatial Abilities ($t(404) = 3.324$, $p = .001$) and Verbal Abilities ($t(404) = 2.146$, $p = .032$) scores while females had higher Declarative Memory ($t(404) = -4.413$, $p < .001$) Factor scores.

Figure 1

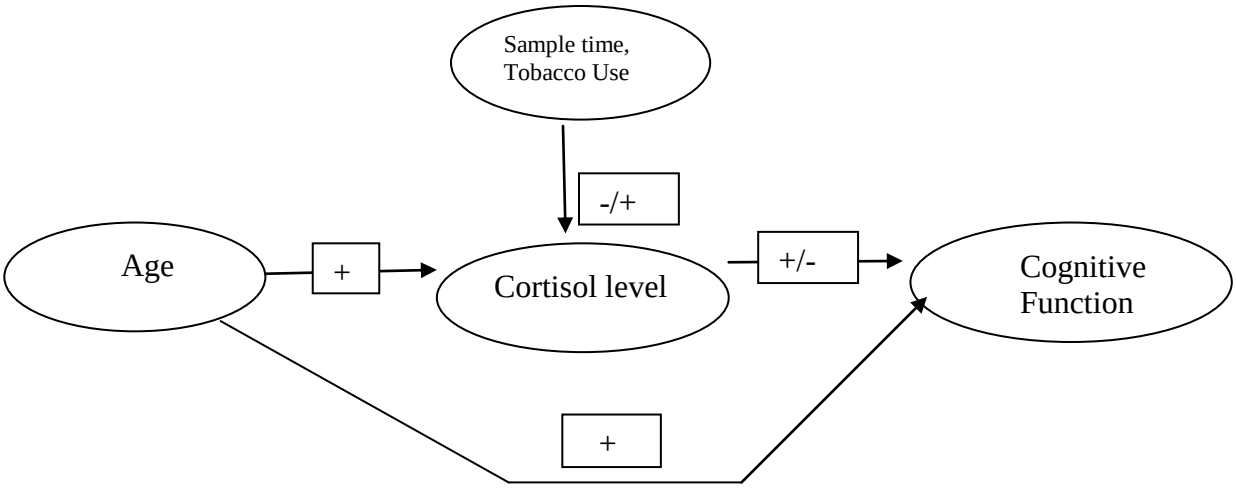
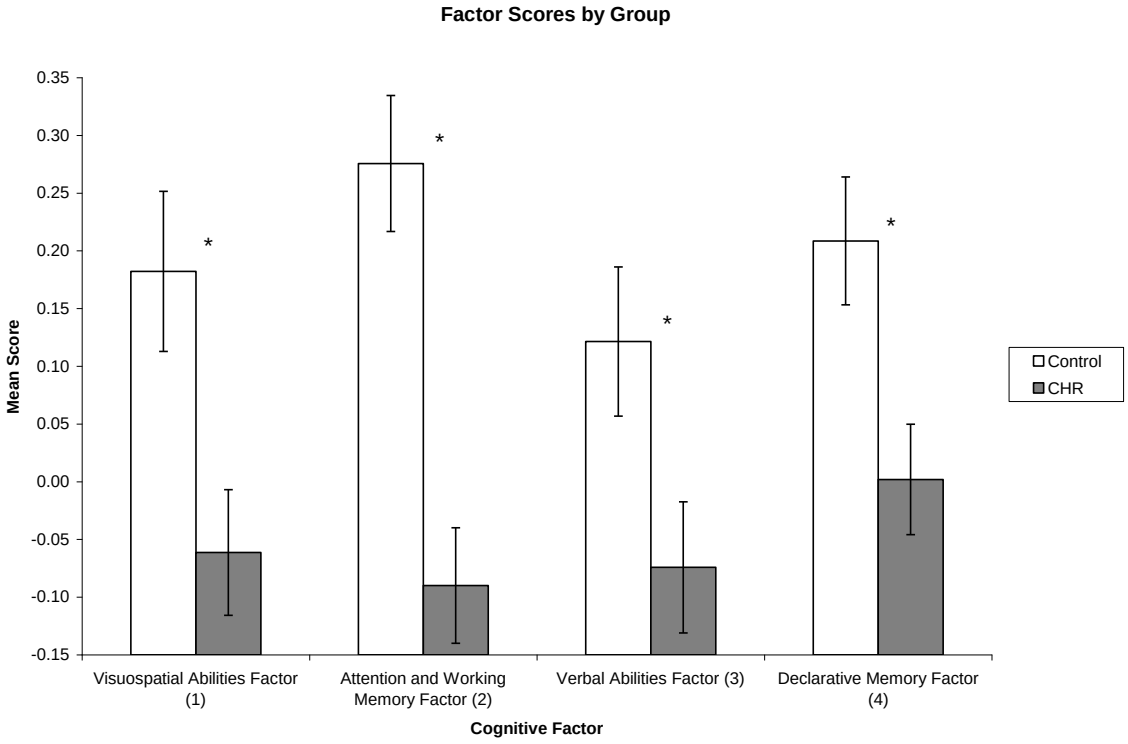


Figure 1: Cortisol is hypothesized to partially mediate the relationship between age and cognitive function. Cortisol levels also vary as a function of sample time and tobacco use, which are assumed to be unrelated to age.

Figure 2



Note. * significant at one-tailed $p < .05$

Figure 2: Mean factor scores are plotted. Age was regressed out of Attention and Working Memory and Verbal Abilities Factor scores. The control group had higher scores on factor 1 ($t(404) = 2.739$, one-tailed $p = .003$), factor 2 ($t(404) = 4.745$, one-tailed $p < .001$, factor 3 ($t(353.441) = 2.616$, one-tailed $p = .005$), and factor 4 ($t(341.464) = 2.821$, one-tailed $p = .003$). t-tests for unequal variances were used for factors 3 and 4.

Figure 3

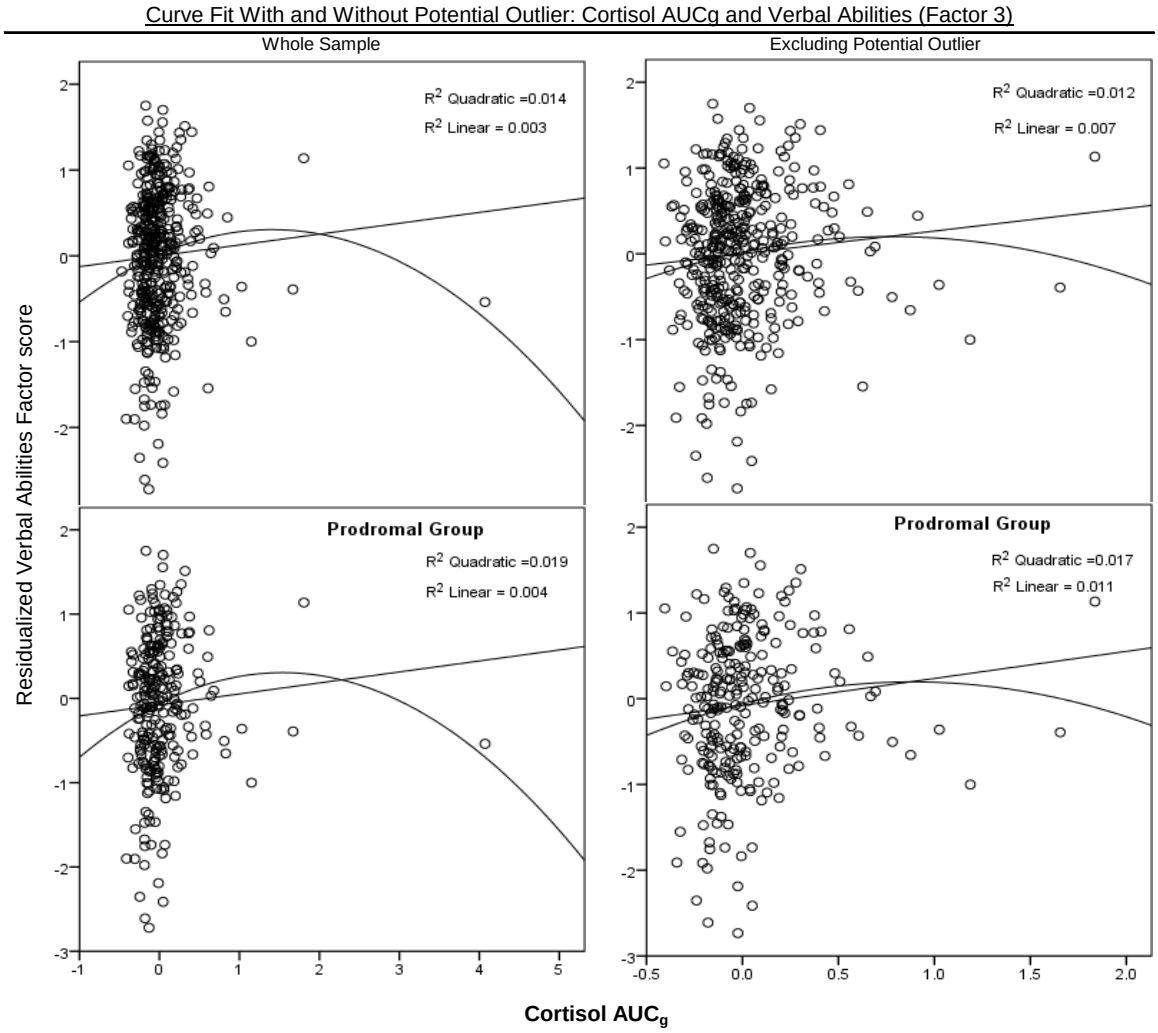


Figure 3: The relationship between cortisol and Verbal Abilities is plotted with and without a potential outlier. Removing this outlier affected the magnitude of linear and quadratic relationships in the overall and prodromal group, but it does not appear to change the shape of the relationships.

Figure 4

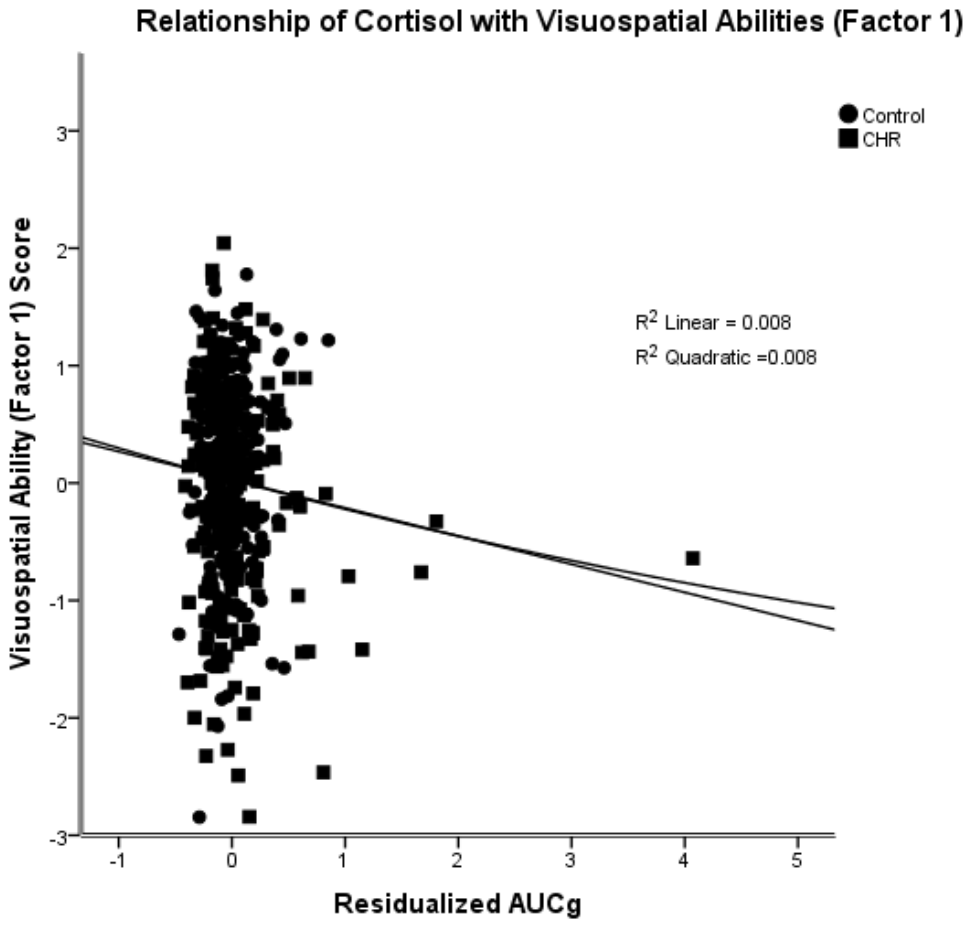


Figure 4: Scatter plot of the relationship between cortisol and visuospatial abilities in the overall sample. Linear and quadratic R^2 values for the overall sample are shown. The linear component was significant in the overall sample and accounted for a significant amount of variance in cognitive scores. It was also significant and accounted for significant variance in the CHR group.

Figure 5

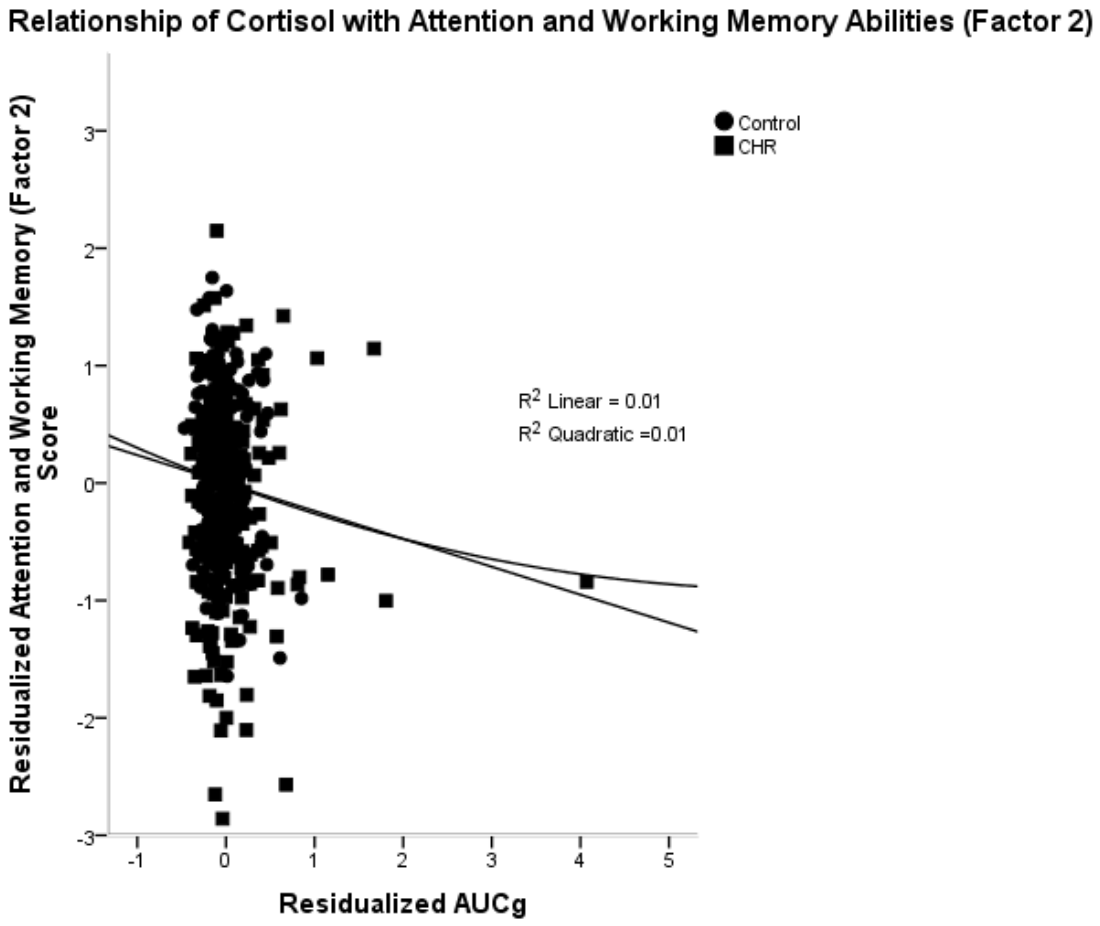


Figure 5: Scatter plot of the relationship between cortisol and attention and working memory abilities. Linear and quadratic R^2 values for the overall sample are shown. The linear component was significant in the overall sample and accounted for a significant amount of variance in cognitive scores. It was also significant and accounted for significant variance in the control group.

Figure 6

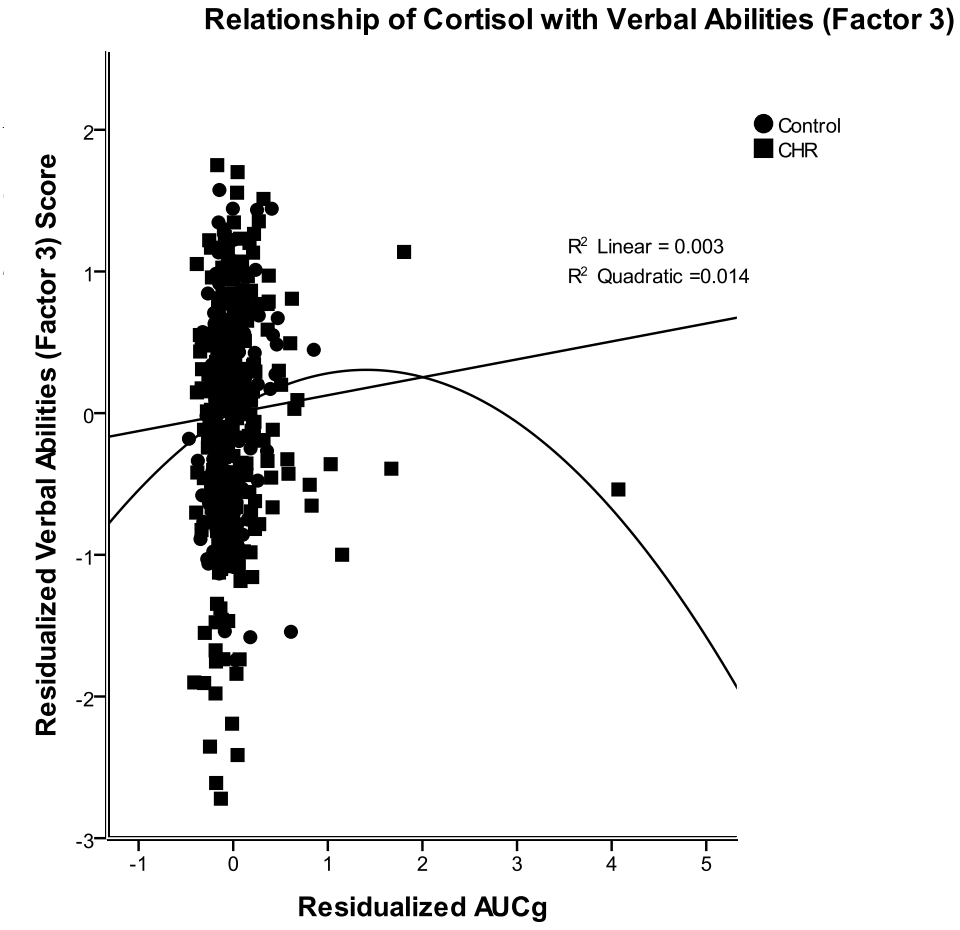


Figure 6: Scatter plot of the relationship between cortisol and verbal abilities. Linear and quadratic R^2 values for the overall sample are shown. The quadratic component was significant in the overall sample and accounted for a significant amount of variance in cognitive scores. It was also significant and accounted for significant variance in the CHR group.

Figure 7

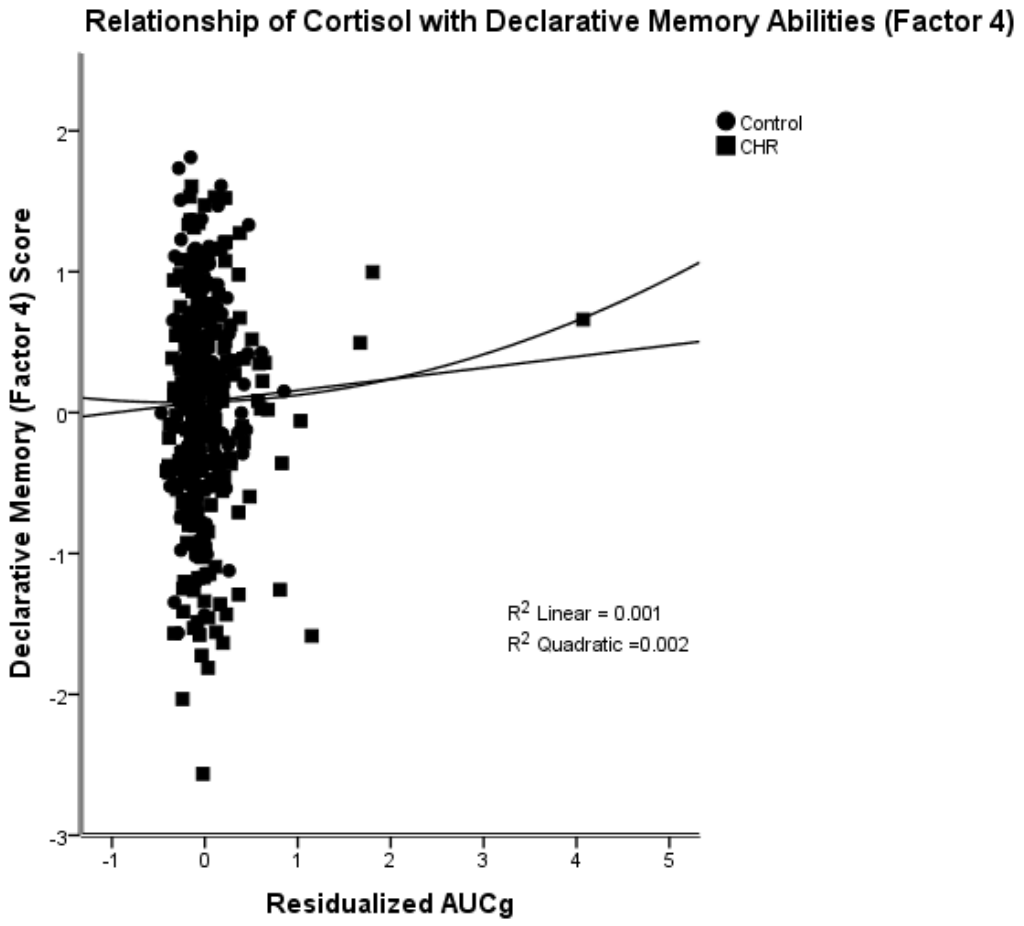


Figure 7: Scatter plot of the relationship between cortisol and attention and declarative memory abilities. Linear and quadratic R^2 values for the overall sample are shown. Neither the linear nor quadratic component was significant in any analysis.

Appendix 1

Curve Fit: Relationship of Cortisol with Cognitive Factors without controlling for age effects in cortisol

	Visuospatial Abilities (Factor 1)				Attention & Working Memory (Factor 2)				Verbal Abilities (Factor 3)				Declarative Memory (Factor 4)			
Component	R^2	β			R^2	β			R^2	β			R^2	β		
Whole Sample (n = 406)																
Linear	.008	-0.091	-1.785	.038*	.010	-0.102	-1.996	.024*	.003	0.054	1.063	.144	.003	0.055	1.073	.142
Quadratic	.008	-0.019	0.24	.405	.011	0.022	0.277	.391	.015	-0.168	-2.142	.017*	.003	0.01	0.13	.449
Control Group (n = 149)																
Linear	.011	0.104	1.222	.112	.022	-0.15	-1.769	.040*	.006	0.078	0.915	.181	.000	0	0.089	.465
Quadratic	.014	0.071	0.699	.243	.036	-0.139	-1.39	.084	.008	-0.054	-0.536	.297	.001	0.031	0.309	.379
CHR Group (n = 257)																
Linear	.019	-0.136	-2.14	.017*	.005	-0.072	-1.121	.132	.004	0.065	1.017	.155	.007	0.084	1.31	.096
Quadratic	.023	0.11	1.026	.153	.005	-0.011	-0.103	.459	.022	-0.224	-2.088	.019*	.007	-0.01	-0.09	.464

Note. One-tailed p-values used. * p < .05

Appendix 1: Results of curve estimation procedure, reconducted without accounting for age effects in cortisol AUC_g. R^2 values indicate the proportion of variance in factor scores accounted for by cortisol AUC_g in each model. β values indicate the regression coefficient for each linear or quadratic model, while t statistics and p values indicate the significance of these coefficients. Results did not differ from those shown in Table 11.