What Is the Functional Significance of Hippocampal Pathology in Schizophrenia?

by Morris B. Goldman and Colin P. Mitchell

Abstract

The hippocampal formation (HF) is one of the brain structures most consistently altered in schizophrenia, yet the contribution of HF pathology to severe mental illness is poorly understood. We present evidence that our current ignorance is attributable to the fact that the anterior HF is heavily involved in schizophrenia but has been inadequately examined by schizophrenia investigators. We propose that the anterior HF in humans, and its counterpart in rodents (ventral HF), constrain diverse responses to psychological stimuli and that disruption of this function contributes to schizophrenia. While current data suggest that hallmark symptoms of schizophrenia most likely result from the role of the anterior HF in the integrated neurocircuit that includes the prefrontal cortex, ventral striatum, and ventral tegmental area, better characterized and phylogenetically preserved neurocircuits may be similarly affected by anterior HF pathology and account for associated findings of the disorder. We propose that focusing on the impact of ventral HF pathology on these simpler circuits and functions in rodents may provide insight into the pathophysiology of severe mental illness in humans. We review several associated findings in schizophrenia to assess the likelihood that each could be a product of this putative anterior HF dysfunction and could therefore be productively studied in rodents by probing ventral HF function.

Keywords: Hippocampal formation, neuroendocrine, vasopressin, prepulse inhibition, psychological stress, HPA axis.


Background

Absence of Link Between Hippocampal Formation Pathology and Dysfunction in Schizophrenia. Postmortem neuropathologic investigations and in vivo neuroimaging studies indicate that the hippocampal formation (HF: defined here as the hippocampus proper, dentate gyrus, and subiculum but excluding structures in the parahippocampal gyrus, e.g., the entorhinal cortex) is one of the brain regions most consistently altered in schizophrenia (Lawrie and Abukmeil 1998; Nelson et al. 1998; Harrison 1999; McCarley et al. 1999; Selemon and Goldman-Rakic 1999; Wright et al. 2000; Greene et al. 2001b; Harrison and Eastwood 2001; Heckers 2001; Sawa and Snyder 2002). Converging data from electrophysiologic (Heath 1977; Halgren et al. 1978; Heath et al. 1981; Fish et al. 1993) and structural imaging studies (Kanemoto et al. 1996; Weinberger 1999; Maier et al. 2000; Lawrie et al. 2001; but see Marsh et al. 2001) link these changes to psychosis. Efforts to more specifically determine the functional impairment produced by these changes have, however, with few exceptions (Pearlson and Marsh 1999; Chakos et al. 2002), been unsuccessful (Chua and McKenna 1995; Staal et al. 1999). For instance, altered memory and learning, two functions that are closely associated with this structure and are impaired in schizophrenia, have not consistently been linked to structural evidence of HF pathology (Heckers et al. 1998; Marsh et al. 1999; Pearlson and Marsh 1999; Gur et al. 2000; Sanfilipo et al. 2000; but see Marsh et al. 2001; Torres et al. 1997; Szaszko et al. 2002).

Some have suggested that these changes in hippocampal structure may be a consequence of, rather than a contributor to, the mental illness (McEwen 1997; Arango et al. 2001; Ganguli et al. 2002). In particular, the extreme psychological stress of having schizophrenia might be adequate to alter HF morphology. Indeed, extreme levels of stress disrupt neurogenesis in the hippocampus, diminish dendritic density, and even destroy cells (Sapolsky 1992, 2000). Both excessive (Magarinos and McEwen 1995; Magarinos et al. 1996, 1997, 1999; Gould et al. 1998; Lupien et al. 1998; Conrad et al. 1999;
functions, and particularly that of its anterior segment, is critical to normal HF function. Stress-induced hippocampal atrophy may be responsible for the smaller hippocampi in women who suffered severe sexual abuse as children (Sapolsky 2000), but studies of identical twins only one of which was exposed to combat (Gilbertson et al. 2002), and of primates exposed to different psychological stress regimens (Lyons et al. 2001), suggest that stress does not diminish hippocampal volume; instead, it appears that smaller hippocampi increase vulnerability to stress-associated behavioral disorders. Furthermore, most data suggest that diminished HF volume precedes the onset of schizophrenia, although further loss of HF tissue may ensue (Pantelis et al. 2003). Thus, current data do not indicate that diminished HF volume is likely to be a product of the psychological stress associated with schizophrenia, although it remains possible that prenatal or neonatal physical or psychological stress experienced by the mother may disrupt HF development (Koenig et al. 2002), or that the HF of neonates at risk of schizophrenia is more vulnerable to these insults. In these latter instances one would still anticipate a clearer link between structural damage and functional impairment.

**Anterior/Ventral HF May Not Be Involved in Memory or Learning.** Beyond its role in memory and learning, little is known about what the HF actually does in mammals (Cohen et al. 1999), although it is implicated in many central nervous system (CNS) functions. In fact, even its role in memory and learning seems minimal when CNS insults occur early in neurodevelopment (Bachevalier and Beauregard 1993; Szeszko et al. 2002). In the event that insults occur later in life, only the posterior (primates)/dorsal (rodent) segment is consistently involved (Meibach and Siegal 1977; Moser and Moser 1998b; Maguire et al. 2000; Vann et al. 2000; Broadbent et al. 2001; but see O'Driscoll et al. 2001). In the adult rodent there is no clear evidence that the ventral HF plays any obligatory role in memory function (Moser et al. 1993, 1995; Moser and Moser 1998a; Richmond et al. 1999). The anterior (primate)/ventral (rodent) segment is activated by novel stimuli of diverse origins (Moser and Moser 1998a; Shouno and Matsumoto 2001; Strange and Dolan 2001; Kohler et al. 2002), and as pertinent objects become more familiar, posterior HF activity seems to increase while anterior HF activity diminishes (Strange et al. 1999). Some have argued that these data support an obligatory role of the anterior HF in encoding information (Zeineh et al. 2003). A better understanding of basic HF functions, and particularly that of its anterior segment, is likely a prerequisite to dissecting the contribution of HF pathology to schizophrenia (Nelson et al. 1998; Christensen and Bilder 2000).

**Anterior HF Changes May Be More Associated With Schizophrenia.** Indeed, structural imaging (Kovelman and Scheibel 1984; Suddath et al. 1989; Bogerts et al. 1990; Lieberman et al. 2001; Szeszko et al. 2002), functional imaging (Medoff et al. 2001), in vivo electrophysiologic measures (Sem-Jacobsen and Petersen 1956; Heath 1975), and preliminary postmortem neurochemical studies (Gao et al. 2002) specifically implicate the anterior HF in schizophrenia. For instance, most (Suddath et al. 1990; Shenton et al. 1992; Bilder et al. 1995; Csernansky and Josh 1998; but see Narr et al. 2001; Velakoulis et al. 2001) studies that have differentiated anterior and posterior HF volume have found greater changes in the anterior segment, which also has been reported in nonaffected first degree relatives (O'Driscoll et al. 2001). Hippocampal neuroactivity and blood flow are elevated at baseline in schizophrenia (Heckers 2001), and this too has been localized to the anterior segment (Medoff et al. 2001). Diminished anterior HF volume in schizophrenia may also contribute to impaired functions mediated by other brain structures implicated in the illness. Thus, anterior HF volume predicts performance on executive functions (Szeszko et al. 2002) and blood flow in the prefrontal cortex during executive task functions (Weinberger et al. 1992), providing a potential link between structure pathology and cognitive dysfunction characteristic of the illness. Outside of a report linking left anterior HF volume and positive symptoms of psychosis (Rajaprabhakaran et al. 2001), the anterior HF has not been linked to hallmark symptoms of the illness (e.g., delusions, hallucinations, thought disorder, social withdrawal).

**Extrinsic Connections and Other Properties of the HF.**

One way to begin to understand the function of a brain structure is to examine its intrinsic and extrinsic connections with other brain regions. The ventral (temporal) and dorsal (septal) projections of the HF in rodents more or less parallel the anterior and posterior HF connections in humans and other primates (West 1995; Braak et al. 1996; Moser and Moser 1998b). When we use the terms “anterior” and “posterior” here, we are referring to human or primate studies; “ventral” and “dorsal” refer to rodent studies. While there is remarkable structural uniformity between cross sections along the longitudinal axis of the HF, it appears the structure may be separable into two distinct units along this axis (Colombo et al. 1998; Moser and Moser 1998b; Strange et al. 1999). In the rodent, the afferent and efferent targets of the dorsal and ventral HF do not overlap or project to each other (Dolorfo and
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Amaral 1998a, 1998b; Hock and Bunsey 1998; Moser and Moser 1998b) (figure 1). Furthermore, this separation is also largely preserved in the second order projections. Thus, entorhinal projections to and from the amygdala, the sensory (dorsal) and the prefrontal cortices (ventral)—and subcortical projections from the lateral septum to the hypothalamus (Risold and Swanson 1996)—can be mapped back to ventral or dorsal HF (figure 1). Some structures are directly innervated by only one of the segments, such as the mammillary bodies (dorsal), or the shell of the nucleus accumbens (NAC) and the prefrontal cortex (ventral). These differences in neural connectivity are associated with differences in electrophysiology (Sametsky et al. 2001; Vreugdenhil et al. 2001) and neurochemistry (Verney et al. 1985). In particular, concentrations of monoamines, including dopamine, are higher in the ventral segment (Verney et al. 1985).

Anterior/Ventral HF and Neocortical Circuit Linked to Psychosis. The ventral segment in the rodent consti-

tutes a key component of a functionally integrated neurocircuit (Thierry et al. 2000) that in humans is frequently implicated in psychosis and in modulating responses to psychological stress (Moghaddam 2002) (figure 2). For instance, the ventral HF stimulates dopamine activity in the shell of the NAC (Brenner and Bardgett 1999; Legault et al. 2000; Legault and Wise 2001), the site at which dopamine is thought to promote psychosis in humans (Abi-Dargham et al. 1998; Yang et al. 1999; Thierry et al. 2000) and where the therapeutic actions of neuroleptics are thought to take place (Bardgett and Henry 1999; Brenner and Bardgett 1999; Taepavarapruk et al. 2000). Novelty also enhances dopaminergic activity in the NAC via ventral HF projections (Legault and Wise 2001), linking novel stimuli to the aforementioned circuit and neurochemistry illustrated in figure 2.

Evidence That Ventral HF Manipulations Reproduce Alterations in This Neocortical Circuit Relevant to Psychosis in Humans. Further evidence suggesting the ventral HF in rodents may be relevant to understanding schizophrenia in humans comes from animal studies showing that neonatal (day 7) lesions of the ventral (but not dorsal or adult) HF reproduce certain findings from in vivo and postmortem studies in patients (Lipska et al. 1993; Swerdlow et al. 2000b). Thus, neonatal ventral hippocampal formation lesions (NVHFL) induce structural changes in the efferent targets illustrated in figure 2 (Halim and Swerdlow 2000; Khang et al. 2000) by, for instance, altering dendritic length and spine density of pyramidal neurons in the prefrontal cortex and in spiny neurons in the NAC (Halim et al. 2001); and diminishing concentrations of N-acetylaspartate in the prefrontal cortex (Bertolino et al. 2002). Analogous changes in N-acetylaspartate were also seen in the prefrontal cortex of pri-

mates with neonatal lesions (Bertolino et al. 1997). Many changes, particularly those related to dopaminergic activ-

ity, appear postpuberty in the rat (~day 56), analogous to the onset of symptoms in schizophrenia patients (Lipska et al. 1993; Wan et al. 1998; Giorgi et al. 2001; O’Donnell et al. 2002). Some of these findings are also seen in rodents with reversible inactivation of the neonatal ventral HF using tetrodotoxin, or other more physiological inter-

ventions that preferentially affect the ventral HF (Brake et al. 1999; Greene et al. 2001a), suggesting that a less dra-

matic insult more comparable to what could occur in schizophrenia might also produce these changes (Lipska et al. 2002). A number of the changes in this neurocircuit activity are apparent only during stress (Wan et al. 1998; Giorgi et al. 2001; Molteni et al. 2001; Chrapusta et al. 2003), suggesting that NVHFL may mediate the influence of psychological stress on this circuitry (Moghaddam 2002). Together, these data reinforce the idea that anterior

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Figure 1. Afferent and efferent connections to the HF in the rat, highlighting the separation of the ventral (shaded) and dorsal (clear) projections

Note.—HF = hippocampal formation; PFC = prefrontal cortex.

1 Available data suggest that this separation is also seen in pri-

mates (including humans) along the anterior/posterior axis of the HF. Note the dorsal projections in the rodent are to structures implicated in learning and memory, while the ventral projections are to structures that in humans are associated with schizophrenia.
Figure 2. Connections of the ventral HF with a neurocircuit that in humans is frequently implicated in schizophrenia

Note.—HF = hippocampal formation; NVHFL = neonatal ventral hippocampal formation lesions; PFC = prefrontal cortex; VTA = ventral tegmental area.

HF pathology underlies the hallmark symptoms of schizophrenia and that studying the involvement of the ventral HF in this neocortical circuit will lead to fundamental insights into psychosis.

Barriers to Studying the Ventral HF Role in This Neocortical Circuit in Rodents: An Alternative Approach. Several investigators have offered theories attempting to explain how hippocampal pathology produces psychosis. These include disruption of the structure's putative role in (1) filtering excessive sensory stimuli (Swerdlow and Geyer 1998; Grace 2000), (2) preventing associations with redundant or irrelevant stimuli (Schmajuk and Tyberg 1991; Adler et al. 1998; Maren 1999), (3) suppressing conscious awareness of redundant information (Helmsley 1996; Gray 1998; O'Donnell and Grace 1998), and (4) appropriately signaling increased arousal and the need for novel responses (Kimble 1968; Christensen and Bilder 2000). Unfortunately, we are a long way from extending our current knowledge of hippocampal function to understanding the mechanism of these processes and relating them to psychosis. Alternatively, just as the structural impact of HF pathology in schizophrenia could perhaps be more easily studied by examining relatively simple neurocircuits, it is possible that the functional significance of HF pathology could be more easily clarified by examining its functional impact on these relatively simple circuits.

Hypothesis

We propose a hypothesis based on these principles, that is, that hippocampal pathology in schizophrenia has an analogous structural and functional impact on both simple and complex neurocircuits, and that studying the former (i.e., structural and functional impact on simple neurocircuits) will inform the latter. Specifically, we hypothesize that (1) the anterior HF normally constrains the responses of diverse neurosystems to psychological stimuli, and (2) HF pathology in schizophrenia disrupts this inhibitory function, thereby contributing to the hallmark symptoms and associated findings of severe mental illness (figure 3).
Figure 3. Model positing that the anterior HF normally limits responses of diverse neurosystems to psychological stress and that disruption of this function contributes to multiple findings, including core features of schizophrenia¹

The distinction between psychological and physical stimuli is by no means obvious, and many events clearly include both components. By psychological stimuli we mean events whose potential significance to homeostasis depends largely on the interpretation of exogenous sensory data or past experience, in contrast to endogenous sensory data alone. As a prelude to our review of specific findings relevant to the above hypothesis, we first review evidence indicating that the ventral HF in rodents modulates the impact of psychological stress and that persons with schizophrenia are more vulnerable to psychological stimuli.

Ventral HF Modulation of the Impact of Psychological Stress. Increasing evidence supports the concept that separate CNS pathways process psychological and physical stress and that the anterior/ventral HF is integral to the former (see Romero and Sapolsky 1996; Lopez et al. 1999 for general review). The HF's influence on stress responses extends beyond its involvement in the neurocircuity illustrated in figure 2, and the HF is directly implicated, for instance, in hypothalamic homeostatic functions (Nettles et al. 2000; Herman et al. 2002; but see Lipska et al. 1998; Moghaddam 2002). The previously noted responsiveness of the anterior HF to novel exogenous sensory data and of altered dopamine activity following stress in NVHFL rats (Chrapusta et al. 2003) may reflect the involvement of the HF in processing psychological stimuli (Knight 1996). The concept that HF activity modulates the impact of stress is supported by studies demonstrating that ventral (but not dorsal) HF lesions enhance, and electrical stimulation diminishes, the occurrence of stomach ulcers following psychological stress (Henke 1990).

Other data on the behavioral response to psychological stress in NVHFL animals may appear to challenge the assertion that this structure constrains responses to psychological stress. Thus, NVHFL, in contrast to adult lesions (day 21), can reduce immobility during swim stress (Daenen et al. 2001), promote exploration of novel environments, and diminish anxiety in an open field (as indexed by diminished droppings) (Daenen et al. 2002a). Furthermore, adult lesions of the ventral, but not dorsal, HF have been associated with less anxiety in a brightly lit chamber (again measured by fecal droppings) and more time in the open arms of an elevated plus maze (Kjelstrup et al. 2002). Other studies show that adult ventral HF lesions reduce food neophobia, which is a very characteristic behavior in rodents (Burns et al. 1996). These findings cannot be attributed to the stress-induced hyperactivity (Burns et al. 1996; Daenen et al. 2002a), but they also cannot be attributed to a general reduction in fear, because animals with ventral HF lesions continue to exhibit contextual fear conditioning (Kjelstrup et al. 2002). Instead,
these data suggest that ventral HF lesions "unmask" the otherwise prepotent response to psychological stress (whether it be approach or avoidance, flight or fight) by removing the inhibitory component (Daenen et al. 2001; Kjelstrup et al. 2002). The validity of this interpretation is not yet established, and it is not clear that the impact of the ventral HF is independent of its influence on prefrontal activity (Moghaddam 2002).

**Vulnerability to Psychological Stimuli in Schizophrenia.** Others have suggested that schizophrenia is associated with increased vulnerability to psychological stress, even proposing that HF (Walker and Diforio 1997; Chrapusta et al. 2003) or prefrontal (Moghaddam 2002) pathology is likely responsible. Psychological stress frequently precedes psychotic relapses in schizophrenia (Nuechterlein and Dawson 1984; Gispen-de Wied 2000; Siris 2000). Objective assessment of the clinical consequences of environmental stress (Knobler 2000), stressful life events (Bebbington et al. 1993; Ventura et al. 2000), and interpersonal criticism (Docherty et al. 1998; Rosenfarb 2000) supports the role of stress in relapses of the illness, as does the efficacy of medications (Carpenter et al. 1999) and cognitive-behavioral therapies (Garety et al. 2000, Sensky et al. 2000) that ameliorate the impact of stress. This susceptibility to stress may precede the onset of the illness (Tienari 1991; Gispen-de Wied 2000) and thus is not simply a consequence of psychosis. Schizophrenia patients appear to be particularly vulnerable to the stress of everyday life, rather than unique or acute events that they may be quite skilled at blocking out (Norman and Malla 1994; Myin-Germeys et al. 2001). On the whole, these data suggest that persons with schizophrenia are more vulnerable to the adverse impact of psychological stress. Whether this is associated with HF pathology is unclear, as is the issue of whether stress is fundamentally related to the illness or merely promotes exacerbations.

**Candidate Findings in Schizophrenia Suggestive of Impaired Anterior HF Constraint of Responses to Psychological Stress**

This next section addresses whether specific findings in schizophrenia are likely to be a product of impaired anterior HF constraint of responses to psychological stress. We have divided our assessment of each candidate finding into two parts roughly corresponding to parts 1 and 2 of our hypothesis. Thus, table 1 summarizes whether the finding is modulated by (1) ventral/anterior HF activity or lesioning, (2) psychological stress, or (3) dopaminergic agents. The last column is relevant to addressing whether findings are likely confounded by neuroleptic usage (e.g., whether they are reproduced by neuroleptics), as well as whether they are closely associated with the illness (e.g., whether they are exacerbated by dopaminergic agents). Table 2 summarizes whether findings in patients (1) have been linked to the anterior HF pathology, (2) are exacerbated by dopaminergic agents.

**Table 1. Evidence that candidate findings in schizophrenia can be modeled in rodents with ventral HF manipulations**

<table>
<thead>
<tr>
<th>Neurosystem</th>
<th>Candidate finding</th>
<th>(1) Modulated by ventral/anterior HF</th>
<th>(2) Modulated by psychological stress</th>
<th>(3) Altered by dopaminergic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroendocrine</td>
<td>♂ HPA axis</td>
<td>++++</td>
<td>++++</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>♂ pAVP</td>
<td>++</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Motor</td>
<td>♂ Stereotypic behavior</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>♂ Pacing</td>
<td>++++</td>
<td>±</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>♂ PPI</td>
<td>+++</td>
<td>?</td>
<td>++</td>
</tr>
<tr>
<td>Autonomic</td>
<td>♂ HR responses</td>
<td>++</td>
<td>++++</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>♂ SCR</td>
<td>–</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Social</td>
<td>♂ Avoidance</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Note.—Avoidance = interaction with unfamiliar conspecific; HF = hippocampal formation; HPA = hypothalamic-pituitary-adrenal; HR = heart rate; pAVP = plasma arginine vasopressin; PPI = prepulse inhibition; SCR = skin conductance response.

1 The table shows the authors' assessments of evidence indicating whether (1) the finding is reproduced with ventral HF manipulations, particularly NVHFL; (2) the finding is exacerbated by psychological stress; (3) the finding is ameliorated by dopamine antagonists, exacerbated by agonists. ++++ = strong; +++ = moderately strong; ++ = moderate; + = weak; ± = conflicting; — = negative; ? = unclear/insufficient data. Negative assessments indicate that either there appears to be no effect or it is the opposite of that which would support the hypothesis.
Table 2. Evidence that candidate findings in schizophrenia have been linked to anterior HF and psychological stimuli

<table>
<thead>
<tr>
<th>Neurosystem</th>
<th>Candidate finding</th>
<th>(1) Linked to anterior HF pathology</th>
<th>(2) Linked to psychological stimuli</th>
<th>(3) Not attributable to confounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroendocrine</td>
<td>↑ HPA axis</td>
<td>±</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>↑ pAVP</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Motor</td>
<td>↑ Stereotypic behavior</td>
<td>?</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>↑ Pacing</td>
<td>?</td>
<td>+</td>
<td>±</td>
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<tr>
<td></td>
<td>↓ PPI</td>
<td>++</td>
<td>?</td>
<td>++</td>
</tr>
<tr>
<td>Autonomic</td>
<td>↑ HR responses</td>
<td>?</td>
<td>++</td>
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<td></td>
<td>↓ SCR</td>
<td>?</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Social</td>
<td>↑ Avoidance</td>
<td>±</td>
<td>+++</td>
<td>+</td>
</tr>
</tbody>
</table>

Note.—Avoidance = diminished social interaction; HF = hippocampal formation; HPA = hypothalamic-pituitary-adrenal; HR = heart rate; pAVP = plasma arginine vasopressin; PPI = prepulse inhibition; SCR = skin conductance response.

The table shows the authors’ assessments of extent that evidence indicates whether (1) the finding is more pronounced in those with evidence of HF pathology; (2) the finding is exacerbated by psychological stress; and (3) the finding cannot be attributed to recognized confounds (e.g., medication, nonspecific stress, institutionalization). ++++ = strong; +++ = moderately strong; ++ = moderate; + = weak; ± = conflicting; − = negative; ? = unclear/insufficient data. Negative assessments indicate that either there appears to be no effect or it is the opposite of that which would support the hypothesis.

We chose eight candidate findings based on existing knowledge of their neuroregulation and whether the HF was specifically implicated. All but “avoidance” would be considered to be associated findings, in that they do not reflect hallmark symptoms of schizophrenia. A glance at tables 1 and 2 will make it clear that we cannot confidently make many of these assessments at present. Still, we felt this section was important to include, as it illustrates a preliminary test of the hypothesis and can suggest directions for future research. Three of the eight candidate findings—stereotypic behavior, skin conductance responses, and heart rate responses—are summarized only very briefly, as we consider it unlikely that they can reveal mechanisms of impaired anterior HF constraint of stress responses. For these three findings, we have not summarized the literature review used to generate assessments in tables 1 and 2, but interested readers can contact us for that information.

Stereotypic Behavior. Motor abnormalities (Flaum and Schultz 1996; Tarrant and Jones 1999) and in particular stereotypic behavior (Walker et al. 1994; Ismail et al. 1998; Walker et al. 1999; Wolff and O’Driscoll 1999) are commonly described in schizophrenia, clearly predating the neuroleptic era (Bleuler 1911). Hippocampal lesions induce stereotypic motor responses in rodents, but this effect has been described with only dorsal lesions (Lipska and Weinberger 1994a). Thus, at present there is no reason to suggest that the anterior/ventral HF is involved in these findings.

Skin Conductance Responses. Some but not all (Critchley et al. 2000) studies implicate the HF in skin conductance responses (SCRs) (Knight 1996; Williams et al. 2000), but the association is with posterior, not anterior, HF (Knight 1996; Williams et al. 2000). Findings are markedly influenced by antipsychotic medications (Zahn et al. 2001). In general, drug-free patients compared to healthy controls have an elevated level of skin conductance, increased spontaneous SCRs, diminished reactivity, and subtle deficits in habituation (Zahn et al. 2001). Overall, these findings appear consistent with elevated arousal and emotional withdrawal from psychological stimuli (Zahn and Pickar 1993; Dawson et al. 1994)—that is, not with removal of an inhibitory response to psychological stress. For these reasons, and because other confounding factors have not been adequately examined, we have also excluded this measure from further discussion.

Heart Rate Responses. The ventral HF, and the ventral subiculum in particular, are highly connected with hypothalamic centers modulating the autonomic nervous system (Silverman et al. 1981; Risold and Swanson 1996). Recent transneuronal labeling with pseudorabies virus demonstrates that the stellate ganglion (which innervates the heart) is extensively connected with the ventral, but
not the dorsal, HF (Westerhaus and Loewy 2001). Electrical and glutamatergic stimulation of dorsal and ventral HF diminish heart rate (HR), although ventral effects are greater (Ruit and Neafsey 1988). Basal HR is consistently elevated in drug-free patients (Zahn et al. 2001). Available data are conflicting regarding the extent that HR normalizes with recovery; furthermore, medication is clearly a confounding factor (Zahn et al. 1997; Toichi et al. 1999; Agelink et al. 2001; Olbrich et al. 2001). Reports of spontaneous variation in HR, which are thought to provide a measure of both parasympathetic and sympathetic activity (Cohen et al. 2001), are conflicting at present in schizophrenia (Agelink et al. 2001; Zahn et al. 2001). HR responses to cognitive tasks and various other forms of psychological stress appear to be blunted in schizophrenia (Albus et al. 1982; Zahn et al. 2001), but avoidant coping strategies or medication effects may be responsible (Zahn et al. 2001). The relevance of these findings to the hypothesis is further in question because of (1) the absence of studies of HF lesions, (2) evidence suggesting that ventral HF effects on HR are mediated by the prefrontal cortex (Ruit and Neafsey 1990), (3) the recognized impact of level of attention (Bernston et al. 1998) and general physical condition (Agelink et al. 1998) on HR, and (4) the extreme sensitivity of HR to psychological stress. The latter fact suggests that increases in HR may simply be a physiological response to the stress of psychosis.

**Neuroanatomy of Neuroendocrine Findings.** We next review the remaining five candidate findings, two of which arise from the neuroendocrine system. Hypothalamic-pituitary-adrenal (HPA) axis activity (Selye 1946; Lopez et al. 1999) is perhaps the most commonly reported index of stress response. The HPA axis and secretion of the antidiuretic hormone plasma arginine vasopressin (pAVP) are modulated by projections arising from the brainstem and forebrain that relay in perihypothalamic structures surrounding the parventricular nucleus and supraoptic nucleus in the hypothalamus (Kohler 1990; Cunningham and Sawchenko 1991; Herman et al. 1995) (figure 4). The hypothalamic magnocellular neurons that secrete pAVP into the peripheral circulation, like the adjacent parvocellular neurons that regulate adrenocorticotropin secretion from the anterior pituitary, arise from the summation of concurrent inhibitory and excitatory afferents (Leng et al. 2001). In particular, GABAergic relays in the perihypothalamic area modulate both neuroendocrine systems via parallel glutamatergic pathways arising from the HF (Boudaba et al. 1996; Herman et al. 2002) (figure 4). Thus, the ventral HF in rodents, and most likely the anterior HF in humans, is well situated to inhibit HPA axis and pAVP activity independently of its influence on prefrontal activity (Moghaddam 2002).

Figure 4. The Inhibitory Influence of the ventral HF in the rat on the peripheral activity of the HPA axis and the antidiuretic hormone pAVP

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**Note.** ACTH = adrenocorticotropic; AP = anterior pituitary; CNS = central nervous system; CRH = corticotropin-releasing hormone; HF = hippocampal formation; HPA = hypothalamic-pituitary-adrenal; MAGN = magnocellular neurons of the PVN; PARV = parvocellular neurons; pAVP = plasma arginine vasopressin; PP = posterior pituitary; PVN = paraventricular nucleus; SON = supraoptic nucleus.

1 Structures and projections shown in gray represent main stimulatory influences on the two neuroendocrine systems. Central components of these neuroendocrine systems are shown within the large box, and peripheral portions are shown outside of it. Projections from the ventral HF are relayed in the lateral septum, where they innervate on neurons surrounding the PVN. PARV in the PVN secrete CRH, vasopressin (AVP), and oxytocin (not shown) into the hypophysial portal circulation, where they bind to receptors in the AP and cause secretion of ACTH. ACTH then binds to the adrenal gland, causing release of corticosterone (cortisol in most mammals). Note that corticosterone then feeds back at multiple levels in the CNS to further modulate the inhibitory effects of the ventral HF as well as other structures. The diagram also emphasizes that pAVP may provide a less ambiguous measure of CNS function than the HPA axis. Thus, AVP is directly secreted into the peripheral bloodstream from the PP via neural projections arising from the MAGN and the SON, and has one primary function at the kidney that can be accurately assessed. The interruption of the projections from the ventral HF to the septum (see ---) denotes the site of lesions that produce enhanced HPA axis and pAVP in response to psychological stress in rodents.
1. HPA axis response to psychological stress and its modulation by the ventral HF. The ventral HF modulates HPA responses to psychological (e.g., novelty, conditioned or unconditioned fear, social isolation, restraint, acoustic stress) but not physical stress (e.g., hypovolemia, ether, hypernatremia) (Romero and Sapolsky 1996; Herman et al. 1998; Emmert and Herman 1999; Van De Kar and Blair 1999), providing strong support for the concept that the HF is specifically implicated in psychological stress. Part of this effect is mediated by glucocorticoid negative feedback on the HF; that is, cortisol (humans) or corticosterone (rodents) binds to receptors in the hippocampus to terminate the HPA response (Jacobsen and Sapolsky 1991; Thrivikraman et al. 2000).

Prolonged HPA axis activity following diverse psychological stress (e.g., restraint, acoustic startle, open field exposure, novelty) and diminished HPA response to glucocorticoids (i.e., blunted glucocorticoid negative feedback) are the hallmarks of ventral HF lesions in adult rodents (Patacchioli et al. 1989; Herman et al. 1998; Nettles et al. 2000; but see Kjelstrup et al. 2002). Dorsal HF lesions have no effect on stress-induced HPA axis activity (Herman et al. 1992; Herman et al. 1998; Lopez et al. 1999). NVHFL appear to prolong the HPA axis response to footshock (Chrapusta et al. 2003) and to increase the response to acoustic startle (Mitchell and Goldman, in press). It is unclear whether these effects are greater than those in the adult, whether they appear only after puberty, or whether they are reversed by neuroleptic treatment (table 1). Thus, available data strongly suggest that the ventral HF constrains HPA axis responses to psychological stress, but the relevance to animal models of schizophrenia, and particularly the NVHFL, is not clear.

2. HPA axis regulation: Relationship to HF pathology and psychological stress in schizophrenia. Basal HPA activity (Rao et al. 1995; Gispen-de Wied 2000; Jansen et al. 2000) is essentially normal in schizophrenia (but see Van Cauter et al. 1991; Walder et al. 2000), while reports of responses to physical stress are conflicting—that is, blunted (surgery: Kudoh et al. 1997, 1999; pain: Breier et al. 1988), intact (e.g., hypoglycemia: Breier 1989; Kathol et al. 1992; exercise: Jansen et al. 2000), and enhanced (hypoglycemia: Elman et al. 1998). At least part of this discrepancy may be explained by whether there was a significant psychological component, as the two surgical studies with blunted responses were performed while patients were under anesthesia. Responses to psychological stress are, however, also frequently blunted (Albus et al. 1982; Jansen et al. 2000), which is the opposite of what the hypothesis would predict. This blunting is associated with avoidant coping strategies (Jansen et al. 2000), suggesting that patients simply ignore the acute stressor (Gispen-de Wied 2000; Lupien 2000). One means of trying to get around this is to use a combined physical/psychological stress that might be harder to ignore, for instance, the cold pressor, which provokes pain and produces reliable (i.e., blood pressure changes and pain) responses in schizophrenia (Frohman et al. 1966; Ax et al. 1969). In support of the hypothesis, preliminary data indicate that schizophrenia patients do exhibit prolonged HPA axis responses with this stressor (Goldman et al. 2003) and with hypoglycemia, another combined physical/psychological stressor (Elman et al. 1998). The association with anterior HF volume has not been determined.

There is clearer evidence for blunted glucocorticoid negative feedback. Diminished glucocorticoid feedback is frequently reported in schizophrenia (Asnis et al. 1986; Tandon et al. 1991; Goldman et al. 1993), and several studies implicate the HF. Thus, there have been reports of reduced density of corticosteroid receptors in the HF (Lopez-Figueroa et al. 2001; Webster et al. 2002). In addition, in vivo studies of negative feedback obtained under conditions most likely to reflect HF influences—that is, the diurnal trough of cortisol levels (Young et al. 1994, 1998)—also suggest impaired HF regulation in patients with schizophrenia (Goldman and Wood 2000). These results are not found in affective disorders (Posener et al. 2001). Hippocampal activity, as measured by changes in positron emission tomography in response to infused cortisol, is higher in schizophrenia than control subjects (Ganguli et al. 2002). This might be the opposite of what one would predict, although it is difficult to draw conclusions without knowing the impact on neuroendocrine function.

1. pAVP response to psychological stress and its modulation by the ventral HF. The other neurohormone that is well situated to be inhibited by the ventral HF is vasopressin. While most types of physical stress increase pAVP, diverse types of psychological stress (e.g., isolation, cold stress, restraint, novelty, startle, conditioned fear, electric shock) normally have no effect on or transiently inhibit pAVP (Edelson and Robertson 1986; Yagi 1992; Onaka and Yagi 1993; Jezova et al. 1995). Available data suggest this inhibition by psychological stimuli arises from forebrain structures (e.g., bed nucleus of the stria terminalis) (Woods et al. 1969; Onaka and Yagi 1998), including the ventral HF. Thus, HF lesions in the adult rat limited to the sites of the hypothalamic projections (ventral subiculum and ventral CA1) blunt the normal inhibition of pAVP by acoustic startle (Nettles et al. 2000). Preliminary data suggest that a similar effect is found in NVHFL animals (Mitchell and Goldman, in press).

2. pAVP regulation: Relationship to HF pathology and psychological stress in schizophrenia. Evidence of episodic enhanced pAVP function in schizophrenia pre-
dates the neuroleptic era. Unexplained impairments in water excretion that vary with acuity of psychosis were first noted in patients with psychotic disorders in the 1920s (Targowa 1923), and since the 1980s it has been recognized that pAVP activity accounts for this impaired water excretion and varies with psychosis (Raskind et al. 1987; Goldman et al. 1988, 1997; Emsley et al. 1989). Recognized influences, such as neuroleptics, appear to have been eliminated as potential confounds (Emsley et al. 1990; Riggs et al. 1991; Goldman et al. 1996a, 1996b, 1997; but see Kawai et al. 2001). Furthermore, anterior HF pathology has been linked to these findings. Thus, abnormalities in pAVP regulation, and specifically the pAVP response to acute psychosis (induced by the psychotomimetic methylphenidate), are greater in the subset of schizophrenia patients with diminished anterior HF volumes (Elkashef et al. 1996; Goldman et al. 1997; Luchins et al. 1997) (figure 5). The fact that the increase in psychotic symptoms was similar in the two groups of patients, and that stress normally has no effect on or suppresses pAVP, suggests that the pAVP responses are not attributable to the stress of psychosis per se (Goldman et al. 1997). Other data also suggest that the pAVP response to mixed psychological stress is greater in schizophrenia (Elman and Breier 2002; but see Kudoh et al. 1998), although the relationship to HF volume is unknown.

The salutary effects of the atypical neuroleptic clozapine on abnormalities in neuroendocrine function in schizophrenia reinforce the concept that these findings are fundamentally related to HF pathology underlying the mental illness. Thus, clozapine normalizes water balance and improves clinical functioning in schizophrenia (Canuso and Goldman 1999), normalizes the enhanced cortisol response to serotonergic agonists (Breier et al. 1993; Kahn et al. 1993), and may be clinically most effective in those with altered HPA activity (Owens et al. 1993). Furthermore, clozapine has unique actions at hippocampal sites (Robertson and Fibiger 1992; Guo et al. 1995; Scarr et al. 2001): it downregulates hippocampal 5-HT₆ receptors (Fredrick and Meador-Woodruff 1999), upregulates D₂ and D₃ hippocampal receptors (Ritter and Meador-Woodruff 1997), and reverses the inhibition by dopamine of NMDA activity in the CA1 region of the hippocampus (Otmakhova and Lisman 1999).

**Neuroanatomy of Motor Responses.** Another神经系统 that is clearly modulated by the ventral HF during psychological stress is the motor system. Motor responses are closely linked to the neurocircuit shown in figure 2, although they may rely less on the prefrontal cortex (but see Lipska et al. 1998). The extent that the HF impact on motor responses is independent of the prefrontal cortex will likely influence the ease with which findings can be interpreted and extrapolated from rodents to humans.

Prepulse inhibition (PPI) refers to the reduction of the startle (i.e., motor) response to a provocative stimulus ("pulse") when it is immediately preceded (30–500 milliseconds) by a nonstartling stimulus ("prepulse"). Acoustic stimuli produce the most reliable reductions (i.e., >50%) and have been studied the most, but tactile and other sensory stimuli produce analogous effects. In fact, the effect is seen even if the prepulse is from one type of sensory modality and the pulse another (Blumenthal 1999). In rodents and primates, PPI is usually defined as the percentage reduction of whole body startle in the presence of a prepulse, while in humans it is usually defined as the percentage reduction in a very limited component: eyeblink intensity (Swerdlow et al. 2000a; Winslow et al. 2002). Converging evidence suggests that PPI reflects automatic protection of sensory processing from psychological stimuli (Perlstein et al. 1993; Norris and Blumenthal 1996; Braff et al. 2001; Postma et al. 2001) and that specifically the inhibition by the prepulse prevents the normal withdrawal and reorienting response that otherwise occurs with startle (Fendt et al. 2001). Studies of PPI thus differ from those of other candidate findings, in that we are assessing the failure of a recognized modifier (i.e., prepulse) to inhibit a response to a psychological stimulus (i.e., pulse), rather than the response to the stimulus per se.

PPI in animals is regulated at the brainstem and occurs even during sleep (Fendt et al. 2001). Like other motor responses, it is modulated by the neurocircuit outlined in figure 2 (Swerdlow et al. 2000a, 2000b). The involvement of the ventral HF in PPI is demonstrated by electrophysiologic data showing that ventral HF stimulation produces changes in local field potential (a measure of afferent neural activity) in the pedunculopontine tegmental nuclei and caudal pontine nuclei (i.e., the brainstem sites that regulate PPI) via relays in the NAC (Civillico et al. 2001). In addition, ventral, but not dorsal HF, lesions in the adult rat produce small deficits in basal PPI but dramatically enhance the ability of dopaminergic agonists, such as apomorphine, to disrupt PPI (Swerdlow et al. 2000b; but see Swerdlow et al. 2000a; Braff et al. 2001). NVHF lesions produce more marked disruption; that is, PPI is significantly diminished in the basal (i.e., no-drug) state (Lipska et al. 1995; Swerdlow et al. 2000b). Like other findings in NVHF, these deficits are not seen until the animal reaches puberty (Lipska et al. 1995; Swerdlow et al. 2000b). Other interventions that alter ventral HF function and may replicate risk factors for schizophrenia (e.g., social isolation) (Greene et al. 2001a; but see Pryce et al. 2001) also appear to impair PPI.

While the ventral HF is implicated in PPI, the role of the dorsal HF and the mechanisms of ventral HF influences have been difficult to unravel. Thus, deficits in PPI are also seen with temporary inhibition (GABA_A agonist) or inactivation (tetrodotoxin) of the adult ventral HF, and with dorsal infusions (Zhang et al. 2002b). In contrast, the same authors report that NMDA disrupts PPI only when infused into the ventral HF (Zhang et al. 2002a). The latter finding occurs even in rats whose connections with the NAC are severed (Swerdlow et al. 2002), suggesting that the effects are modulated, or at least relayed, by other structures illustrated in figure 2 (i.e., ventral tegmental area or prefrontal cortex). Some (Bast et al. 2001b) but not all (Zhang et al. 2002b) of the effects are reversed by neuroleptics. Distinguishing ventral from dorsal HF effects has been vexing, suggesting that there may be several ways in which HF manipulations alter PPI (Zhang et al. 2002b).
2. PPI: Relationship to HF pathology in schizophrenia. Diminished PPI is one of the most robust and reproducible findings in schizophrenia (Braff et al. 2001). The findings in patients cannot be attributed to recognized factors (Kumari et al. 1999; Parwani et al. 2000; Swerdlov et al. 2000a), although the relationship to impaired attention or motivation has not been entirely resolved (Dawson et al. 2000). PPI has been associated in normals with increased activity of the right anterior HF (measured with functional magnetic resonance imaging [Kumari et al. 2003]). Persons with schizophrenia had both reduced PPI and proportionately reduced HF activity, consistent with the concept that HF activity contributes to PPI. While reduced anterior HF volume has been linked to other electrophysiologic measures (Egan et al. 1994; Kawasaki et al. 1997; but see Waldo et al. 1994), the relationship to diminished PPI has not been explored.

Neuroanatomy of Social Behavior. Impairments in social interaction are core features of schizophrenia, and the neurobiology of social behavior is one of the more exciting fields in neuroscience. Thus, animal models are potentially of great interest. Impaired social interactions can be produced in animals by a number of interventions that may be relevant to the pathophysiology of schizophrenia (Sams-Dodd 1995; Bachevalier et al. 2001; Insel and Young 2001; Kirkpatrick et al. 2001; Meaney 2001; Amaral 2002). Social interactions, particularly with unfamiliar conspecifics, are forms of psychological stress that theoretically could recruit the ventral HF. In addition, because subcortical structures with direct connections to the ventral HF regulate these activities, the study of social interactions may involve relatively preserved neurocircuits across mammalian species (Insel and Young 2001; Meaney 2001; Amaral 2002).

1. Avoidance modulation by the ventral HF. Extensive adult HF lesions restricted mainly to the dorsal segment appear to actually increase social interaction between unfamiliar conspecifics (Bannerman et al. 2001), while smaller adult lesions of either structure have no effect (Becker et al. 1999). In contrast, NVHFL damage disrupts adult social behavior in rats (Sams-Dodd et al. 1997; Becker et al. 1999; but see Daenen et al. 2002b) and primates (Bachevalier et al. 1999). Unlike other findings in NVHFL, impaired social behavior is apparent in prepubertal as well as adult animals (Sams-Dodd et al. 1997) and is exacerbated, rather than ameliorated, by clozapine (which often improves social deficits in schizophrenia) (Sams-Dodd et al. 1997). This reported impairment in social behavior in NVHFL, to be consistent with our hypothesis, would presumably be due to a failure to inhibit an otherwise prepotent avoidance response. Clarifying whether impairments are due to disruption of social behavior per se is also hindered by the fact that social behaviors are multidimensional—that is, influenced by multiple factors (social memory: Becker and Grecksch 2000; Alvarez et al. 2001; affect regulation: Psatta 1979; Vorel et al. 2001; Kjelstrup et al. 2002; motor activity: Drevets et al. 1999; novelty preference: Burns et al. 1996; behavioral sequencing: Maaswinkel et al. 1996, 1997). Thus, it is perhaps not surprising that different paradigms produce different conclusions (Daenen et al. 2002b).

2. Avoidance: Relationship to HF pathology and psychological stress in schizophrenia. Social withdrawal is a core deficit in many persons with schizophrenia, and clinical observation indicates that it is markedly exacerbated by psychological stress. Studies in humans also suggest a role for the HF in social behaviors, although not specifically in schizophrenia (Seeck et al. 1999). Thus, seizure patients with right temporal lobe epilepsy have impaired social function (scored on the basis of employment and social relations) compared to other seizure patients, and the impairment is negatively correlated to left hippocampal volume and age of onset (Seeck et al. 1999). Studies of negative symptoms and the deficit syndrome do not, however, support a link to diminished HF volume (Pearlson and Marsh 1999; but see Buchanan et al. 1993). Some structural imaging studies show a relationship between deficit symptoms and diminished white matter in the frontal lobe, which could be secondary to diminished projections from the anterior HF (Sanfilipo et al. 2000). Thus, while the concept that impaired social interactions could reflect a failure to constrain responses to psychological stress and the expanding ability to model social withdrawal in rodents are alluring, there is not much evidence at present to link this deficit in schizophrenia to anterior HF pathology.

Discussion
The HF is one of the neural structures that is most consistently altered in schizophrenia (Harrison 1999), yet its contribution to severe mental illness is unknown. We draw attention to the fact that the HF may be divisible into two functionally distinct structures bisecting its longitudinal axis and that the anterior portion appears to be more associated with schizophrenia. Specifically, the anterior segment appears to have a limited role in memory and learning but has extensive neural connections to circuits implicated in schizophrenia and to others regulating phylogenetically preserved functions that also appear impaired in many patients with severe mental illness. This distinction and its implications appear not to have been appreciated by many investigators. We propose a hypothesis based on the idea that hippocampal pathology disrupts these neurocircuits and func-
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Several of these previous models conceptualize the HF as clearly involved (Christensen and Bilder 2000) is new—Schmajuk and Tyberg 1991; Bilder et al. 1995; Gray (Kimble 1968; Mednick 1974; Conrad and Scheibel 1987; Velakoulis et al. 2001); many would likely state that cur- rent evidence is inadequate to assert that anterior and ven- tral HF are structurally and functionally homologous; oth- ers might contend that any relevant HF influence on other neurocircuits is likely mediated by the prefrontal cortex (Moghaddam 2002); some would certainly argue against the idea that psychological stress vulnerability is relevant to schizophrenia or that the HF serves a specific role in constraining diverse responses to psychological stimuli; and many will be uncomfortable with the vagueness asso- ciated with the concept of psychological stress. Our ideas are thus speculative, but their potential utility should be apparent in that they capitalize on recent advances in sys- tems neuroscience and thus provide new opportunities for translational research into the mechanisms of severe mental illness.

Relationship to Others’ Views of HF Pathology and Stress Vulnerability in Schizophrenia. This review is one of several over the past 35 years that have attempted to link HF pathology to the cognitive dysfunction under- lying schizophrenia. Neither the concept that this structure specifically modulates responses to psychological stress (Kimble 1968; Mednick 1974; Conrad and Scheibel 1987; Schmajuk and Tyberg 1991; Bilder et al. 1995; Gray 1998) nor the idea that anterior HF pathology is particu- larly involved (Christensen and Bilder 2000) is new. Several of these previous models conceptualize the HF as associating the current sensory data stream with previous sensory experience and in so doing establishing the potential significance of new sensory stimuli and hence enabling integrated “motor” (in the broadest sense) responses. Psychological stress may simply test the integrity of these poorly understood processes. Our proposal differs, however, in emphasizing that HF pathology also produces related changes in the structure and func- tion of other neurosystems that are better characterized and preserved across species, providing alternative means for investigating the nature and significance of these changes. Specifically, we propose an approach by which one may gain insight into how complex cognitive functions have been disrupted without having to first under- stand their normal operations. These ideas can be readily tested, thereby leading to a refinement or rejection of the concepts we have put forth.

Assessment of Candidate Findings. We assessed whether several findings in schizophrenia are likely to be a product of this putative impairment in anterior HF function and can be further studied in rodents with NVHFL. This section served as both a preliminary assessment of the hypothesis and an illustration of its potential. We excluded three findings (i.e., stereotypic behavior, SCRs, and HR responses) based on evidence that they do not appear to be closely linked to anterior/ventral HF structure or activity. Future studies could indicate that our assessment was premature. For others (avoidance, pac- ing), the role of the anterior HF or the relationship to psy- chological stress is unclear. Changes in neuroendocrine (i.e., HPA axis and pAVP) activity and in PPI are at pre- sent the most appealing candidates, although their suit- ability is also far from established. In particular, we pro- pose that the neuroendocrine findings in the subset of schizophrenia patients with impaired water excretion reflect the hypothesized HF dysfunction, that this subset of patients offers a prototype of this anterior HF pathol- ogy, and that this subset’s salutary response to the atypical neuroleptic clozapine provides additional opportunities to better localize and define the nature of anterior HF dys- function. We are currently testing these ideas.

Schizophrenia or Psychosis? Among the many ques- tions that this review raises is whether HF pathology is relevant to psychosis in general or schizophrenia in partic- ular. We do not know. Our contention is that psychiatric investigators are only beginning to establish a nosology that conforms to the pathophysiology of severe mental illness. Our task is to first learn the “language of the brain”—for instance, how the brain parses, processes, and reintegrates different types of information—and then we will be able to start to define how disruption of these
functions contributes to severe mental illness. Our goal here has been to offer one example of how we may now be in a position to break new ground.

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