Hippocampal Abnormalities in Psychiatric Disorders

I. Introduction

Hippocampus is one of the regions in which different psychiatric disorders show abnormalities. Volume reduction in hippocampus has been reported in schizophrenia (Nelson et sl., 1998; Wright et al., 2000), posttraumatic stress disorder (Gilbertson et al., 2002), depression (Brambilla et al., 2002), autism (Aylward et al., 1999), and borderline personality disorder (Driessen et al., 2000). A natural question to ask here is: Why are these phenotypically different disorders show common abnormalities in hippocampus? Indeed, there have been efforts to understand this overlap across disorders, with the hippocampal atrophy due to stress being the most prominent explanation (Sala et al, 2004; Teicher, 2003). Despite large number of studies investigating hippocampal abnormalities in various disorders, however, there have been relatively few attempts to incorporate what has been achieved and what needs to be considered in this area of research. This paper summarizes previous findings on hippocampal abnormalities in schizophrenia, posttraumatic stress disorder (PTSD), depression, and borderline personality disorder (BPD), presents a hypothetical explanation for this overlap across different disorders including the hippocampal atrophy model, and suggests some limitations of prior research that should be

considered in the future.

II. Neuroimaging Findings

1. Schizophrenia

Studies have shown that hippocampal volumes are smaller in schizophrenic patients compared to the controls (Nelson et al., 1998; Wright et al., 2000). Although Copolov et al. (2000) had suggested that left hippocampal volume reduction is consistently related to schizophrenia, later studies have shown that there is no significant effect of laterality (Velakoulis, 2001). There is no evidence of difference between male and female (Nelson et al., 1998; Wright et al., 2000). Left hippocampal volume loss has been reported to be correlated with the severity of negative symptoms (Matsumoto et al., 2001; Rejarethinam et al., 2001).It is not yet clear when hippocampal abnormalities occur in the course of illness although a few studies had suggested that hippocampal volume reduction takes place during adolescence (Giedd et al., 1999; Jacobsen, 1998). Questions remain as to whether hippocampal volume reduction is a time-limited process in adolescence and how it is related to the onset of pathology (early vs. late onset) and the prognosis.

2. Posttraumatic Stress Disorder (PTSD)

Reduced hippocampal volumes have been found in PTSD patients who experienced either

combat-related (Bremner et al., 1995; Gurvits et al, 1996) or non-combat events (Bremner et al., 1997; Stein et al., 1997). It is unclear, however, whether hippocampal volume reduction is unilateral or bilateral in PTSD because different studies have reported inconsistent findings. Results have shown volume reduction in left (Bremner et al., 1997), right (Bremner et al., 1995; Schuff et al., 1997), or both hippocampi (Bremner et al., 2003; Gurvits et al., 1996). Hippocampal volume in PTSD has been reported to be negatively correlated with cognitive deficits, especially memory (Bremner et al., 1995; Gurvits et al, 1996). One recent study compared hippocampal volumes of monozygotic twins in which one of the twin pairs was exposed to combat and the other was not (Gilbertson et al, 2002). The result of this study showed that hippocampal volume of the co-twin who had not been exposed to trauma could accurately predict the severity of symptoms of their co-twin who had been exposed to combat and developed PTSD, suggesting that reduced hippocampus may be a predisposing factor of disorder.

3. Depression

Reduced hippocampal volumes have also been found in unipolar depression with remitted patients (Sheline et al., 1999) and with current depressive patients (Bell-McGinty et al., 2002; Vythilingam et al., 2002). Hippocampal shrinkage in unipolar depression has been reported to be positively correlated with the duration of illness (Bell-McGinty et al., 2002; Sheline et al., 1999).

Like PTSD, the laterality of hippocampal volume reduction is unclear. Results have shown volume reduction in left (Vythilingam et al., 2002), right (Bell-McGinty et al., 2002), or both hippocampi (Sheline et al., 1999). One possible reason for the inconsistency of results may be the heterogeneity of the patient population in the study. For example, one recent study compared depressive patient with and without the history of childhood abuse and found that only the abused group of patients showed significant hippocampal volume loss compared to both the non-abused group and the controls (Vythilingam et al., 2002). Non-abused depressive patients did not have reduced hippocampus compared to the non-depressive controls. An important question remains unanswered: Is hippocampal volume reduction a predisposition or a consequence of depression? Moreover, most research has focused on unipolar mood disorder and little is known about possible hippocampal abnormalities in bipolar disorder.

4. Borderline Personality Disorder (BPD)

Although there had been relatively little research on hippocampal volume reduction in BPD patients, some recent studies have found reduced hippocampal volume in BPD patients (Driessen et al., 2000; Rusch et al., 2003; Schmahl et al., 2003). The focus of research in BPD patients has been repeated childhood maltreatment which is frequently reported by these patients. The laterality of hippocampal abnormalities in BPD is unclear. Some findings indicate bilateral volume reduction

(Driessen et al., 2000; Schmahl et al., 2003) whereas others suggest unilateral (left) volume reduction (Rusch et al., 2003). Furthermore, most studies involved women BPD patients. Although it is true that there are much more women BPD patients than men, scarce of research with men BPD patients makes it almost impossible to examine whether there are any differences between genders. It is also unclear whether hippocampal volume reduction is a predispositional factor to the disorder or a consequence of it.

III. Hypothetical Explanation – Hippocampal Atrophy Theory

The most prominent explanation for the hippocampal volume reduction in various disorders including schizophrenia, PTSD, depression, and BPD is hippocampal atrophy due to stress. Hippocampal neurons are highly sensitive to neurotoxic effects of glucocorticoid increase which results from stressful experience (Sapolsky, 2000), and animal studies have shown reduced hippocampal neurons after exposure to stressful events (Sapolsky, 1996). According to hippocampal atrophy theory, some psychiatric disorders such as those mentioned above are related to acute or chronic stress; thus hippocampal neuronal loss and cognitive impairments are reported (Sala et al., 2004). In many studies, “stress” that schizophrenic, PTSD, depressive, or BPD patients were exposed to is acute traumatic event (e.g., combat) or chronic abuse in childhood (e.g., sexual abuse). For some disorders like schizophrenia and depression, “stress” also can mean repeated

schizophrenic or depressive episodes. Although hippocampal atrophy theory makes sense in that hippocampus plays an important role in regulating stress (Sala et al., 2004) and that stress is a general concept that can be applied to different disorders, there are some limitations that needs attention.

Firstly, the direction of influence is unclear – does hippocampal volume loss come before or after the onset of a particular disorder? In other words, the question of whether hippocampal reduction is a predisposition or a consequence of a disorder remains unanswered. Different explanations are proposed for different disorders. For example, hippocampal volume reduction results from childhood abuse in BPD patients and from combat exposure in PTSD patients. For depressive patients, some studies have suggested childhood abuse as being responsible for the loss of hippocampal neurons (Vythilingam et al., 2002), whereas others have proposed repeated depressive episodes as being the source of stress that damages hippocampus. All these explanations make it difficult to figure out whether hippocampal volume loss is an event that precedes the onset of a disorder or a result of having that disorder. It might be that hippocampal volume reduction is both a risk factor and a consequence of a disorder; it might be one or the other depending on which disorder we are talking about. Whichever the case, this is an issue that must be clarified.

Secondly, it is unclear why only some psychiatric disorders show hippocampal abnormalities and not others. If stress is responsible for the neuronal loss in hippocampus, why not

all disorders show this phenomenon? For example, if repeated depressive episodes are the source of stress for unipolar depression patients, how about bipolar patients? Those suffering from panic disorder with agoraphobia will certainly experience distress when they are outside in a crowd. If childhood abuse is an important stressful event that damages hippocampal neurons, it should be noted that the history of abuse is present in disorders other than the ones commonly mentioned in hippocampal atrophy theory as well. All psychiatric disorders are associated with stress though the specifics may differ among them. The hippocampal atrophy theory needs to justify why the selected disorders are assumed to be related to stress while others are not so.

IV. Conclusion and Future Directions

Hippocampal volume reduction has been found in many psychiatric disorders including schizophrenia, PTSD, depression, and BPD. This area has been a focus of attention recently and much effort has been made to explain the findings. It will be exciting to see how hippocampal abnormalities are related to various disorders since this small region in the brain is known to play a critical role in cognitive and emotional functioning in human. However, there are some limitations in previous research that will need consideration in the future.

Firstly, most studies had been cross-sectional and correlational in nature. Thus it was not clear from the results whether hippocampal abnormalities precede or follow the onset of disorder.

Longitudinal studies with high risk group will help clarify the direction of influence. Gilbertson et al.(2002)'s study with monozygotic twins in which only one of the co-twins was exposed to trauma (who then either did or did not develop PTSD) illustrates an excellent example where one can claim that hippocampal volume reduction is a predisposing factor for and not a consequence of PTSD. There might be cases where disorder precedes hippocampal neuronal loss. There simply has to be more studies with elaborate design to examine whether the direction of influence is one way or the other (or maybe both – a reciprocal relationship).

Secondly, more efforts should be made to propose theories explaining *how* the loss of hippocampal neurons affects or is affected by different psychiatric disorders. Although a large number of studies show hippocampal volume reduction is associated with different disorders, there are few theories that can be used as a framework to interpret such findings. Up to date, the hippocampal atrophy theory is the most common, if not the only, explanation to understand the research findings. This theory is not without limitations of its own as mentioned in the previous section (although it can also be said that no theory is without faults; this is one of the reasons why there should be many theories that attempts to explain the same findings from different perspectives).

Thirdly, the heterogeneity of patient population should be considered. Even among patients with the same diagnosis differ in significant ways. For example, the duration of illness or the

number of episodes has been frequently considered in studies with schizophrenic and depressive patients, and these indeed have shown to be related to different findings. Other factors that need consideration in designing a study include the type of stress in PTSD (acute stress vs. chronic stress), experience of childhood abuse, and severity of symptoms (which is partly related to the duration of illness). Another important factor that should always be considered is comorbid disorders. While some studies have appropriately reflected the issue of comorbidity in their research design (mostly by excluding patients who have comorbid disorders), other studies have neglected this issue altogether. For example, a large proportion of BPD patients are also diagnosed as depression. Thus if this comorbid condition is not considered, the results might be flawed. Overall, there are many factors that contribute to the heterogeneity of patient population and these will be at least partly responsible for the inconsistencies in previous findings.

In conclusion, neuroimaging studies suggest that hippocampal volume reduction is found in various psychiatric disorders such as schizophrenia, PTSD, depression, and BPD. Hippocampal atrophy due to stress has been much used as a framework to explain these findings, but more theories are yet to be proposed. Although there were some limitations in previous studies that need consideration, there is little doubt that they will be addressed in the near future.

References

Aylward, E. H., Minshew, N. J., Goldstein, G., Honeycutt, N. A., Augustine, A. M., Yates, K. O., Barta, P. E., & Pearlson, G. D. (1999). MRI volumes of amygdala and hippocampus in non-mentally retarded autistic adolescents and adults. *Neurology, 53*, 2145-2150.

Bell-McGinty, S., Butters, M. A., Meltzer, C. C., Greer, P. J., Reynolds, C., & Becker, J. T. (2002). Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. *American Journal of Psychiatry, 159*, 1424-1427.

Brambilla, P., Barale, F., Caverzasi, E., & Soares, J. C. (2002). Anatomical MRI findings in mood and anxiety disorders. *Epidemiologia e psichiatria sociale, 11*, 88-99.

Bremner, J. D., Randall, P., Scott, T. M., Bronen, R. A., Seibyl, J. P., Southwick, S. M., Delaney, R. C., McCarthy, G., Charney, D. S., & Innis, R. B. (1995). MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *American Journal of Psychiatry, 152*, 973-981.

Bremner, J. D., Randall, P., Vermetten, E., Staib, L., Bronen, R. A., Mazure, C., Capelli, S., McCarthy, G., Innis, R. B., & Charney, D. S. (1997). Magnetic resonance imaging-based

measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse - a preliminary report. *Biological Psychiatry, 41*, 23-32.

Bremner, J. D., Vythilingam, M., Vermetten, E., Southwick, S. M., McGlashan, T., Nazeer, A., Khan, S., Vaccarino, L. V., Soufer, R., Garg, P. K., Ng, C. K., Staib, L. H., Duncan, J. S., & Charney, D. S. (2003). MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *American Journal of Psychiatry, 160*, 924-932.

Copolov, D., Velakoulis, D., McGorry, P., Mallard, C., Yung, A., Rees, S., Jackson, G., Rehn, A., Brewer, W., & Pantelis, C. (2000). Neurobiological findings in early phase schizophrenia. *Brain Research Reveiws, 31*, 157-165.

Driessen, M., Hermann, J., Stahl, K., Zwaan, M., Meier, S., Hill, A., Osterheider, M., & Petersen, D. (2000). Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of general psychiatry, 57*, 1115-1122.

Giedd, J. N., Jeffries, N. O., Blumenthal, J., Castellanos, F. X., Vaituzis, A. C., Fernandez, T., Hamburger, S. D., Liu, H., Nelson, J., Bedwell, J., Tran, L., Lenane, M., Nicolson, R., & Rapoport, J.L. (1999). Childhood-onset schizophrenia: progressive brain changes during adolescence. *Biological Psychiatry, 46*, 892-898.

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience, 5*, 1242-1247.

Gurvits, T. V., Shenton, M. E., Hokama, H., Ohta, H., Lasko, N. B., Gilbertson, M. W., Orr, S. P., Kikinis, R., Jolesz, F. A., McCarley, R. W., & Pitman, R. K. (1996). Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biological Psychiatry, 40*, 1091-1099.

Jacobsen, L. K., Giedd, J. N., Castellanos, X., Vaituzis, C., Hamburger, S. D., Kumra, S., Lenane, M. C., & Rapoport, J. L. (1998). Progressive Reduction of Temporal Lobe Structures in Childhood-Onset Schizophrenia. *American Journal of Psychiatry, 155*, 678-685.

Matsumoto, H., Simmons, A., Williams, S., Pipe, R., Murray, R., & Frangou, S. (2001). Structural magnetic imaging of the hippocampus in early onset schizophrenia. *Biological Psychiatry, 49*, 824-831.

Nelson, M. D., Saykin, A. J., Flashman, L. A., & Riordan, H. J. (1998). Hippocampal volume reduction in schizophrenia as assessed by magnetic resonance imaging: A meta-analytic study. *Archives of general psychiatry, 55*, 433-440.

Rajarethinam, R., DeQuardo, J. R., Miedler, J., Arndt, S., Kirbat, R., Brunberg, J. A., & Tandon, R. (2001). Hippocampus and amygdala in schizophrenia: assessment of the relationship of

neuroanatomy to psychopathology. *Psychiatry Research: Neuroimaging Section, 108*, 79-87.

Rusch, N., van Elst, L. T., Ludaescher, P., Wilke, M., Huppertz, H. J., Thiel, T., Schmahl, C., Bohus, M., Lieb, K., Hesslinger, B., Hennig, J., & Ebert, D. (2003). A voxel-based morphometric MRI study in female patients with borderline personality disorder. *Neuroimage, 20*, 385-392.

Sala, M., Perez, J., Soloff, P., Ucelli di Nemi, S., Caverzasi, E., Soares, J. C., & Brambilla, P. (2004). Stress and hippocampal abnormalities in psychiatric disorders. *European Neuropharmacology, 14*, 393-405.

Sapolsky, R. M. (1996). Why stress is bad for your brain. *Science, 273*, 749-750.

Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry, 57*, 925-935.

Schmahl, C. G., Vermetten, E., Elzinga, B. M., & Bremner, J. D. (2003). Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Research, 122*, 193-198.

Schuff, N., Marmar, C. R., Weiss, D. S., Neylan, T. C., Schoenfeld, F., Fein, G., & Weiner, M. W. (1997). Reduced hippocampal volume and n-acetyl aspartate in posttraumatic stress disorder. *Annals of the New York Academy of Sciences, 821*, 516-520.

Sheline, Y. I., Sanghavi, M., Mintun, M. A., & Gado, M. H. (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *Journal of Neuroscience, 19*, 5034-5043.

Stein, M. B., Koverola, C., Hanna, C., Torchia, M. G., & McClarty, B. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine, 27*, 951-959.

Teicher, M. H., Anderson, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., & Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience and Biobehavioral Reviews, 27*, 33-44.

Velakoulis, D., Stuart, G. W., Wood, S. J., Smith, D. J., Brewer, W. J., Desmond, P., Singh, B., Copolov, D., & Pantelis, C. (2001). Selective bilateral hippocampal volume loss in chronic schizophrenia. *Biological Psychiatry, 50*, 531-539.

Vythilingam, M., Heim, C., Newport, J., Miller, A. H., Anderson, E., Bornen, R., Brummer, M., Staib, L., Vermetten, E., Charney, D. S., Nemeroff, C. B., & Bremner, J. D. (2002). Childhood trauma associated with smaller hippocampal volume in women with major depression. *American Journal of Psychiatry, 159*, 2072-2080.

Wright, I. C., Rabe-Hesketh, S., Woodruff, P. W., David, A. S., Murray, R. M., & Bullmore, E. T. (2000). Meta-analysis of regional brain volumes in schizophrenia. *American Journal of*

Psychiatry, 157, 16-25.