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Short communication

Comparison of Hippocampal Volumes in Schizophrenia, Schizoaffective and Bipolar Disorder

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ABSTRACT

The reduction of hippocampal volume was frequently reported in schizophrenia, but not in bipolar disorder. This volume reduction is associated with clinical features of schizophrenia, in particular with working and verbal memory impairments. Schizoaffective disorder, as a specific disorder sharing clinical features of both schizophrenia and bipolar disorder is rarely analyzed as a separate disorder in neurobiological studies. The aim of this study was to compare hippocampal volumes in separate groups of patients with schizophrenia, schizoaffective and bipolar disorder. Hippocampal volumes were estimated using high resolution magnetic resonance imaging in 60 subjects, 15 subjects in each patient and one healthy volunteer (control) group. There were no significant differences in hippocampal volume between bipolar disorder and control group. Hippocampal volume was statistically significantly reduced in the group of patients with schizophrenia and schizoaffective disorder, compared to either bipolar disorder or control group, thus supporting the hypothesis that hippocampal volume reduction could be considered as a possible neurobiological basis for clinical aspects of schizophrenia and schizoaffective disorder associated with working and verbal memory impairment.

Key words: *hippocampal volume, schizophrenia, schizoaffective disorder, bipolar disorder*

Introduction

Schizophrenia, schizoaffective disorder and bipolar disorder, even though classified under different diagnostic classes based on the prominence of mood symptoms[1,2], share psychotic features as one of the most prominent features of clinical presentation. Since different clinical features can be viewed as possible dysfunctions in different parts of neuronal network involved in complex aspects of human behavior[3,4], possible common neurobiological basis for psychotic features and different neurobiological basis for mood features of these disorders can be suggested. Even though patients with schizoaffective disorder display both psychotic symptoms and mood symptoms, in studies of the neurobiological basis of psychiatric disorders, schizoaffective disorder is often included as either part of schizophrenia patient group or as part of bipolar disorder patient group[5–12]. Assuming that there is a different neurobiological basis for psychotic and mood features, this approach could seriously impede research results, whereas on the other hand, research focusing on the schizoaffective patient group can provide valuable results for the interpretation of the specificity of neurobiological findings for all three diagnostic categories[13–15].

Overall hippocampal volume reduction, hippocampal cell loss and white matter volume reduction have frequently been described in neuropathological studies in schizophrenia[16–20]. Modern in vivo imaging studies that allow for the differentiation between hippocampus and adjacent structures support these findings[7,8,21–25]. These structural changes were more pronounced in schizophrenia patients with formal thought disturbances and deficit symptoms and associated in particular with working and verbal memory impairment[25–28]. Most studies have

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not reported hippocampal volume reduction in bipolar disorder[9,10,22,29], and to the best of our knowledge there were no studies analyzing separately the group of patients with schizoaffective disorder.

The aim of this study was to compare hippocampal volumes in separate groups of patients with schizophrenia, schizoaffective and bipolar disorders.

Subjects and Methods

The study included 60 subjects, 15 in each patient and one healthy subjects group. Age, gender, age at onset, and number of episodes were recorded for all subjects. Psychiatric diagnoses were made by two independent psychiatrists, and only the subjects fulfilling both Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition (DSM-IV)[2] and International Classification of Diseases, Tenth Revision (ICD-10)[1] criteria were included. Magnetic resonance imaging was performed in the absence of acute episode symptoms. Control group consisted of healthy volunteers. The following exclusion criteria were applied on all study subjects: history of perinatal brain damage, comorbid mental or other disorder of central nervous system, serious general health condition, age bellow 18 or above 60, left-handedness or ambidexterity. The study was approved by the local ethics committee and informed consent obtained from all participants.

Magnetic resonance images were acquired using a 2 T Prestige Gyrex scanner (General Electrics/Elscint). A 1.1-mm-thick coronal series (3D gradient echo; repetition time 25 ms; echo time 6 ms; field of view 180×220 mm, matrix 200×256) was processed on O2 (Silicon Graphics) workstation using OmniPro (Elscint/General Electrics) software. Regions of interest were delineated manually by a single rater blind to the study group, based on well-known neuroanatomical and neuroradiological criteria[30]. The dorsal boundary is alveus, ventral boundary hippocampal fissure and temporal lobe white matter, and the lateral boundary the temporal horn of the lateral ventricle. The medial boundary was defined in rostro-caudal direction by the medial edge of the *Gyrus ambiens*, the uncal fissure, and the hippocampal fissure. Thus delineated, the structure includes *Cornu ammonis* and *Gyrus dentatus*. The first rostral slice was the one at the tip of the temporal horn of the lateral ventricle, and the last caudal slice analyzed was the one where both pairs of mesencephalic colliculi were still visible. Descriptive statistics was used to analyze demographic, clinical and volumetric data. A one-way analysis of variance was used to test for group differences in hippocampal volumes. All analyses were interpreted at 5% level of significance.

Results

Demographic and clinical features of study subjects are shown in Table 1. There is no statistically significant difference in gender and duration of disorder among study groups. The difference in age of onset is statistically significant among all patient groups. Patients with bipolar disorder are significantly older than healthy control ($p < 0.001$), schizophrenia ($p < 0.00001$), and schizoaffective group ($p = 0.02$). Patients with schizoaffective disorder are significantly older than patients with schizophrenia ($p = 0.02$).

Hippocampal volume in both hemispheres is statistically significantly reduced in schizophrenia and schizoaffective disorder compared to healthy control group. There is no statistically significant difference in hippocampal volume between bipolar disorder and healthy control group. In the right hippocampus, the volume reduction is statistically significant even when comparing the schizophrenia and bipolar patient group. Volume differences per study groups are presented in Table 2.

Comparison of left and right hippocampal volumes shows that left hippocampal volumes are smaller, but in this subject sample the difference is statistically significant only in the group of patients with bipolar disorders (Table 3).

Discussion

All patients included in the study were chronic patients, and there was no significant difference in the duration of disorders between the groups. The differences

TABLE 1
DEMOGRAPHIC AND CLINICAL FEATURES OF STUDY SUBJECTS

	Healthy control N=15		Schizophrenia N=15		Schizoaffective disorder N=15		Bipolar disorder N=15	
Age (years)	X=38 (SD=11.9)		X=34 (SD=6.13)		X=44 (SD=8.85)		X=54 (SD=4.8)	
Gender								
F M	9	6	10	5	8	7	10	5
Age at onset (years)	NA		X=26 (SD=4.10)		X=32 (SD=5.04)		X=45 (SD=6.4)	
Duration of disorder (years)	NA		X=8 (SD=5.25)		X=12 (SD=6.11)		X=9 (SD=4.9)	
Number of episodes	NA		4		7		5	
MAN DEP	NA	NA	NA	NA	4	3	3	2

F – female, M – male, NA – not applicable, MAN – manic, DEP – depressive

TABLE 2
HIPPOCAMPAL VOLUME DIFFERENCES PER STUDY GROUPS (P VALUES)

HL				
	HC	SCH	SCHAFF	BIP
HC	NA	0.001083	0.000464	0.123484
SCH	0.001083	NA	0.994769	0.343651
SCHAFF	0.000464	0.994769	NA	0.227089
BIP	0.123484	0.343651	0.227089	NA
HR				
HC	NA	0.004664	0.012312	0.881365
SCH	0.004664	NA	0.988565	0.038975
SCHAFF	0.012312	0.988565	NA	0.085345
BIP	0.881365	0.038975	0.085345	NA

HL – left hippocampus, HR – right hippocampus, HC – healthy control, SCH – schizophrenia, SCHAFF – schizoaffective disorder, BIP – bipolar disorder, NA – not applicable

TABLE 3
VOLUME DIFFERENCES BETWEEN LEFT AND RIGHT HIPPOCAMPUS (P VALUES)

Healthy control	Schizophrenia	Schizoaffective disorder	Bipolar disorder
0.580950	0.116369	0.222198	0.001005 (L R)

L – left, R – right

in age of onset are characteristic of the particular disorder[31], and therefore the difference in age among all patient groups is statistically significant. Due to the small number of patients in the study sample, the results are to be taken cautiously, but since the number of subjects involved in other similar studies is often small as well, most of the conclusions in recent literature are based on meta-analyses of previously published results[7–9,23,24,29]. In this context, studies comparing these disorders in the same sample are of particular importance[5,13–15].

The reduction of hippocampal volume in schizophrenia was confirmed in this study, whereas there was no significant reduction in the bipolar disorder. These results are in consistence with most of the previous studies, as already presented in the introduction[7–10,16–25,29]. Hippocampal volume was statistically significantly reduced in the group of patients with schizoaffective disorder, thus supporting the hypothesis that hippocampal volume reduction could be considered as a possible neurobiological basis for clinical aspects of schizophrenia and schizoaffective disorder associated with working and verbal memory impairment[25–28]. Whether this volume reduction could be attributed to cell loss, white matter reduction or some other underlying mechanism, remains to be elucidated[16–20].

Volume reduction affected both left and right hippocampi, and it was not expected that only left hippocampal volume would be statistically significantly reduced in schizophrenia, or consequently in schizoaffective patient group, since according to the literature review, such findings could be expected in first-episode patient groups[7–9,22–24]. There was no reversal of cerebral asymmetry, as left hippocampal volumes were generally smaller than right within a patient group, which is consistent with literature data[7,9]. The size of the sample was too small to test for gender differences, but the influence of gender was not expected in the chronic patient groups[7–9,22–24].

These results support the conclusion that hippocampal volume reduction could be considered as possible neurobiological basis for clinical impairments shared by schizophrenia and schizoaffective disorders, in particular verbal and working memory impairments.

REFERENCES

1. WORLD HEALTH ORGANIZATION, The ICD-10 Classification of Mental and Behavioral Disorders. Tenth Revision (WHO, Geneva, 1992). — 2. AMERICAN PSYCHIATRIC ASSOCIATION, Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition (American Psychiatric Press, Inc., Washington, DC, 1995). — 3. GOLDMAN-RAKIC PS, Annu Rev Neurosci, 11 (1988). — 4. ANDREASEN NC, Science, 275 (1997) 1586. — 5. MARNEROS A, DEISTER A, ROHDE A, Eur Arch Psychiatry Clin Neurosci, 241 (1991) 187. — 6. BILDER RM, WU H, BOGERTS B, ASHTARI M, ROBINSON D, WOERNER M, LIEBERMAN JA, DEGREEF G, Int J Psychophysiol, 34 (1999) 197. — 7. WRIGHT IC, RABE-HESKETH S, WOODRUFF PWR, DAVID AS, MURRAY RM, BULLMORE ET, Am J Psychiatry, 157 (2000) 16. — 8. SHENTON ME, DICKEY CC, FRUMIN M, MCCARLEY RW, Schizophr Res, 49 (2001) 49. — 9. MCDONALD C, ZANELLI J, RABE-HESKETH S, ELLISON-WRIGHT I, SHAM P, KALIDINDI S, MURRAY RM, KENNEDY N, Biol Psychiatry, 56 (2004) 411. — 10. MCDONALD C, MARSHALL N, SHAM PC, BULLMORE ET, SHULZE K, CHAPPLE B, BRAMON E, FILBEY F, QURAISHI S, WALSHE M, MURRAY RM, Am J Psychiatry, 163 (2006) 478. — 11. NESVAG R, LAWYER

G, VARNAS K, FJELL AM, WALHOVD KB, FRIGESSI A, JONSSON EG, AGARTZ I, Schizophr Res, 98 (2008) 16. — 12. WOBROCK T, SITTINGER H, BEHRENDT B, D'AMELIO R, FALKAI P, Eur Arch Psychiatry Clin Neurosci, 259 (2009) 28. — 13. RADONIC E, HENIGSBERG N, UZUN S, FOLNEGOVIĆ-ŠMALC V, Period Biol, 100 (1998) 201. — 14. GETZ G, DELBELLO MP, FLECK DE, ZIMMERMAN ME, SCHWIERS ML, STRAKOWSKI SM, Scizophr Res, 55 (2002) 55. — 15. RADONIC E, HENIGSBERG N, RADOS M, MIMICA N, FOLNEGOVIC-SMALC V, Coll Antropol, 32 (2008) 139. — 16. BOGERTS B, MEERTZ E, SCHONFELDT-BAUSCH R, Arch Gen Psychiatry, 42 (1985) 784. — 17. FALKAI B, BOGERTS B, Eur Arch Psychiatry Neurol Sci, 236 (1986) 154. — 18. JESTE DV, LOHR JB, Arch Gen Psychiatry, 46 (1989) 1019. — 19. COLTER N, BATTAL S, CROW TJ, JOHNSTONE EC, BROWN R, BRUTON C, Arch Gen Psychiatry, 44 (1987) 1023. — 20. HECKERS S, HEINSEN Y, BECKMAN H, Biol Psychiatry, 29 (1991) 556. — 21. GUR RE, TURETSKY BI, COWELL PE, FINKELMAN C, MAANY V, GROSSMAN RI, ARNOLD SE, BILKER WB, GUR RC, Arch Gen Psychiatry, 57 (2000) 769. — 22. VELAKOULIS D, WOOD SJ, WONG MT, MCGORRY PD, YUNG A. PHILLIPS L, SMITH D, BREWER W, PROFFITT T, DESMOND P, PANTELIS C, Arch Gen Psychiatry, 63 (2006) 250. — 23. VITA A, DE PERI L, SILENZI C, DIECI M, Schizophr Res, 82 (2006) 75. — 24. STEEN RG, MULL C, MCCLURE R, HARNER RM, LIEBERMAN JA, Br J Psychiatry, 188 (2006) 510. — 25. GUR RE, COWELL PE, TURETSKY BI, GALLACHER F, CANNON T, BILKER W, GUR RC, Arch Gen Psychiatry, 55 (1998) 145. — 26. GOLD JM, WEINBERGER DR, Curr Opin Neurobiol, 5 (1995) 225. — 27. NESTOR PG, SHENTON ME, MCCARLEY RW, HAIMSON J, SCOTT SMITH R, O'DONNELL B, KIMBLE M, KIKINIS R, JOLESZ FA, Am J Psychiatry, 150 (1993) 1849. — 28. THOMA RJ, MONNIG M, HANLON FM, MILLER GA, PETROPOULOS H, MAYER AR, YEO R, EULER M, LYSNE P, MOSES SN, CANIVE JM, JINS, 15 (2009) 182. — 29. STOLL AL, RENSHAW PF, YURGELUN-TODD DA, COHEN BM, Biol Psychiatry, 48 (2000) 505. — 30. DUVERNOY HM, The human brain: surface, three-dimensional sectional anatomy and MRI. (Springer Verlag, Wien, New York, 1995). — 31. FOLNEGOVIĆ-ŠMALC V, FOLNEGOVIĆ Z, KULČAR Ž, Br J Psychiatry, 156 (1990) 368.

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USPOREDBA VOLUMENA HIPOKAMPUSA U SHIZOFRENIJI, SHIZOAFEKTIVNOM I BIPOLARNOM POREMEĆAJU

S A Ž E T A K

Smanjenje volumena hipokampusa čest je nalaz u shizofreniji, ali ne i u bipolarnom poremećaju. Ovo smanjenje volumena povezano je s kliničkim obilježjima shizofrenije, posebice oštećenjima radnog i verbalnog pamćenja. Shizoafektivni poremećaj, specifični poremećaj u kojem se ispoljavaju klinička obilježja i shizofrenije i bipolarnog poremećaja, rijetko se analizira kao zasebni poremećaj u neurobiološkim istraživanjima uopće. Cilj ovog istraživanja bio je usporediti volumen hipokampusa u zasebnim skupinama pacijenata sa shizofrenijom, shizoafektivnim i bipolarnim poremećajem. Za mjerenje volumena hipokampusa rabljena je metoda oslikavanja mozga magnetskom rezonancijom visoke rezolucije na 60 ispitanika, po 15 u svakoj skupini oboljelih kao i u skupini duševno zdravih dobrovoljaca (kontrolna skupina). Nema statistički značajnih razlika u volumenu hipokampusa između pacijenata s bipolarnim poremećajem i kontrolne skupine. Volumen hipokampusa statistički je značajno smanjen u skupinama pacijenata sa shizofrenijom odnosno sa shizoafektivnim poremećajem, o odnosu na skupinu s bipolarnim poremećajem kao i na kontrolnu skupinu. Ovaj rezultat podržava pretpostavku da smanjenje volumena hipokampusa može predstavljati neurobiološku podlogu kliničkih obilježja shizofrenije i shizoafektivnog poremećaja povezanih s oštećenjima radnog i verbalnog pamćenja.