

ORIGINAL ARTICLES

Enlargement of the Third Ventricle in affective disorders

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ABSTRACT

Introduction : There have been inconsistent reports of dilation of the third ventricle (III-V) in bipolar disorder. Within the lateral walls of III-V are hypothalamic nuclei which mediate the neuroendocrine, sleep, appetite and autonomic disturbances which characterise a depressive episode.

Methods : The III-V width, immediately anterior to the mamillary bodies, was measured in 74 bipolar I or II subjects (m=25, f=49, mean age 36.1(11.3yr) and 33 healthy controls (m=17, f=16, mean age 35.6(12.6yr) from MRI coronal inversion recovery scans.

Results : Bipolar subjects had significantly ($t=2.16$, $p=0.03$) wider III-V (0.45(0.15cm) than controls (0.40(0.12cm). Examining data with a General Linear Model with gender and diagnoses as categoric variables and age as a continuous variable, III-V width depended significantly on gender ($p=0.016$), age ($p<0.001$) and differed significantly ($p=0.03$) between bipolar subjects and controls. The rate of III-V dilation was estimated to be 0.0048cm/yr in male bipolar subjects and 0.0040cm/yr in females.

Comment : Bipolar disorder is associated with increased III-V width and progressive dilation. It is proposed that dilation may be associated with dysfunction of hypothalamic nuclei in the III-V lateral walls.

Key words: Magnetic resonance imaging, bipolar affective disorder, newco radiology, third ventricle volume

Many of the biological features of an affective episode are subserved by hypothalamic nuclei adjacent to the walls of the third ventricle (III-V) (Williams et al. 1995). A well established finding in depressive disorder is hypercortisolaemia (Watson et al. 2002). This is mediated by corticotrophin releasing factors (CRF) from the paraventricular nucleus of the hypothalamus controlling the release of ACTH from the anterior pituitary which, in turn, acts on the adrenals releasing corticosteroids (the HPA axis). A recent MRI study has reported a decreased pituitary size in unipolar and bipolar disorder which may reflect dysfunction of this axis (Sassi et al. 2001).

Many of the vegetative symptoms of a depressive episode, for example autonomic disturbance, sleep disorder and appetite

disregulation leading to weight loss are regulated by hypothalamic nuclei. Earlier studies found a link between dilation of the third ventricle and late onset depression (Dahabra et al. 1998) and post-stroke depression (Starkstein et al. 1988). In a recent review, Soares and Mann (1997) concluded "Suggestions of enlargement of the third ventricle needs to be replicated in controlled volumetric studies". A subsequent MRI study failed to find a significant reduction in III-V volume in bipolar subjects (Brambilla et al. 2001) in contrast to the earlier MRI study of Strakowski in first episode mania (Strakowski et al. 1993). To help resolve uncertainties the current study with increased statistical power was undertaken. We have measured third ventricle width in 74 bipolar and 33 comparison subjects.

METHODS

The scans of 74 bipolar subjects who took part in earlier studies (El Badri et al. 2001; Moore et al. 2001) were re-examined with the approval of the Newcastle and North Tyneside Joint Ethics Committee. All participants had given written informed consent to the earlier studies after this had been fully explained to them by an investigator. All subjects suffered bipolar disorder, initially diagnosed using DSM-III-R criteria, and latterly DSM-IV criteria backed with the standardised interview, SCID-IV (Sptizer et al. 1994). Of the 74 subjects, 59 were clinically euthymic at the time of scanning. 15 suffered a treatment-resistant disorder and were symptomatic when scanned. 33 healthy comparison subjects had been recruited from the friends and families of the patient group and also from employees of the university and their families. The groups of patients and comparison subjects had been recruited to be matched as closely as possible for group mean age and intellectual abilities. The demographic data is contained in Table I.

All subjects underwent MRI supervised by a consultant neuroradiologist (VMcA). They were scanned on a single instrument, a GE Max plus 0.5 tesla scanner. Identical scanning sequences were used which generated T1, T2, proton density and inversion recovery scans (Moore et al. 2001). The scans had been examined (VMcA) for significant intracranial pathology before they were included in data set. 4 subjects were excluded from the study. The primary measurement, the maximum width of the third ventricle, was measured using coronal inversion recovery scans, 5mm. thick with and interslice separation of 1mm. A Seescan image analyser was used to make the all quantitative measurements. All scans were measured independently by two raters for RB and PD who were blind to the diagnoses of the subjects. The midline of the 5cm. MRI slice, used for III-V width measurements, crosses the hypothalamus from anterior margin of the mamillary bodies to the point at which the fornix emerges from the upper margins of the hypothalamus. The principal nuclei present in the walls of the third ventricle in this section would be the paraventricular,

TABLE 1. Demographic characteristics of patients and comparison subjects

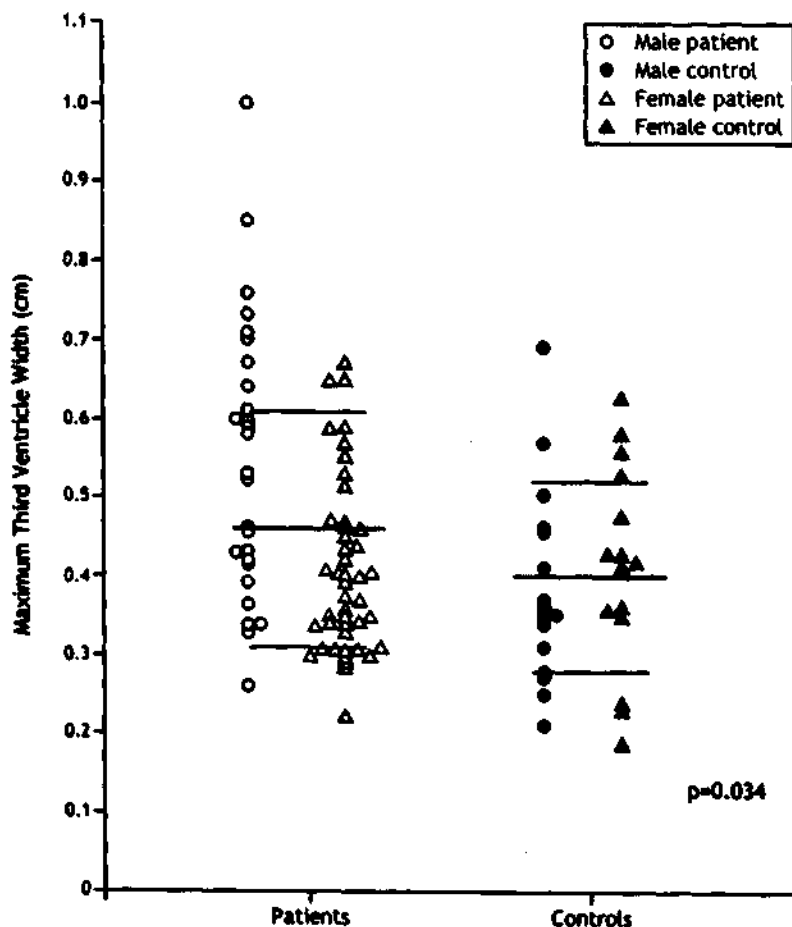
	Bipolar Group	Comparison Group
n	74	33
m:f	25:48	17:16
mean age (yr)	36.1(11.3)	35.6(12.6)
age range (yr)	21-63	19-63

TABLE 2 Effect of bipolar disorder and gender on third ventricle width

Group	n	(regression line gradient(sd)x103, cm/yr	Correlation coefficient R ² x100	p
All females	61	2.13(1.41)	4	0.134
Female patients	45	3.26(1.57)	7	0.043
Female controls	16	-0.706(3.28)	0.4	0.833
All males	43	6.31(1.78)	23	0.001
Male patients	26	7.21(2.39)	27	0.006
Male controls	17	2.46(2.15)	9	0.241

Legend to figure.

A comparison of the third ventricle width in bipolar patients and controls



posterior, dorsolateral and some of the ventromedial nuclei(Williams et al. 1995) although individual nuclei could not be visualised on the scans.

The inter-rater reliability between the two raters PD and RB were examined. Their measured mean ventricle widths differed non-significantly by only 0.05cm (13%). The Pearson correlation coefficient was 0.96 and the regression line was RB width=6.61x10⁻²+0.87 PD width (p=0.014), demonstrating excellent inter-rater reliability in the study.

All data was checked to ensure that it did not deviate from normality using the Anderson Darling method. Statistical analysis of data was carried out using the Minitab package (Minitab Inc, PA). The statistical power of the study was calculated using the G-Power programme (www.psych.uni-dusseldorf.de). The study had an 80% power to detect moderate size effects (Cohens f = 0.28) at a 5% significance level.

RESULTS

The principal result of the study is shown in Figure 1. Preliminary analysis of data indicated bipolar subjects have significantly (t=2.16, p=0.03) wider third ventricles (0.45(0.15cm) than the control subjects (0.40(0.12cm). Inspection of Figure 1 suggests that the ventricle width in male subjects exceeds that in females. Thus the ventricle width was subject to analyses of covariance using a General Linear Model with gender and diagnoses as categorical variables and age as a continuous variable. Ventricle width depends significantly upon gender (F=6.23, p=0.016) and age (F=16.5, p<0.001) but after these factors are taken into account, bipolar subjects have significantly wider third ventricles than comparison subjects (F=4.8, p=0.03).

The effects of age upon third ventricle width were explored by measuring the correlation between it and age separately in males and females, patients and controls

The gradients of the regression lines of III-V width on subject ages and the Pearson correlation coefficients expressed as R² are in table 2. Age effects are most markedly

seen in male patients. In all males, the age contribution is significant and represents 23% of the total variance. The gradient of the regression equation of the third ventricle width on an age is the yearly rate of dilation of the third ventricle. The difference between the rates of dilation in patients and controls (0.00721 – 0.00246, i.e. 0.00475 cm/year) is significant ($p < 0.05$, $z = 2.66$) and represents the contribution which could be ascribed to the presence of bipolar disorder.

In female subjects, the correlation of age and third ventricle width is small (4% of variance). Nevertheless, in female patients, linear regression shows there is still a significant ($p < 0.05$) annual rate of ventricular dilation of 0.0040 cm/year. Data indicates that in BD males and possibly females, there is an ongoing process which leads to greater ventricular dilation rates than is seen during the ageing of controls.

DISCUSSION

The principal result of the study is the increased width of the third ventricle in bipolar subjects when compared to healthy controls. Our sample covered an age range from adolescence to retirement but was a heavily bias towards young subjects, the median age was 35 years, the 25% and 75% quartiles were 27 and 40 years respectively and only 15 subjects were aged over 50 years. Thus, the contribution of elderly subjects to ventricular dilation in the sample was small. This explains the low (3% to 7%) and non-significant contribution of ageing in controls to the III-V width variance of the sample. In bipolar patients, ageing made a modest (21%) but significant contribution to the variance in ventricle width. Regression analysis showed the dependence of ageing to III-V width was highly significant and remarkably similar in both male (0.0048cm/yr. and female (0.040, cm/yr) bipolar subjects although females overall did not show a net III-V dilation with age. A potential confounding variable in female subjects could be timing in the reproductive cycle, and the onset of menopause. Unfortunately no attempt was made to control these other than to exclude pregnancy at the time of scanning). Clearly, there are unidentified additional contributors to III-V width

variance in all subjects and this may, in part explain some of the uncertainties in published studies. Strakowski (1993) reported that relatively young subjects suffering a first manic episode had larger III-V volumes than controls. Other studies, predominantly CT, published up to 1997 were reviewed by Soares and Mann (1997) who concluded that a link between bipolar disorder and ventricle width was not established. Recently, Soares (Brambilla et al. 2001), in a study of 22 patients and controls of mixed gender, failed to find a difference in third ventricle volume between controls and bipolar subjects. but did, like ourselves, find III-V dilation with increasing age which was possibly in more marked in bipolar subjects. Different scanning procedures were used in these studies. We were unable to reconstruct the third ventricle spatially from the 5mm thick coronal MRI sections we obtained. This is a significant limitation to our study which may account for differences from other work.

Nevertheless, the study finds increasing dilation of the third ventricle with age. The dilation is more marked in bipolar patients, especially males, than controls. Brambilla et al (2001) reported that their results also favoured a dilation more marked in bipolar patients. Increased III-V width has been linked to late onset unipolar depression (Dahabra et al. 1998) and possibly post-stroke depression (Starkstein et al. 1988). Together, these indicate that there is a process occurring in BD, possibly in the hypothalamus, which results in dilation of the third ventricle.

The pathology of the processes which results in increased III-V width is not known. The increased dilation rate in bipolar subjects suggests that the process is not simply an age-related process. Many but not all studies of bipolar disorder have failed to provide firm evidence of dilation in other parts of the ventricular system (Soares et al. 1997). It is unlikely that III-V dilation is part of a generalised atrophy process specific to BD. The width of III-V increases slowly by approximately 1% each year more than in controls. Confirmation of the dilation could be provided by longitudinal studies in males, but these would require 10 to 20 years to complete and would be confounded by

other disease processes and so further cross-sectional studies with adequate power are indicated in younger subjects.

Direct measurement of hypothalamic volume is not possible at this time, because of difficulties defining its margins on MRI. The hypothalamus contains many nuclei which cannot be differentiated by MRI and have diverse functions making the usefulness of measuring volumes unclear. The coronal section we employed to measure III-V width contains in the ventricle walls nuclei (see earlier) intimately related to the symptoms and signs of an affective episode. In particular, within the ventricle wall is the paraventricular nucleus, the principal efferent and regulator of the autonomic nervous system. Along with the supraoptic nucleus, it secretes CRF and GnRH and is an important regulator of the hypothalamic pituitary axis, the reproductive system and feeding (Gray's Anatomy). Abnormality of hypothalamic function is a unifying factor for many of the signs and symptoms of the depressive episode. Whether a derangement of the hypothalamic function is primary or secondary, the hypothalamus receives widespread inputs from cortical and other centres is capable of providing a link between psychological symptoms and the well-established biological symptoms of a depressive episode. If dilation results from hypothalamic changes, these may, in turn, impair its ability to regulate homeostasis in a wide variety of biological functions in response to higher centre inputs. The resulting depressive episode may be maintained in part by the dysfunction it causes.

Abnormalities of the HPA axis in bipolar disorder are not confined to the hypothalamus. Recently it has been reported that the pituitary volume is decreased in bipolar disorder (Sassi et al. 2001), in unipolar disorder (Krishnan et al. 1991) but not in seasonal affective disorders (Schwartz et al. 1997). Interestingly, eating disorders associated with hypercortisolaemia, also show decreased pituitary volume (Doriswarmi et al. 1990, 1991). It is unclear how a wide III-V (possibly indicating small hypothalamus), linked to a small pituitary would lead to hypercortisolaemia in depressive episode and more complex HPA dysregulation in euthymic bipolar subjects

(Watson et al. 2002). Combined MRI/neuroendocrine studies may help resolve these uncertainties.

To date, there are no putative mechanisms for a specific progressive dilation of III-V. Studies of the risk factor for other neurodegenerative disorders affecting younger people may be of assistance in identifying the process. The hypothalamus, as mentioned earlier, is difficult to image quantitatively. Neuropathological studies on the hypothalami of well characterised brains of younger bipolar subjects may help understanding of the contribution of hypothalamic dysfunction to mood disorders.

ACKNOWLEDGEMENT

The authors are pleased to acknowledge the generous support to the Theodore and Vada Stanley Foundation. We wish to thank Mrs. M. Cheek for her patience and care in preparing this manuscript.

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