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Hippocampal volume reduction in 22q11.2 deletion syndrome

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Abstract

Hippocampal volume reduction and decreased memory skills form a characteristic neurofunctional alteration observed in schizophrenia. Individuals affected with 22q11.2 deletion syndrome (22q11DS), while exhibiting memory deficits throughout development, are also at high risk for developing schizophrenia. The present study sought to investigate hippocampal volume reduction as separate of global grey matter reduction in a large, independent sample of individuals with 22q11DS. Volumetric data from structural magnetic resonance imaging was obtained for 43 individuals affected with 22q11DS, aged 6–39 years of age, as well as for 40 healthy individuals matched for age and gender. Drawing of the amygdala was included to enhance the delineation of the hippocampus, and circumscription of both the amygdala and the hippocampus were executed using an increased resolution matrix. After controlling for total grey volume reductions observed in affected individuals, a significant decrease in hippocampus volume was observed in the 22q11DS group, driven by significant bilateral volumetric reduction of the body of the hippocampus. These results are discussed in reference to memory and cerebral alterations already reported in 22q11DS. Further, the specific implications of hippocampus body volume reduction are outlined in light of its anatomical relationships and its function in memory. Finally, reduction of hippocampal volume in 22q11DS is examined in the context of psychiatric risk status associated to the deletion.

Keywords: Hippocampus; Amygdala; VCFS; Memory; Schizophrenia

1. Introduction

The hippocampus receives input from all cortical association areas (Amaral & Witter, 1989) and serves as the final processing station of complex sensory information (Small, 2002). Moreover, it is recognized as a central structure for the functional neuroanatomy of different memory processes (Moscovitch et al., 2005). Recent evidence of hippocampal volume reduction (Heckers, 2001; McCarley et al., 1999) and functional alteration (Cirillo & Seidman, 2003; Weiss & Heckers, 2001) in individuals with schizophrenia suggests that the hippocampus also plays a central role in schizophrenic disorders.

To date, one study reports medial temporal lobe reduction in association with 22q11.2 Deletion Syndrome (22q11DS) (Eliez, Barnea-Goraly, Schmitt, Liu, & Reiss, 2001a); however, it remains unclear if this reduction is independent from grey matter density loss also characteristic of this population. This neurogenetic syndrome, also referred to as velo-cardio-facial syndrome (VCFS) (Shprintzen et al., 1978), is an autosomal dominant condition affecting approximately 1 out of 4300–7000 live births (Oskarsdottir, Vujic, & Fasth, 2001). It is usually caused by a 3 mb *de novo* deletion on the long arm of chromosome 22 (Shaikh et al., 2000). Important cerebral volumetric changes are associated with the deletion, such as reduced grey and white matter volumes (Eliez, Schmitt, White, & Reiss, 2000), reduced parietal and temporal lobes volumes (Eliez et al., 2001a; Eliez et al., 2000), reduced cerebellum and vermis volumes (Devriendt, Thienen, Swillen, & Fryns, 1996; Eliez, Schmitt, White, Wellis, & Reiss, 2001b), thalamic volume decrease (Bish, Nguyen, Ding, Ferrante, & Simon, 2004) and basal ganglia hypertrophy (Eliez, Barnea-Goraly, Schmitt, Liu, & Reiss, 2002; Kates et al., 2004). Cognitive development in affected individuals is characterized by learning difficulties (Swillen et al., 1999), speech and language difficulties (Glaser et al., 2002), attention deficits (Gothelf et al., 2004; Sobin et al., 2004) and below-average IQ (Golding-Kushner, Weller, & Shprintzen, 1985; Swillen et al., 1997).

Recent investigations into memory functions in 22q11DS reveal below-average performances in children and adolescents (Bearden et al., 2001), as well as adults (Henry et al., 2002).

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These performances occur in a risk-for psychosis context: transient psychotic experiences occur in up to 50% of adolescents and young adults with the deletion (Baker & Skuse, 2005; Debbané, Glaser, David, Feinstein, & Eliez, 2006), and 20–30% of affected individuals are reported to develop schizophrenia during adulthood (Murphy, Jones, & Owen, 1999). Given associations between decreased memory functions, reduced hippocampal volume and risk for psychosis (Lawrie et al., 2002; Wood et al., 2003), a precise delineation of hippocampal morphometry in 22q11DS can contribute valuable information to the underlying neural substrates of memory impairments and corollary psychiatric risk associated to the syndrome.

The objective of the present study is to examine hippocampal volume in a large and independent sample of individuals affected with 22q11DS. We argue that a robust finding of volumetric reduction of the hippocampus should be present after controlling for total grey matter volume. We perform sub-regional analyses of the hippocampus to screen for morphological specificities within the structure. The amygdala is employed as a control structure, and its volume is tabulated in order to provide greater specificity for hippocampus delineation (Nelson, Saykin, Flashman, & Riordan, 1998). On the basis of our previous report, we hypothesize that amygdala volume will not yield any group differences. We hypothesize that individuals with 22q11DS will exhibit reduced hippocampal volumes, independent of total grey matter reduction.

2. Materials and methods

2.1. Subjects

2.1.1. Individuals with 22q11.2 DS

Forty-three children and young adults (16 male, 27 female) with 22q11DS ages 6–37 (mean = 16.7 ± 8.7) participated in the study. All participants were right-handed, except for six affected individuals and three controls. The sample had a mean full-scale IQ score of 69.4 ± 11.5 as measured by the Wechsler Intelligence Scales for Children or Adults (WISC-III or WAIS-III). Participants were recruited through local patient associations. Thirty-six of the participants in the study had *de novo* deletions on chromosome 22q11.2 as confirmed by fluorescent in situ hybridization (FISH), and one had a familial deletion. Written informed consent was received from all parents and/or subjects under protocols approved by the Institutional Review Board of the Geneva University School of Medicine.

2.1.2. Comparison group

The comparison group was comprised of 40 typically developing individuals (17 males, 23 females) ages 6–39 (mean: 15.1 ± 7.9), with a mean IQ of 111.1 ± 13.4. Individuals were recruited through a newsletter distributed in public schools and the community. All participants were screened for the absence of neurological and psychiatric disorders through a medical intake interview and screening forms (Medical and Developmental History Form, the CBCL for individuals younger than 18, and the SCL-90 for individuals 18 and older). There were no significant differences between the two groups on age, gender, and handedness.

2.2. DNA analysis

Blood was collected from children with 22q11DS. The deletions were verified and their extent determined by two-color FISH, with cosmid probes cD0832 and c350, specific for the proximal and distal deletion regions respectively (Karayiorgou et al., 1995; Kurahashi et al., 1997).

2.3. MRI protocol

Magnetic resonance images were obtained using a Philips Intera 1.5 T scanner. Coronal images were acquired with a 3D volumetric pulse sequence using the following scan parameters: TR = 35 ms, TE = 6 ms, flip angle = 45°, NEX = 1, matrix size = 256 × 192, field of view = 24 cm^2. Resulting images were 124 contiguous slices with a thickness of 1.5 mm and in-plane resolution of 0.94 mm × 0.94 mm.

2.4. Image processing and measurement

SPGR image data were imported into the software program *BrainImage* v5.24 (http://www.spnl.stanford.edu/tools/brainimage.htm). This program permits semi-automated image analysis incorporating the following steps: (0) reslicing into ispotropic voxels (0.94 mm × 0.94 mm × 0.94 mm), (1) correction of voxel intensity non-uniformity, (2) realignment according to AC–PC plane, (3) removal of non-brain tissues, (4) segmentation of the brain into constituent tissue types using a constrained fuzzy algorithm based on voxel intensity and tissue boundaries. Details of these procedures have been published elsewhere (Reiss et al., 1998).

For all procedures, manual and automated, raters were blinded to subjects' identifying and diagnostic information. Circumscription of mesial temporal structures (amygdala and hippocampus) was performed based on a previously published protocol (Kates, Abrams, Kaufmann, Breiter, & Reiss, 1997). SPGR datasets were transformed from a 256 × 256 to a 512 × 512 resolution using bicubic interpolation in order to allow for more precision in the delineation of a region of interest (ROI).

Amygdala and hippocampus ROI delineations are represented in Fig. 1. Drawing of the amygdala was performed coronally, beginning on the slice where the anterior commisure first crosses the midline of the brain. Drawing began

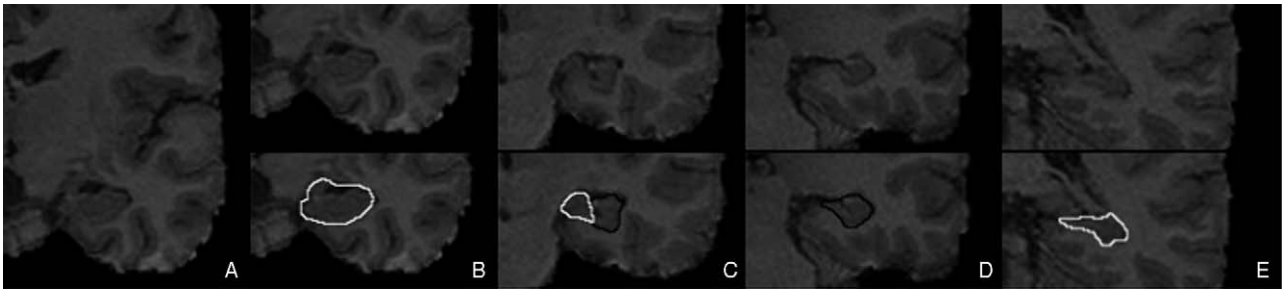

Fig. 1. Illustration of region of interest drawing of the hippocampus and subdivisions. Location of the left hippocampus is shown in (A). Hippocampus drawing is done in the rostro-caudal direction, beginning with the hippocampal head (B). The transition from head to body is defined when the fimbria is clearly distinguishable, dividing the hippocampus in two parts: the head medially (in white) and the body laterally (in black) (C). After this transition slice, hippocampal body is drawn (D), until the first slice on which the crus fornix becomes fully visible. The latter slice defines the most anterior slice of the hippocampal tail. Hippocampal tail (E; in white) is then delineated until it disappears.

infero-laterally, moving medially at the border between the amygdala and the white matter tract inferior to it. In the posterior regions of the amygdala, the superior border was partially defined by the presence of the entorhinal sulcus. The amygdala was drawn until it disappeared posteriorally. The anterior-most slice of the hippocampus was determined by the presence of landmarks: the alveus, the point where the superior horn of the lateral ventricle first points medially, the intensification of grey matter signal and an increased separation between grey and white matter, and the development of the laminar structure that distinguishes the hippocampus from the amygdala. Subsequent to the delineations, we divided the total hippocampus into head, body and tail segments. Duvernoy (1998) states that the hippocampal body has a highly characteristic shape on coronal sections, and is medially delimited by the fimbria (Duvernoy, 1998). Further, he illustrates how the junction between head and body is located when the uncus appears (in the caudo-rostral direction). According to these anatomical considerations, we used the following criterion: the coronal slice where the fimbria clearly divides the hippocampus in two parts (the body laterally and the head medially) was chosen as a transition slice to draw both structures (Fig. 1). In cases where the fimbria was not clearly illustrated, we selected the slice where the uncus disappears (from antero-posterior perspective). Hippocampal segments anterior to this section were defined as the head of the hippocampus, and hippocampal segments after this section constituted the body of the hippocampus. The following transition between hippocampal body and tail is commonly delimited on the first coronal slice on which the crus fornix becomes fully visible (Maller, Reglade-Meslin, Anstey, & Sachdev, 2006). We followed this transition using the crus fornix as the main transition landmark between body and tail of the hippocampus. Thereafter, volumes were measured and reliability analyses based on 10 datasets were conducted. Intraclass correlation coefficients were 0.93 and 0.94 for the amygdala and hippocampus, respectively.

2.5. Statistical analyses

Volumetric data met the necessary criteria (independence, normality, and homogeneity of variance) for employing parametric statistical analyses. ANOVA was used to compare the groups on mean total grey and white matter. Multiple analyses of covariance (MANCOVA) was utilized to determine whether the 22q11DS and comparison groups had a unique pattern of combined left and right volumes in the amygdala and hippocampus structures (total tissue values of the amygdala and the hippocampus) when covarying for total grey matter volume. For all sub-regional volumetric comparisons (right and left amygdala, right and left subdivisions of the hippocampus—head, body and tail), follow-up ANCOVA tested for specific group differences while adjusting for group differences in overall grey matter volume. Thereafter, significant parameters were first covaried for age to test for any potential effect. Then, the significant parameters were also covaried for IQ, as some authors have suggested that controlling for IQ yields a different analysis of brain morphology associated to 22q11DS (van Amelsvoort et al., 2001). An alpha of 0.05 (two-tailed) was used as the threshold for statistical significance in all analyses.

3. Results

Total brain tissue volumes (grey and white together) were approximately 12% smaller in the 22q11DS group relative to the comparison group (ANOVA; $F(1,81) = 28.9$; $p < 0.0001$). Reductions in total tissue were comparable for the left and right hemispheres when analyzed separately. Further segmentation of grey and white matter was conducted to describe group differences in total brain volumes (Table 1). Total grey matter volume in the brain was reduced (mean = 11.3%; ANOVA; $F(1,81) = 20.6$; $p < 0.0001$) to a similar degree as for white matter (12.1%; $F(1,73) = 11.6$; $p < 0.001$).

MANCOVA indicated a significant pattern of hippocampal morphological variation distinguishing persons with 22q11DS from comparison subjects (Wilks Lambda of 0.761; $F(8,73) = 2.86$; $p = 0.008$). Follow-up ANCOVA specifically indicated a significant bilateral reduction of the body of the hippocampus, and trend-like significance for the tail of the hippocampus (driven by right tail volumetric estimates) in the 22q11DS group compared to the control group (Table 1). When Age was introduced as a covariate, results remained unchanged. When IQ was included as a covariate, only the body of the hippocampus remained significantly reduced in the 22q11DS group ($F(3,78) = 4.14$, $p = 0.045$). Volumetric estimates of the amygdala did not yield any significant differences between groups.

Table 1
Segmented total tissue, grey and white volumetric comparisons, amygdala and hippocampus comparisons for 22q11DS vs. control subjects[a]

	22q11DS	Control	F	p value
Whole brain				
Total tissue	1105.9 ± 128.8	1251.1 ± 116.5	28.9	0.0001
Total grey	659.8 ± 81.4	743.8 ± 87.5	20.6	0.0001
Total white	446.1 ± 89.1	507.3 ± 73.3	11.6	0.001
Amygdala				
Total tissue	2.12 ± 0.42	2.21 ± 0.45	0.07	0.792
Left	1.09 ± 0.24	1.13 ± 0.23	0.03	0.958
Right	1.03 ± 0.21	1.08 ± 0.25	0.20	0.653
Hippocampus				
Total tissue	3.34 ± 0.46	3.85 ± 0.44	7.38	0.008
Head-total	1.72 ± 0.33	1.89 ± 0.31	1.48	0.227
Body-total	1.06 ± 0.20	1.30 ± 0.18	17.5	0.0001
Tail-total	0.48 ± 0.14	0.56 ± 0.12	3.83	0.054
Left-total	1.58 ± 0.27	1.81 ± 0.21	8.48	0.005
Right-total	1.69 ± 0.25	1.94 ± 0.23	10.01	0.002
Head-left	0.83 ± 0.20	0.90 ± 0.17	0.68	0.411
Head-Right	0.90 ± 0.16	0.99 ± 0.16	1.95	0.167
Body-left	0.51 ± 0.11	0.63 ± 0.09	17.81	0.0001
Body-right	0.55 ± 0.11	0.67 ± 0.11	11.93	0.001
Tail-left	0.24 ± 0.08	0.28 ± 0.06	2.56	0.114
Tail-right	0.24 ± 0.07	0.28 ± 0.08	4.14	0.045

[a] Volume estimates are expressed in cm^3.

In our sample, repeated-measures ANOVA revealed conventional right-left asymmetry in both subject groups, with right hippocampal volumes significantly larger than left hippocampal volumes ($F(1,81) = 41.37$, $p < 0.0001$) and no detectable difference between the groups by side ($F(1,81) = 0.227$, $p = 0.635$).

4. Discussion

The present study reports a bilateral hippocampal body reduction in 22q11DS, independent of overall volumetric grey matter reductions; this result does not differ when age or IQ are included in the analysis. Amygdala volumes were not found to differ between groups, confirming our preliminary finding (Eliez et al., 2001a). A right > left asymmetry of hippocampus volume was found in both groups, which is consistent with normal and clinical hemispheric morphology (Pegues, Rogers, Amend, Vinogradov, & Deicken, 2003; Weiss, Dewitt, Goff, Ditman, & Heckers, 2005). We discuss the implications that hippocampal body volume reduction can bear on memory function in 22q11DS, and how they relate to previously described morphological alterations. Further, we draw parallels

between 22q11DS and schizophrenia, and how these inform future research avenues in this genetically homogeneous population.

4.1. Implications for memory processes in 22q11DS

Research on neurogenetic disorders demonstrates how volumetric reduction in cerebral areas can alter related functionality (Karmiloff-Smith et al., 1998). Recent functional MRI studies illustrate how the body of the hippocampus acts as a spatiotemporal convergence segment of separate sensory input during associative learning (Small et al., 2001). The hippocampus not only associates the two spreading activations converging along the body segment, but also plays a determinant role in recalling the information minutes after encoding (Small, 2002). Thus alterations to the body of the hippocampus in 22q11DS could selectively impair binding operations that associate different sources of information (auditory and visual, for example), leaving other associations relatively intact (verbal–verbal, for example). While studies report memory impairments in 22q11DS using standardized assessment tools (Henry et al., 2002; Lajiness-O'Neill et al., 2005), more specific association and recall procedures are needed to better assess the consequences of regional hippocampal volume reduction found in the present report.

Concurringly, volume reduction of the hippocampal body could alter recollection-based memory performances, as they involve the integration of a target and related contextual information (Mandler, 1980). Several authors suggest that the hippocampus participates in recollection-based retrieval (Aggleton & Shaw, 1996; Yonelinas, 2001), but that familiarity-based recognition is not affected by hippocampal alterations (Mayes, Holdstock, Isaac, Hunkin, & Roberts, 2002; Vargha-Khadem et al., 1997). Further examination of memory for context in 22q11DS is necessary to determine the functional impact of decreased hippocampal volume observed in affected individuals. We have recently suggested that individuals with 22q11DS exhibit alteration of basic timing mechanisms (Debbané et al., 2005). Volume alteration of the hippocampus body could also impair memory for temporal context in affected individuals (Mayes et al., 2002).

4.2. Parallels between 22q11DS and schizophrenia

A decrease of hippocampal volume has been repeatedly observed in individuals with schizophrenia (Nelson et al., 1998). However, while some studies show greater posterior hippocampal volumetric reduction in patients with schizophrenia (Hirayasu, Shenton, Salisbury, & McCarley, 2000), others suggest anterior hippocampus volumetric reduction (Pegues et al., 2003; Szeszko et al., 2003), and still, others report diffuse hippocampal reduction in schizophrenia (Rajarethinam et al., 2001; Weiss et al., 2005). These discrepancies could be due to different factors, especially parcellation techniques, as most of these studies arbitrarily divide the hippocampus into anterior and posterior segments. The functional division along the longitudinal axis of the hippocampus stresses the importance of a tri-partite parcellation in structural imaging studies (Small, 2002).

Parallels between memory alterations in 22q11DS and in schizophrenia can also be observed. Recall procedures are known to yield greater memory impairments in individuals with schizophrenia (Aleman, Hijman, de Haan, & Kahn, 1999). Authors have suggested that the basis of recollection deficits in schizophrenia pertains to a difficulty in linking the separate aspects of an episode into a coherent and distinctive whole (Danion, Rizzo, & Bruant, 1999; Rizzo, Danion, van der Linden, & Grange, 1996), a task usually sustained by the hippocampus (Aggleton & Brown, 1999; Yonelinas & Levy, 2002). Furthermore, it has been observed that familiarity-based recognition is relatively unimpaired in individuals with schizophrenia, but that recollection-based recognition tasks yield substantial deficits (Achim & Lepage, 2003; Linscott & Knight, 2001; Pelletier, Achim, Montoya, Lal, & Lepage, 2005). Individuals with 22q11DS, who show increased prevalence of schizotypy (Baker and Skuse, 2005) and a 20–30% rate of schizophrenic morbidity (Murphy et al., 1999), do exhibit memory alterations in recall procedures (Henry et al., 2002). Further examination of familiarity and recollection processes are needed to better delineate the influence of hippocampal body alteration in this population.

The present study reports hippocampal body volume reduction in a group of individuals with 22q11DS. One major limitation to this study is the absence of specific memory tasks that could be associated to hippocampal volumes in order to assess the relationship between structure and function in this population. Research is under way to examine the specific memory processes that could be impaired by such structural alteration. Further research is also needed to clarify the relationship between hippocampal volume and risk for schizophrenia in this population. Finally, a detailed account of the mnemonic strengths and weaknesses in relation to morphological and functional cerebral alterations in 22q11DS are necessary to the formulation of adapted educative and therapeutic strategies.

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