Thalamic reductions in children with chromosome 22q11.2 deletion syndrome

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INTRODUCTION
Chromosome 22q11.2 deletion syndrome (22q) encompasses DiGeorge and velocardiofacial (VCFS) syndromes [1]. It is a congenital condition resulting from a deletion at chromosome 22q11.2 and has a prevalence of at least 1 in 4000 live births. The most systematically observed manifestations of 22q include cleft palate, heart defects, T-cell abnormalities, and neonatal hypocalcemia, as well as facial dysmorphisms and mild to moderate cognitive deficits [2]. Along with an overall delay in early cognitive, psychomotor, and language development and an overall IQ typically in the range 70–85, a subset of deficits are evident in the areas of visuospatial and numerical performance [3,4]. Children with 22q also show an extremely high incidence of psychopathology, especially schizophrenia, as they reach adulthood. Specifically, it is estimated that around 30% of all children with 22q will develop a schizophrenia spectrum disorder [5].

Specific patterns of brain abnormalities have also been demonstrated in 22q and it has been hypothesized [4] that some of these, particularly in the posterior parietal lobule, may provide the underlying cause of key aspects of the cognitive dysfunction displayed in this group. Generally, total brain volume appears to be reduced by 8–11% in children with 22q compared to normally developing children [6,7]. A relatively consistent pattern of focal volume reductions has also emerged from the literature. Cortical reductions have been demonstrated in the left parietal lobe [6,7], right temporal, parietal and occipital lobes [7,8]. Additionally, given the total brain volume reductions in this group, the suggestion of a relative frontal lobe increase has been indicated by a number of studies [6–8]. Investigations of subcortical structures have also demonstrated abnormalities in this group. Specific white matter volume reductions have been demonstrated in the cerebellum, as well as abnormal basal ganglia structures, such as increased size in the caudate head [9]. Our recent data [10], using voxel-based morphometry, support previous findings that children with 22q have enlarged lateral ventricles, which appear to overlap the typical location of the corpus callosum, anterior and posterior cingulate gyrus, as well as the superior portion of the thalamus, particularly in the medial, and posterior region.

With the significant neurological, cognitive, and psychological anomalies demonstrated by individuals with 22q, it is necessary to determine which areas of the brain may be directly or indirectly linked to the dysfunctional behaviors. Much research has supported the view that the thalamus plays an important role in visuospatial processing [11–15]. Specifically, the pulvinar has been demonstrated to be necessary for the spatial registration of visual features [11,12], engaging attention at new locations [15], and may be partially responsible for spatial neglect syndromes [14]. Given these connections between thalamic processing and visuospatial attention, and our current data demonstrating possible expansion of the lateral ventricles into the posterior thalamic region, we hypothesized that direct measurement of the thalamus would reveal volumetric reductions in children with 22q when compared to normally developing children. Particular interest will be paid to the posterior region of the thalamus, given the specific aforementioned connections between the pulvinar nucleus and visuospatial processing.
MATERIALS AND METHODS

MRI was performed on 36 total participants, 18 children with 22q (mean (±s.d.) age 118.6±17 months) and 18 typically developing children (125.0±23.8 months). Diagnosis of chromosome 22q11.2 deletion was confirmed using fluorescent in situ hybridization. All participants and their parents voluntarily signed a written consent form prior to participation. The experimental protocol was approved by the Institutional Review Board of the Children's Hospital of Philadelphia.

MRI was performed on a 1.5 T Siemens Magnetom Vision scanner (Siemens Medical Solutions, Erlangen, Germany). For each subject, a high-resolution 3D structural MRI was obtained. The structural MRI was acquired using a T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) sequence with the following parameters: repetition time (TR) 9.7 ms, echo time (TE) 4 ms, 12 flip angle, matrix size 256 × 256, slice thickness 1.0 mm, yielding 160 sagittal slices with in-plane resolution of 1 × 1 mm. Total brain volume measures were determined as part of a previous study (Simon et al. submitted).

Two independent tracers determined the volumetric measures of the whole thalamus (TH) and the posterior portion of the thalamus, including the pulvinar. For simplicity we will refer to the latter region as the posterior thalamus (PT). Tracers were blind to the group status of the individual while tracing. The first tracer (JB) completed volumetric measures, using MRICro software (version 1.36, build 7) for all 36 participants, while the second tracer completed volumetric measures on 10 pseudo-randomly selected participants (5 22q patients, 5 controls) for the purpose of reliability measures. All results discussed, beyond reliability measures, are based on the volumetric measures of the first tracer. Volumetric measures were computed by using the axial and sagittal views to trace the outline of the total thalamus. Upon determining that the total thalamus was included within the trace, a volumetric analysis was performed on the region of interest (ROI) to determine the volume within the borders of the trace.

The volume of the PT was determined by using the predetermined total volumetric measure of the thalamus. The pulvinar volume was determined using a previously developed method [11,18]. The anterior border of the pulvinar was approximated by the plane perpendicular to the anterior tip of the posterior commissure. The posterior border was determined as the posterior border of the total thalamus. Thus, to determine the volume of the posterior thalamus, inclusive of the pulvinar, the volume anterior to the posterior commissure was subtracted from the total thalamic volume (see Fig. 1 for representative participants).

RESULTS

Inter-rater reliabilities for total thalamic and posterior thalamic volumes were determined using intra-class correlation coefficients. The reliability for the total thalamic volume was 0.91 and for the posterior thalamic volume was 0.89. A multivariate ANCOVA was used to determine whether group differences occurred for both the total thalamic volume and the posterior thalamic volume. The model used group as the independent variable, total thalamic and posterior thalamic volumes as dependent variables, and age, gender, and total brain volume as covariates. For the overall model, the total brain volume was a significant co-variate for the combination of the total thalamic and posterior thalamic volumes (F(2,31)=7.702, p=0.002), indicating that group differences for the combination of total thalamic and posterior thalamic volumes can be explained in terms of overall brain volume reduction. However, investigation of the separate univariate models yielded different results. For the total thalamic volume, the total brain volume was again a significant co-variate (F(1,32)=15.775, p=0.000), and the group difference did not survive the co-variate (F(1,32)=0.806, p=0.376). However, for the posterior thalamic volume, the total brain volume co-variate only showed a trend towards significance (F(1,32)=3.620, p=0.066), yet the group effect was significant, even after covarying for total brain volume, age, and gender (F(1,32)=5.113, p=0.031). This indicates that posterior thalamic volumes were smaller in children with 22q and that this result cannot be explained solely by reductions in overall brain volume. Relative to normally developing children, the total brain volume in this sample was reduced by 9.9%, the total thalamic volume was reduced by 9.2%, and the posterior thalamus was reduced by 22.7% (Table 1).

DISCUSSION

These data demonstrate a specific volume reduction of the thalamus in children with 22q when compared with the normally developing children. Specifically, total brain volume reductions account for the reductions in the thalamus of children with 22q, but do not account for the reductions limited to the posterior thalamus. Although the reduction in posterior thalamus may be related to the overall reduction in brain volume for 22q children, the degree of reduction in the posterior portion of the thalamus, an area known to contain the pulvinar nucleus, is reduced beyond the level expected by the overall volumetric reductions. These alterations of the posterior thalamic volumes in children with 22q are consistent with a number of underlying assumptions regarding this disorder. The extensive volumetric decrease in the posterior portion of the

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Age (months)</th>
<th>Total volume (mm³)</th>
<th>Thalamus (mm³)</th>
<th>Pulvinar (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22q11.2</td>
<td>18</td>
<td>118.6</td>
<td>1243100.0</td>
<td>118077.1</td>
<td>2828.78</td>
</tr>
<tr>
<td>Controls</td>
<td>18</td>
<td>125.0</td>
<td>1364500.0</td>
<td>12847.89</td>
<td>3655.61</td>
</tr>
</tbody>
</table>

Fig. 1. Axial view of MRI image of representative participants from each group. (a) Normal control. (b) 22q. Blackened area indicates total thalamic outline for the given slice. White line demonstrates location of posterior commissure. Posterior thalamus was defined as volume posterior to the anterior tip of the posterior commissure.
thalamus and relative sparing of the anterior portion of the thalamus is consistent with the suggestion of an anterior to posterior gradient in brain abnormalities in 22q [6,7,9]. The alterations in the posterior portion of the thalamus may also help to explain the deficits found in visuospatial processing in this group [12,13]. Specifically, our previous behavioral data in a spatial cueing paradigm reveal patterns consistent with those reported in a previous thalamic lesion study [4,15]. Therefore, studies using individuals with thalamic lesions and individuals with posterior thalamic volume reductions have established the role of the pulvinar nucleus of the thalamus in using spatial cues to re-orient attention to a particular spatial location.

Given the high incidence of schizophrenia within the 22q population, the relationship between thalamic reductions in these groups is also of interest. Thalamic reductions, specifically in the pulvinar and medial dorsal nuclei, have been reported in individuals with schizophrenia [16,17]. A number of similar visuospatial deficits are also common amongst these groups [19]. The reduction of specific thalamic nuclei volumes in children with 22q may provide a biological marker for both the development of schizophrenia and deficits in visuospatial attentional processing within this group.

In order to investigate the direct behavioral effects of the reduced volumes in the posterior thalamus of children with 22q, functional studies are currently planned. Additionally, longitudinal studies are needed to follow the thalamic reductions into adulthood in this population and conclude whether the thalamic reductions are related to later psychopathology.

CONCLUSIONS

Children with chromosome 22q11.2 deletion syndrome demonstrate a reduction in thalamic volumes consistent with their overall brain volume reductions. Reductions in the posterior region of the thalamus, an area known to be involved in visuospatial processing, is reduced to an even greater extent than that expected by the total volume reductions. Previous findings in this population have demonstrated a number of neurological anomalies but have not focused on relating those measures to specific cognitive performance.

REFERENCES

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