Brain structure and function in velo-cardio-facial syndrome with and without psychosis
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CHAPTER 4

PROCESSING FACIAL EMOTIONS IN ADULTS WITH VELO-CARDIO-FACIAL SYNDROME: A FUNCTIONAL MAGNETIC RESONANCE IMAGING STUDY

Submitted

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ABSTRACT
Velo-cardio-facial syndrome (VCFS) is associated with chromosome 22q11 deletion and deficits in social reasoning for which the neurobiological basis is not known. Therefore, we studied facial emotional processing using functional magnetic resonance imaging in eight adults with VCFS and nine age-IQ matched controls. VCFS subjects, compared to controls had significantly less activation in occipito-temporal brain regions. Genetically determined developmental abnormalities in pathways involved in early face processing may underlie deficits in social cognition in people with VCFS.
INTRODUCTION
Velo-cardio-facial syndrome (VCFS), a genetic disorder associated with a chromosome 22q11 deletion, is characterized by specific deficits in visuoperceptual function, and in social and abstract reasoning that cannot solely be accounted for by their impaired level of overall intelligence (1). These deficits may underlie the frequently reported poor social skills and lack of emotional reciprocity that individuals with VCFS display (2). However, the neurobiological basis for these social impairments is not understood, and the functional neuroanatomy of emotional processing in people with VCFS has yet to be determined. Abnormalities in face perception or in processing facial emotions may partially account for social impairments seen in VCFS. Facial expressions are important cues in social communication with separate emotions differentially activating neural substrates. Also, we reported a neuroanatomical dissociation between conscious (explicit) and unconscious (implicit) processing of facial emotions in the healthy population (3). The ability to consciously recognize emotional expressions is positively correlated with intelligence in learning disabled people, and higher cognitive processes are involved in processing facial stimuli (4). It is therefore difficult to test explicit processing of facial emotion in an intellectually impaired population, such as people with VCFS. In contrast, unconscious processing of emotional facial expressions may be more suitable to study in an intellectually impaired population as it may not rely on detailed cortical representation of faces; rather they may be processed in an automatic, attention-independent, manner employing limbic and paralimbic areas (3). Therefore, we employed functional magnetic resonance (fMRI) imaging to investigate the neural substrate of implicit processing of facial expressions in adults with VCFS and controls with a similar intellectual ability. We predicted that subjects with VCFS would activate different brain regions than their IQ matched controls during implicit emotional processing.
METHOD
We studied eight people (7 females / 1 male, mean (SD) age 34 (9), IQ 72 (10)) with clinical features of VCFS and a 22q11 deletion confirmed by fluorescence in situ hybridisation (FISH) (Oncor Inc, Gaithersburg, MD 20877, USA). We also included nine healthy controls who did not differ significantly in age and IQ (5 females / 4 males, age 37 (11), IQ 73 (16)). All subjects were screened for physical disorder affecting brain function. IQ was determined using the Canavan shortened version of Wechsler Adult Intelligence Scale - Revised (5). Informed consent was obtained after complete description of the study, and the research was approved by the local research Ethics Committee. All subjects were familiarized with the stimuli and task procedure prior to scanning. Ten blocks of eight facial stimuli from the Ekman series (6) were presented to all subjects in 30-seconds phases as described previously (3) (see figure 1).

Subjects were presented with a pseudo-randomized mixture of happy and angry expressions in the “on” phase and neutral expressions in the control “off” phase. Subjects were instructed to attend to and judge the gender of faces during both phases. Echoplanar images were acquired using a 1.5 Tesla GE Signa System (General Electric, Milwaukee, WI). In each of 14 noncontiguous planes parallel to the intercommissural plane, 100 T2*-weighted images depicting blood oxygenation level dependant (BOLD) contrast were acquired (TE = 40 ms, TR = 3000 ms, in-plane resolution = 3.1 mm, slice thickness = 7 mm, slice skip = 0.7 mm). During the same session, a 43- slice, high-resolution inversion recovery echoplanar image of the whole brain was acquired in the intercommissural plane (TE = 73s, TR = 16000 ms, in-plane resolution 1.5 mm, slice thickness = 3 mm), for the purpose of standardization in standard space. The scans were corrected for movement and normalized to stereotaxic coordinates. Each normalized scan was smoothed with a Gaussian kernel (FWHW 14.4 x 14.0 x 12.7 mm) to increase signal-to-noise ratio and to reduce residual differences in gyral anatomy between individuals. Data were analyzed using Statistical Parametric Mapping 99 (www.fil.ion.ucl.ac.uk). Condition-specific effects in every task were assessed by comparing the “on” periods of each task with their respective “off” control conditions. Changes in regional blood flow were determined by applying the general linear model to each voxel. Between-group comparisons of brain activation patterns were performed using t statistics. The resulting statistical parametric maps (SPM t) constitute maps of t values for each voxel for each comparison and were transformed to SPM Z values. The level of significance of volumes of activation was characterized by peak amplitude without a correction for multiple non-indepen dent comparisons. Clusters of voxels which had a peak Z score > 3.00 (threshold P<0.001) were used as a measure of activation.
EXPERIMENTAL PARADIGM

PHASE A  
CHANGING ACCEPTING / REJECTING (HAPPY/ANGRY) EXPRESSIONS 
GENDER JUDGEMENT MALE OR FEMALE

PHASE B  
NEUTRAL (LOW VALENCE) FACIAL EXPRESSIONS

Figure 1

Stimuli used in the experimental tasks. Using a repeated on/off block design, subjects were shown pictures from a standard series representing a mixture of four happy and four angry faces in the on condition and eight neutral faces in the off condition. In both conditions the subjects were asked to judge gender.

RESULTS

All subjects were debriefed after scanning, both groups reported no problems in viewing the faces and performing the task (i.e. judging the gender of the faces they were shown), and there were no group differences in task performance. Between-group analysis revealed an anterior-posterior dichotomy in activation patterns during emotional processing (on-off) with VCFS subjects showing significantly less activity than controls in left fusiform, lingual and middle temporal gyrus, and in right cuneus, cerebellum and left middle frontal regions. In contrast people with VCFS had significantly more activity in right frontal regions (middle, inferior, and precentral gyrus), right nucleus lenticulus, and parahippocampal gyrus (see figure 2 & table 1).
<table>
<thead>
<tr>
<th>Brain region</th>
<th>Side</th>
<th>BA</th>
<th>Tal (x)</th>
<th>Tal (y)</th>
<th>Tal (z)</th>
<th>Z scores</th>
<th>p value</th>
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<tr>
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<tr>
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<tr>
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**Table 1**
The coordinate location and Z scores of regions that had significantly more activation in either the VCFS or control group.
DISCUSSION
We investigated functional neuroanatomy in adults with VCFS during a task of unconscious facial emotional processing. Significant differences between adults with VCFS and controls were found in bilateral occipito-temporal and frontal cortices, and right basal ganglia despite similar task performance. It is unlikely that these differences are due to differences in intellectual functioning as our groups were matched for IQ.

VCFS subjects had significantly less activation in regions that are involved in early visual processing, including regions known to be face perception areas. It has been suggested that the neural network mediating face perception includes a ‘core system’ for visual analysis of faces consisting of three bilateral regions in which inferior occipital gyri provide input to the fusiform and superior temporal regions. These in turn interact with an extended system (e.g. amygdala, insula, limbic system, auditory cortex), to process the meaning of information (including representing emotions) from faces (7). Our results suggest that in people with VCFS this ‘core system’ (occipito-temporal regions) may be less activated during face perception. We hypothesize...
that this could result in further upstream dysfunction in limbic/paralimbic regions that are normally involved in processing meaningful social information (including emotional reciprocity). A growing body of neuroimaging literature suggests that VCFS is associated with genetically determined abnormalities in brain development, which also affects white matter in occipito-temporal regions (8). This may result in aberrant development of cortico-cortical networks including pathways between the visual and somatosensory cortices. The development of cortical face processing systems occurs during postnatal development and plays a critical role in specifying the neural sites that are involved in face processing (9). People with autism, who have extensive social impairments, utilize different neural systems (e.g. frontal regions) for face perception than the traditional fusiform face perception areas (10). Social impairments in people with VCFS resemble those seen in autism and we also found reduced activation in traditional face perception regions and more activation in frontal regions in people with VCFS. We suggest that in people with VCFS the development of cortical face processing systems is abnormal, and that this may partially underlie problems in social functioning in later life.

Our study has several limitations. We used a block design, and event-related designs are needed to evaluate any emotion-specific effects. Our control group consisted of people with intellectual disability and therefore they are not representative of the general population. Further studies are needed to further investigate how social impairments in people with VCFS arise.
REFERENCES