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A preliminary study of orbitofrontal activation and hypersociability in Williams Syndrome

Masaru Mimura · Fumiko Hoeft · Motoichiro Kato · Nobuhisa Kobayashi · Kristen Sheau · Judith Piggot · Debra Mills · Albert Galaburda · Julie R. Korenberg · Ursula Bellugi · Allan L. Reiss

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Abstract Individuals with Williams syndrome (WS) demonstrate an abnormally positive social bias. However, the neural substrates of this hypersociability, i.e., positive attribution bias and increased drive toward social interaction, have not fully been elucidated. Methods: We performed an event-related functional magnetic resonance imaging study while individuals with WS and typically developing controls (TD) matched positive and negative emotional faces. WS compared to TD showed reduced right amygdala activation during presentation of negative faces, as in the previous literature. In addition, WS showed a unique pattern of right orbitofrontal cortex activation. While TD showed medial orbitofrontal cortex activation in response to positive, and lateral orbitofrontal cortex activation to negative, WS showed the opposite pattern. In light of the general notion of a medial/lateral gradient of reward/punishment processing in the orbitofrontal cortex, these findings provide an additional biological explanation for, or correlate of positive attribution bias and hypersociability in WS.

Keywords Williams syndrome · Hypersociability · Facial emotion · fMRI · Orbitofrontal cortex · Amygdala

Introduction

Williams syndrome (WS) is a neurodevelopmental disorder characterized by a hemizygous microdeletion of approximately 20 genes, contiguous with the elastin gene on chromosome 7 (locus 7q11.2) (Francke 1999). Individuals with WS function in the mild to moderate range of intellectual disability but have a distinctive neurocognitive

M. Mimura
Department of Neuropsychiatry,
Showa University School of Medicine,
Tokyo, Japan

M. Mimura · F. Hoeft · N. Kobayashi · K. Sheau · A. L. Reiss
Center for Interdisciplinary Brain Sciences Research (CIBSR),
Stanford University, School of Medicine,
Stanford, CA, USA

J. Piggot
Department of Child and Adolescent Psychiatry and Psychology,
UCLA-NPI,
Los Angeles, CA, USA

M. Kato
Department of Neuropsychiatry,
Keio University School of Medicine,
Tokyo, Japan

D. Mills
School of Psychology, Bangor University,
Gwynedd, UK

A. Galaburda
Department of Neurology, Beth Israel-Deaconess Medical Center,
Harvard Medical School,
Boston, MA, USA

J. R. Korenberg
Center for Integrated Neuroscience and Human Behavior,
The Brain Institute, University of Utah,
Utah, USA

U. Bellugi
Laboratory for Cognitive Neuroscience,
Salk Institute for Biological Studies,
La Jolla, CA, USA

A. L. Reiss (✉)
401 Quarry Rd,
Stanford, CA 94305-5795, USA
e-mail: reiss@stanford.edu

profile characterized by profound visuospatial deficits and relative strengths in some aspects of language and facial identity recognition (Bellugi et al. 2000). Performance of individuals with WS on tasks of facial identity recognition is not correlated with performance on facial expression recognition tasks, and they are less expert in recognition of facial emotions than chronologically age-matched controls (Gagliardi et al. 2003). Individuals with WS are more likely to rate emotional facial expressions as approachable (Frigerio et al. 2006) compared to mentally aged control groups, thus demonstrating an abnormally positive social bias (Bellugi et al. 1999). Studies support the contention that the social interaction of persons with WS is both qualitatively and quantitatively different from that seen in typically developing (TD) individuals (Järvinen-Pasley et al. 2008). This positive attribution bias and increased drive toward social interaction, which is present throughout childhood, has resulted in individuals with WS characteristically being described as "hypersociable" (Doyle et al. 2004).

The neural basis of positive bias in recognition of facial expression in WS remains poorly understood. One brain region known to be involved in facial expression recognition is the amygdala (Skuse et al. 2003). The amygdala codes for the social/emotional salience of both negatively and positively valenced information, and damage to this structure results in profound abnormalities in facial expression recognition (Aggleton 2000). The amygdala has been shown to be activated by both positive and negative facial expressions in healthy persons (Yang et al. 2002). In contrast, studies in WS have reported functional abnormalities of the amygdala. Compared to TD controls, WS individuals exhibit diminished amygdala response to negative (angry or afraid) facial stimuli (Meyer-Lindenberg et al. 2005). In addition, Haas et al. (2009) recently found that individuals with WS exhibit heightened amygdala response to positive (happy) faces and diminished amygdala response to negative (fearful) faces, as assessed by both functional magnetic resonance imaging (fMRI) and event-related potentials (ERP).

Another region underlying facial affect recognition is the prefrontal cortex, particularly the orbitofrontal cortex (OFC). Strong anatomical connections exist between the amygdala and OFC (Ghashghaei et al. 2007; Ishikawa and Nakamura 2003). Individuals with focal frontal damage may present with impaired social cognition including facial emotion recognition (Hornak et al. 2003; Baird et al. 2006). Since structural abnormalities of the OFC have been reported in individuals with WS (Reiss et al. 2004), it is conceivable that OFC dysfunction is involved in abnormal recognition of emotional faces in WS. Indeed, Meyer-Lindenberg et al. (2005) found that individuals with WS, in addition to reduced amygdala activation for negative facial expressions, showed abnormal activation and interactions of prefrontal regions linked to the amygdala, especially the OFC. More specifically, path analyses demonstrated that the OFC did not participate in regulatory interactions with the amygdala in WS, putatively leading to functional disconnection between these two regions.

In the present study we investigated further the possible role of OFC in WS during positive and negative emotional valence face processing. In particular, we sought to dissociate activations between medial and lateral portions of the OFC. Based on a meta-analysis of neuroimaging studies, Kringelbach and Rolls (2004) proposed a medio-lateral gradient of neural activity in response to reinforcers, whereby medial OFC activity is related to monitoring the reward value of reinforcers, and lateral OFC activity is related to the evaluation of punishers. In light of this model, we hypothesized that in TD individuals, facial stimuli with positive emotional valence would be more likely to activate the medial OFC because they are social reinforcers. On the other hand, facial stimuli with negative emotional valence would activate the lateral OFC because they are potentially "punishing" in the social context. In contrast, in WS, we hypothesized that negative emotional valence would activate medial rather than lateral OFC given the propensity of individuals with this condition to regard negative faces as more rewarding and acceptable. An event-related fMRI study of emotional face processing was used to test these hypotheses.

Methods

Subject characteristics

Nine individuals with a diagnosis of WS (eight females; mean age: 33.83 years, standard deviation (SD): 12.13 years) were recruited for this project from a larger multi-site, multi-disciplinary program, which included behavioral, ERP, molecular genetics, histological, and anatomical MRI studies.

All genetic diagnoses were performed using florescence in situ hybridization (FISH) probes for elastin and other genes, consistently found in ELN or flanking the micro-deletion associated with WS (Korenberg et al. 2000). All participants were ELN negative on one chromosome 15. In addition, all participants exhibited the medical and clinical features of the WS phenotype, including cognitive, behavioral and physical profiles (Bellugi et al. 2000).

Controls were 9 TD volunteers (eight females; mean age: 34.85 years, SD: 10.33 years), who were screened for a history of psychiatric or neurological problems using the Symptom Checklist-90-R (< 1 SD of the norm). All participants were native English speakers, and right-handed as assessed using the Edinburgh Handedness Inventory. IQ was assessed using the Wechsler Adult Intelligence Scale,

Third Edition (WAIS-III). All participants gave written informed consent before participation. Experimental procedures complied with the standards of the human subjects committee at Stanford University School of Medicine.

Task design and procedure

Prior to the scan, all subjects undertook a behavior modification program and a practice task in a fMRI simulator to insure that each was capable of performing the tasks. The behavior modification program involved viewing a DVD showing the entire imaging procedure, listening to a CD containing the sounds of the scanner and participating in structured "games" at home that allowed them to "practice" holding their head motionless.

During the acquisition of brain scans, participants performed the match affect paradigm (MAP) and a control gender matching task. The MAP consisted of 90 achromatic face stimuli (Fig. 1) presented in an event-related fMRI paradigm. There were three conditions: two experimental — faces congruent for negative affect (angry-angry) — the negative match task, and faces congruent for positive affect (happy-happy) — the positive match task, and a control condition — faces incongruent for affect (angry-happy). Validation of these affective face stimuli has been reported in a previous publication (Yang et al. 2002).

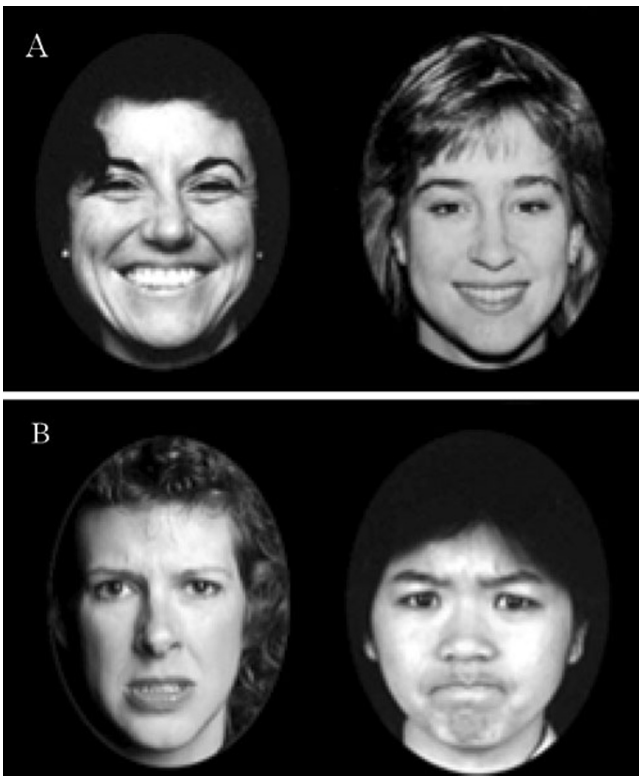

Fig. 1 **a** congruent happy facial expression, **b** congruent angry facial expression

Two faces of different identity were presented simultaneously adjacent to one another and the participant was asked to press button 1 if the facial expressions matched, and button 2 if the facial expressions did not match. Each stimulus was presented for 3 s, with a random, counterbalanced "black" stimuli effecting an interstimulus interval (ISI) of 7, 9 or 11 s; thus each event was 10, 12 or 14 s in duration. Ninety stimuli were presented (30 for each condition) using PsyScope software (http://psyscope.psy.cmu.edu/). No stimulus was presented more than once.

The control task was identical, except that subjects matched the gender (female, male) of the neutral faces rather than emotions. Singe the particular gender was not of interest in our study, there were two conditions, match (female and male combined) and control (non-matched) conditions.

Image acquisition

Structural and functional images were acquired on a 1.5 T GE Signa scanner (General Electric Medical Systems, Milwaukee, Wisconsin) with Echospeed gradients using a custom-built, whole-head coil. Eighteen axial slices (6 mm thick, 1 mm skip) parallel to the anterior and posterior commissures, covering the whole brain, were imaged with a temporal resolution of 2 s using a T2*-weighted, gradient echo, spiral pulse sequence (time to repetition TR= 2,000 msec, time to echo TE=40 msec, flip angle=89°, and 1 interleave) (Glover and Lai 1998). The field of view (FOV) was 240 mm, and the effective in-plane spatial resolution was 4.35 mm. To aid in localization of functional activation, a high-resolution, T1-weighted, spoiled gradient-recalled (SPGR), three dimensional MRI sequence with the following parameters was used: TR=35 msec; TE=6 msec; flip angle=45°; 24 cm FOV; 124 slices in coronal plane; 256×192 matrix; acquired resolution=1.5×0.9×1.2 mm.

Brain imaging analyses

Two approaches were utilized to analyze data: (1) voxel-wise group analyses in standard Montreal Neurological Institute (MNI) space using the standard template provided by SPM, and (2) region-of-interest (ROI) analyses in native space. First, images were reconstructed by inverse Fourier transformation for each of the 135 time points into 64×64×18 image matrices. FMRI data were pre-processed using SPM2 (http://www.fil.ion.ucl.ac.uk/spm).

Images used for voxel-wise analyses were realigned, normalized, and smoothed with a Gaussian filter (8 mm full-width-half-maximum). Individual subject data were high pass filtered at 120 s, and analyzed using a fixed effects model. Positive, Negative and Control conditions were modeled for the MAP task and Gender Match (female

and male conditions combined) and Control conditions were modeled for the Control task. Group analyses were performed with a random effects model. One and two-sample t-tests were conducted for WS and TD individuals for the contrasts Positive > Control, Negative > Control and Positive > Negative for the MAP task and Match > Control for the control task. Brain activation was also correlated with IQ for each group to examine the role of IQ. ROIs used for small volume correction were bilateral amygdalae and medial / lateral OFC using Automatic Anatomical Labeling (AAL) (Tzourio-Mazoyer et al. 2002) ROIs from the Wake Forest University (WFU) Pickatlas (Maldjian et al. 2003). A statistical threshold of $p=0.05$ small volume correction (SVC) was used. Statistical images were overlaid onto a template created from all subjects' SPGRs using MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html). Peak coordinates of brain regions with significant effects were converted from MNI to Talairach space with the mni2tal function (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml). Brain regions were identified from these x, y, and z coordinates with a probabilistic atlas by Chiavaras et al. (2001) for OFC regions and the Talairach & Tournoux atlas (Talairach and Tournoux 1988) for other regions.

Images for the region-of-interest (ROI) analysis were realigned, but normalization and smoothing were not performed. After performing similar individual subjects' analyses as above on these non-normalized, non-smoothed images, ROI analyses were performed. The same AAL ROIs were used but were reverse normalized into each subject's native space using normalization parameters obtained from the transformation of SPGRs to the standard MNI T1 template provided in SPM. The spatial localization of the ROIs was confirmed for accuracy for each subject and ROI. The proportion of significant ($p<0.05$) voxels relative to the voxel count of the entire ROI for each of the six ROIs was calculated. This was done for the contrasts Positive > Control, Negative > Control and Positive > Negative for the MAP task and Match > Control for the control task. Further statistical analyses in native space were performed using Matlab (MathWorks, Natick MA).

Results

Subject characteristics

Two out of nine WS participants were excluded from the analysis due to poor task performance and/ or head-movement which rendered scans unusable. The mean age of WS participants was 34.0 with a SD of 12.7 (all females). They were functioning, on average, in the mild intellectual disability to borderline range of intelligence (FSIQ mean±SD=68±8.7; VIQ 74±8.7; PIQ 65±8.8). Two out of nine healthy volunteers was excluded due to a failure in the recording of behavioral performance data. The mean age of TD participants was 35.7 with a SD of 11.1 (all females). All controls were functioning in the normal range of intelligence (FSIQ 115±12.0; VIQ 112±14.5; PIQ 114±8.2). There was no significant difference in age ($p=0.79$) but there was a significant difference between groups in intelligence (FSIQ, VIQ, PIQ all p's<0.001).

Behavioral performance

There was no significant difference in accuracy between WS and controls in the match of positive valence facial expressions (WS 72.0±29.0%; TD 94.1±4.7%; $p=0.09$) or negative valence facial expressions (WS 65.0±30.4%; TD 81.8±16.5%; $p=0.23$). When we included FSIQ as a regressor, the results were also non-significant (both positive and negative, p's>0.7). Accuracy of the control task was similarly nonsignificant (all p's>0.1).

Brain imaging results

The right medial and lateral OFC as well as the amygdala showed significant interaction effects. Specifically, in both the right amygdala and right lateral OFC (but not left), WS showed significantly reduced activation relative to TD controls in response to negative compared to positive valance face stimuli. On the other hand, the right medial OFC (but not left) showed opposite effects in that WS showed significantly greater activation than TD in response to negative compared to positive emotional face stimuli (Fig. 2). This was true for both whole brain analyses in standard space (except for the amygdala) (Fig. 2a) and ROI analyses in each individual subject's native space (Fig. 2b). ROI analyses in native space further showed that the significant interaction effects in the right amygdala and lateral OFC were mainly driven by significantly smaller activation to negative face stimuli in WS compared to TD controls. For the medial OFC, WS showed significantly reduced activation relative to TD to positive face stimuli and greater activation to negative face stimuli. Whole brain correlation analyses between brain activation and IQ were also performed for each participant group. There were no significant correlations (all p's>0.1). When the analyses were repeated using ROI analyses in native space, there was a significant positive correlation between right lateral OFC activation and IQ for the Positive vs. Negative valance contrast in the WS group ($p=0.01$, uncorrected threshold).

While preliminary due to the small number of subjects, correlation analyses showed significant correlation between right amygdala and lateral OFC activation (contrast positive > negative) in TD controls ($r=0.76$, $p=0.023$), but not in WS

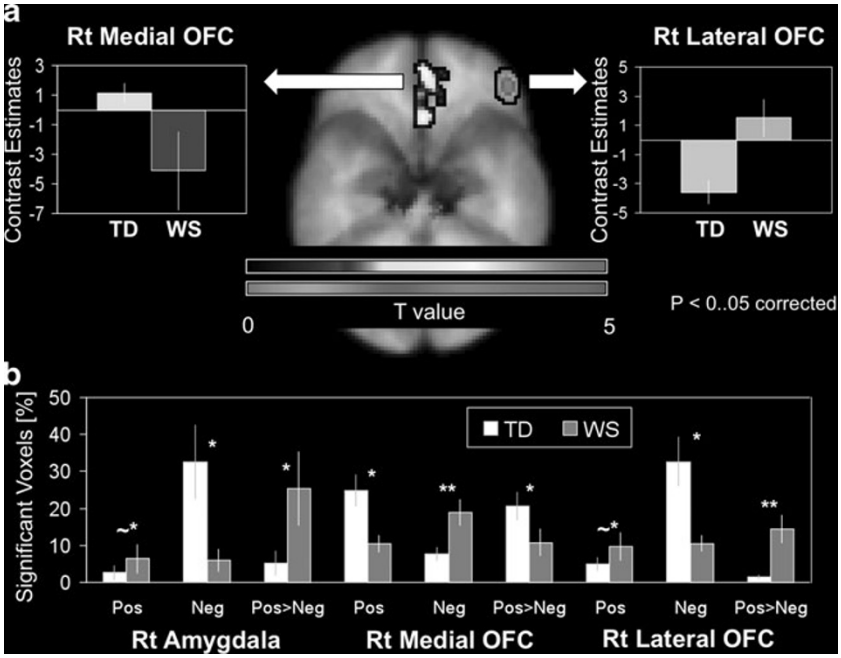

Fig. 2 Brain activation differences between Williams syndrome (WS) and typically developing individuals (TD). **a** Region-of-interest (ROI) analyses in standard space of the right (Rt) medial and lateral orbitofrontal cortex (OFC). Left OFC and bilateral amygdala showed no significant differences and hence are not shown. Results comparing between groups for the contrast Positive > Negative are shown. Bar graphs represent contrast estimates (linear combination of beta weights) extracted from each individual subject from significant voxels. Error bars represent standard error. Peak of Rt lateral OFC (Talairach coordinates: 50 41 -5) corresponds to Rt lateral orbital gyrus (LOG) and Rt medial OFC (Talairach coordinates: 2 48 -14) to Rt medial orbital gyrus (MOG) according to Chiavaras et al. (2001). **b** ROI analyses in native space of bilateral medial and lateral OFC and the amygdala. Significant voxels (%) in each ROI as a function of Group (WS vs. TD) and contrast (Positive > Control, Negative > Control, Positive > Negative). Error bars represent standard error. ~*: $p<0.1$, *: $p<0.05$, **: $p<0.01$

individuals ($r=0.011$, $p=0.49$). Results of the control gender matching task showed non-significant effects in all of these regions and for all analyses.

Discussion

The present fMRI study was designed to ascertain whether individuals with WS would show abnormal brain activation while they were engaged in recognition of positive and negative facial emotions. The study of WS provides a unique opportunity to explore the neural basis of aberrant social behavior in a group of individuals with a common neuro-genetic risk factor. As was claimed by Gagliardi et al. (2003), individuals with WS were able to recognize facial expressions in the sense that their accuracy for the match of both positive and negative valence facial expressions was roughly comparable to TD individuals. However, individuals with WS showed significantly reduced right amygdala activation while they were matching negative faces. Indeed, amygdala activation demonstrated significant interaction effects as a result of group and stimulus type. Individuals with WS showed significantly reduced right amygdala activation in response to negative faces as compared to TD individuals. These results replicate previous findings (Meyer-Lindenberg et al. 2005; Haas et al. 2009), and provide plausible neural correlates for the appetitive social behavior observed in WS.

In addition to reduced amygdala activation, individuals with WS showed a different pattern of right OFC activation from TD individuals. Although Meyer-Lindenberg et al. (2005) reported the absence of OFC activation in their experiment, the present study confirmed our hypothesis and found a unique pattern of distribution of OFC activation in individuals with WS. TD individuals showed significantly greater activation in response to negative than to positive emotional faces in right lateral OFC whereas WS showed comparable activation to negative and positive faces ($p>0.05$). Consequently, WS individuals showed significantly reduced right lateral OFC activation in response to negative emotional faces as compared to TD individuals. This activation pattern in WS is likely not explained by reduction in general cognitive ability since the correlation between native space right lateral OFC ROI activation and IQ was *positive* (i.e., higher IQ — more aberrant activation). On the other hand, individuals with WS had significantly greater activation of the medial OFC in response to the negative versus positive emotional faces contrast as compared to TD individuals. This was true

whether whole brain analyses in standard space or ROI analyses in each individual subject's native space were performed. Significant activation of the amygdala and OFC in the right hemisphere only for this emotion matching task is consistent with the past literature (Alves et al. 2008). (Left hemisphere activation was present but did not reach significance.)

The results could be viewed in terms of the dissociable role of the lateral and medial OFC proposed by Kringelbach and Rolls (2004). Existing data indicate that activity in medial parts of OFC is related to the monitoring, learning, and memory of the reward (positive) value of reinforcers, whereas activity in lateral OFC is related to the evaluation of punishment (negative) value. Relative to TD, WS processed negative faces more in the medial part of OFC, which is considered to be related to reward value representation. In contrast, negative faces activated less the lateral part of OFC in WS relative to TD, the area considered to be related to punishment value representation. Accordingly, the pattern of lateral and medial OFC activation suggests that WS individuals appear to process negative angry faces as more rewarding, just as TD individuals process positive happy faces. On the other hand, activation for positive faces in WS was equivalent in the medial and lateral OFC, which was also different from the activation pattern of TD. The findings from this study should be considered as preliminary as the number of subjects included was small, and further studies with a larger sample are warranted. However, the present results of OFC activation pattern offer additional plausible biological correlates for the positive attribution bias and characteristic hypersociability seen in individuals with WS.

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