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Neural correlates of genetically abnormal social cognition in Williams syndrome

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Williams-Beuren syndrome (WBS), caused by a microdeletion of approximately 21 genes on chromosome 7q11.23, is characterized by unique hypersociability combined with increased non-social anxiety. Using functional neuroimaging, we found reduced amygdala activation in individuals with WBS for threatening faces but increased activation for threatening scenes, relative to matched normal controls. Activation and interactions of prefrontal regions linked to amygdala, especially orbitofrontal cortex, were abnormal, suggesting a genetically controlled neural circuitry for regulating human social behavior.

Social neuroscience continues to grow in importance[1], but little is known about specific genetic factors influencing human social cognition, although social skills are highly heritable and critical for survival. Great interest has therefore been directed at a unique social-behavioral phenotype, high sociability[2,3] and empathy, found in individuals with WBS, who eagerly, often impulsively, engage in social interaction, even with strangers[4]. Associated with this remarkable persistent hypersociability is an undercurrent of anxiety[3]: individuals with WBS show extremely high rates of excessive worrying (57%; ref. 4) and specific phobia (symptoms in 96%; ref. 4). The neural mechanisms underlying this social phenotype remained unknown, partly because of the intellectual impairment usually associated with the syndrome, which limits comparison to a normal control group. We addressed this problem by examining a highly select group of normal-intelligence participants with WBS[5], reasoning that abnormalities found even there would be characteristic of the syndrome and reflect its genetic substrate.

In addition to the amygdala's role in reward, its response and regulation are believed to be central to socially protective neural processing through the monitoring of environmental events such as danger[1]. Lesions of the amygdala and linked cortical regions, such as orbitofrontal cortex (OFC), impair social function[6] and can cause disinhibition[7]. Of great importance to the WBS phenotype, the effects of neonatal amygdala lesions in nonhuman primates suggest dissociable systems for social and non-social fear[6]. In the present study, we used two tasks requiring processing of threatening visual stimuli previously established to reliably engage amygdala[8]. The first task required matching one of two simultaneously presented faces with a different target face of the same emotion (angry or afraid)[8]. In the other task, participants matched one of two simultaneously presented fearful/threatening scenes with an identical target[9]. As a control task, participants matched simple shapes (circles or ellipses). Thirteen participants with WBS and controls matched for age, sex and IQ participated in this study after giving written informed consent (see **Supplementary Methods**).

Performance during the matching tasks (but not the control tasks) did not differ between groups (**Supplementary Table 1**) and showed that the faces task (where all three identities differed) was more difficult for both groups. In normal controls, ventral amygdala was more highly activated for faces than for scenes, as shown previously[8]. The opposite pattern (scenes > faces) was observed in this region in individuals with WBS. Single-subject analyses in native space confirmed these findings (**Supplementary Figs. 1,2**). Controls showed significantly greater amygdala activation for faces than did individuals with WBS, whereas the response was significantly higher for scenes in individuals with WBS than in controls (**Fig. 1** and **Supplementary Table 2**). Subsequent analyses focused on right amygdala, where differential effects were more pronounced. ANOVA of differential BOLD signal change (**Fig. 2**) confirmed a significant group-by-task interaction ($F_{1,46} = 5.7$, $P < 0.03$). Overall amygdala BOLD signal change was comparable for both groups (**Fig. 2b**).

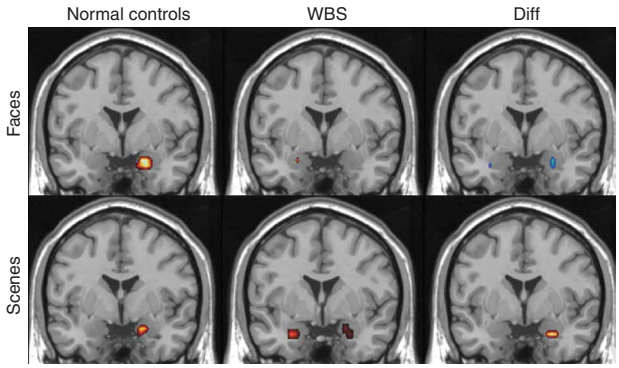

Figure 1 Amygdala activation by task. Significant activations ($P < 0.05$, corrected for multiple comparisons in amygdala region of interest) rendered on normal coronal MRI at ±1 mm to the anterior commissure (left = left) for face (top) and scene (bottom) stimuli. First column: normal controls; second column: participants with WBS; third column: significant differences between groups (blue: normal controls > WBS, red: WBS > normal controls). See **Supplementary Table 2** for detailed statistical information.

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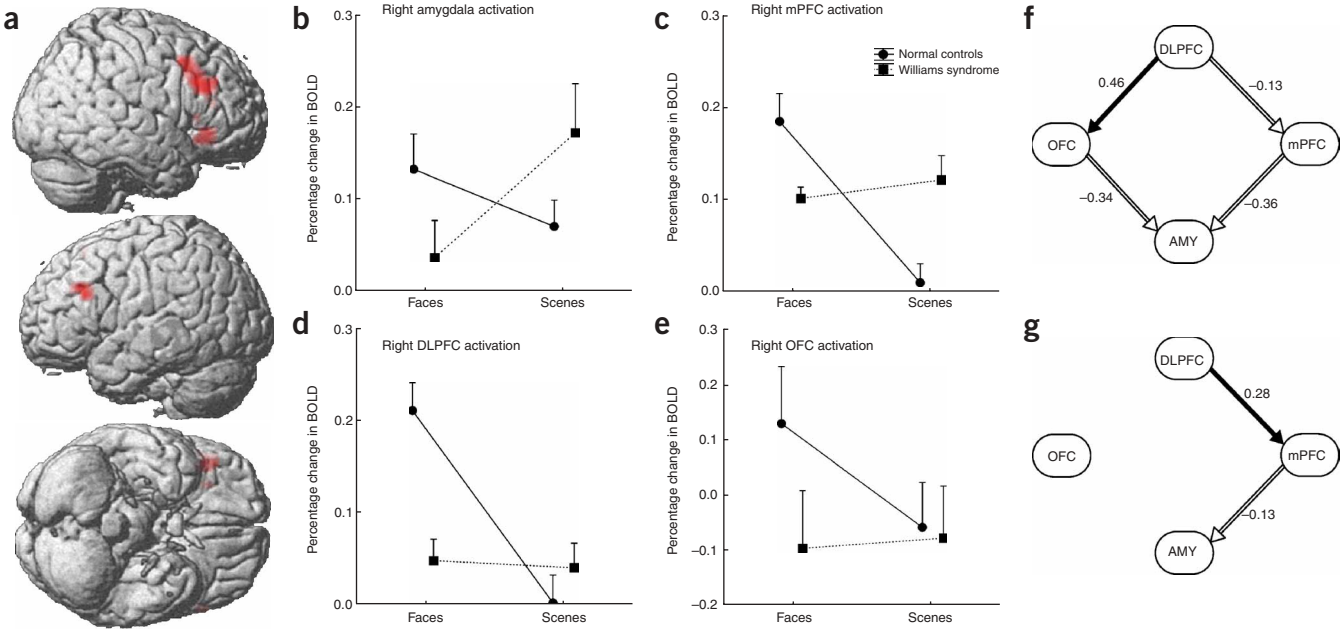

Figure 2 Differential activation and interaction in a network regulating amygdala. (**a**) Group difference in reactivity to face versus scene matching, rendered on standard brain surface at $P < 0.05$, corrected for multiple comparisons. (**b**–**e**) Estimated percentage change in BOLD response (mean ± s.e.m.) at maximum coordinates (**Supplementary Tables 2,3**) in right amygdala (**b**), medial prefrontal cortex (**c**; $F_{1,46} = 17.4$, $P < 0.0002$), dorsolateral prefrontal cortex (**d**; $F_{1,46} = 13.0$, $P < 0.001$) and orbitofrontal cortex (**e**; $F_{1,46} = 10.1$, $P < 0.002$). (**f**–**g**) Best-fitting path models for normal controls (**f**) and participants with WBS (**g**). Positive paths: filled arrows; negative paths: open arrows. AMY, amygdala.

Amygdala reactivity to threatening faces was significantly diminished in individuals with WBS. This was not likely to be attributable to abnormal visual processing because, as previously[5], we did not observe activation differences in the ventral visual stream (**Supplementary Table 3**). As amygdala signaling is critical for appropriate avoidance behavior[1], abnormal activation to threatening faces may contribute to diminished fear of strangers and consequent social disinhibition in individuals with WBS[3] because of reduced responsivity to social danger. Conversely, and again in excellent agreement with the clinical profile of WBS, amygdala reactivity to scenes was not simply preserved, but was in fact abnormally increased. As specific phobia has been associated with increased amygdala reactivity[10], this observation suggests a potential mechanism for high non-social anxiety in WBS[4].

Because abnormal amygdala reactivity in individuals with WBS was not attributable to general functional impairment, our data suggested alterations in amygdala modulation and regulation. We therefore examined whole brain group-by-task interaction maps to identify regions outside the amygdala showing differential reactivity as a function of task (**Fig. 2a** and **Supplementary Table 3**). These were located exclusively in prefrontal cortex (**Fig. 2c–e**), where normal controls differentially activated dorsolateral-prefrontal (DLPFC), medial-prefrontal (MPFC) and orbitofrontal cortex in the more difficult condition (face matching). In contrast, participants with WBS showed a task-invariant pattern: OFC was not differentially activated, and both MPFC and DLPFC were activated to similar degrees in both tasks.

Both MPFC and OFC are densely interconnected with amygdala and DLPFC[11] and have been implicated in the regulation of amygdala function, social cognition[1] and representation of social knowledge[12]. Structural abnormalities in OFC have been reported both in these same participants[5] and in participants with WBS and mental retardation[13]. Our finding of the absence of OFC activation also provides evidence for a deficiency during social processing. OFC activity and OFC-amygdala interactions have been associated with representation and reevaluation of relative reward value and stimulus-reinforcement association learning[14]. In social cognition, OFC-amygdala interactions are hypothesized to link sensory representations with social judgments on the basis of motivational value[1], and OFC lesions are associated with social disinhibition and impaired ability to detect *faux pas*. In this context, our observation of functionally abnormal OFC is consistent with the observations of social disinhibition and impairments in adjusting behavior according to social clues in individuals with WBS[3]. We also found a perigenual MPFC region persistently activated in individuals with WBS. Convergent evidence suggests that dynamic interactions of this area with amygdala are critical for inhibitory amygdala regulation, especially for fear extinction[15]. MPFC has been associated with empathy, representation of social knowledge[12] and integration of emotional information about others and self[1]. Again, the relatively preserved, or even increased, activity of MPFC maps well on phenotypic characteristics of relative social strengths of individuals with WBS, such as increased empathy[2].

To directly investigate regulatory interactions between identified prefrontal regions and amygdala, we employed path analysis[5], a method allowing assessment of functional interregional interactions (which should not, however, be interpreted to indicate direct anatomical connections). Using data from OFC, MPFC, DLPFC and right amygdala during face processing (where both groups showed prefrontal engagement), we obtained a well-fitting model for both participant groups (**Fig. 2f–g**). The final model included efferent pathways from MPFC and OFC to amygdala, and from DLPFC to MPFC and OFC, consistent with anatomical data[11]. The overall pattern of connections within this regulatory system was highly significantly different between groups ($\chi^2(4) = 13.91$, $P < 0.008$). In normal individuals, both MPFC and OFC were strongly negatively linked to amygdala. DLPFC showed a positive interaction with OFC and a negative path to MPFC (**Fig. 2f**).

In contrast, in individuals with WBS, OFC showed no connection either with amygdala or DLPFC (**Fig. 2g**). While the negative link between MPFC and amygdala was similar to that in controls ($\chi^2(1) = 1.87$, $P > 0.17$), DLPFC and MPFC were strongly positively linked in individuals with WBS, a significant difference from the negative interaction in controls ($\chi^2(1) = 4.32$, $P < 0.03$).

Our path analyses suggested that OFC did not participate in regulatory interactions with amygdala in WBS, whereas normal controls showed a highly significant connection of OFC with both amygdala and DLPFC. Moreover, DLPFC, although not directly linked to amygdala, showed a differentiated reciprocal interaction with both ventral prefrontal regions (OFC and MPFC) that was significantly altered in WBS. These results support abnormal regulatory interactions between the PFC and amygdala in WBS. In particular, the finding that OFC was not only not differentially activated but also functionally disconnected from amygdala provided evidence for impairment of this regulatory mechanism in WBS. In normal controls, although signs of path coefficients cannot be directly interpreted as neural excitation or inhibition, our data do indicate a differential network by which DLPFC can adjust amygdala reactivity in both directions according to task demand. Evidence indeed suggests that activation of DLPFC modulates the amygdala in a task-specific fashion[9]. Our data extend understanding of this regulation by illustrating that DLPFC may exert this influence on the amygdala despite the absence of direct connections[11] through reciprocal interactions with MPFC and OFC. It is commonly assumed that a primary role of DLPFC in social cognition is the representation of goal states and consequent modification of relevant social-emotional interactions[1]. Our results suggest a regulatory system through which these goal-directed demands can be neurally instantiated. In WBS, this modulation was significantly altered: OFC connections were absent and interactions between DLPFC and MPFC had a positive sign. Moreover, in individuals with WBS, both DLPFC and MPFC were found to be active to the same degree in both tasks, suggesting that this abnormal modulation is enduring, whereas normal controls recruited only prefrontal cortex as required by task type or difficulty. On the basis of the cross-sectional data presented here, it is impossible to determine whether the abnormal interaction between DLPFC and MPFC represents a primary abnormality or is secondary to the lack of OFC function in this regulatory network in individuals with WBS. We propose that the observed task-independent facilitation of MPFC by DLPFC may represent a compensatory mechanism using the intact pathway in the context of congenitally non-functional OFC in individuals with WBS. Together with nonhuman primate findings of increased social but decreased non-social fear after neonatal amygdala lesions[6], our data suggest the possibility that the opposite pattern of dissociated fear (decreased social fear and increased non-social fear) found in individuals with WBS may be a consequence of a congenital deficiency in a prefrontal system involved in inhibitory amygdala regulation (and by implication, possibly associated with relatively disinhibited amygdala activity during maturation).

In this first study of the neural basis of emotional cognition in WBS, we opted for a low-level baseline task in order to increase our power to detect amygdala activity, which had been hypothesized to be deficient[3]. As our data indicated no reduction of overall magnitude of amygdala activation (**Fig. 2b**), further research should use other emotional stimuli (such as happy or sad, compared to neutral) in fully factorial designs to further characterize amygdala response in WBS and link these suggestive findings to emotional regulation with certainty. We anticipate that identification of an intermediate neural phenotype for a genetically dependent abnormality in social cognition will facilitate the search for specific genes underlying social cognition in individuals with WBS and in healthy individuals.

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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