Neural mechanisms in Williams syndrome: a unique window to genetic influences on cognition and behaviour

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Abstract | Williams syndrome, a rare disorder caused by hemizygous microdeletion of about 28 genes on chromosome 7q11.23, has long intrigued neuroscientists with its unique combination of striking behavioural abnormalities, such as hypersociability, and characteristic neurocognitive profile. Williams syndrome, therefore, raises fundamental questions about the neural mechanisms of social behaviour, the modularity of mind and brain development, and provides a privileged setting to understand genetic influences on complex brain functions in a 'bottom-up' way. We review recent advances in uncovering the functional and structural neural substrates of Williams syndrome that provide an emerging understanding of how these are related to dissociable genetic contributions characterized both in special participant populations and animal models.

Haploinsufficiency
Presence of only a single functional copy of a gene that does not provide sufficient transcript or protein production to assure normal function.

Hypercalcaemia
Abnormally high calcium concentration in the blood.

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doi:10.1038/nrn1906

Williams syndrome (WS) is a neurodevelopmental disorder caused by a hemizygous deletion of ~1.6 megabases, containing ~28 genes, on chromosome 7q11.23 (FIG. 1a). The incidence is usually given as 1 in 20,000 live births, but new prevalence estimates are as high as 1 in 7,500 (REF. 1), which means that WS could account for 6% of all cases of mental retardation of genetic origin[1].

WS was first described as a combination of a distinct facial appearance with growth retardation and cardiovascular abnormalities[2,3], which are present in ~80% of individuals with WS[4]. The cardiovascular and some of the facial features have been linked to haploinsufficiency for elastin (*ELN*)[5]. Other common somatic symptoms are endocrine (for example, transient hypercalcaemia and impaired glucose tolerance), gastrointestinal (constipation, prolapse and diverticula) and orthopaedic (scoliosis or joint contractures) problems[6]. Neurological problems include coordination difficulties (for example, trouble walking down a staircase), hyperreflexia, strabismus, nystagmus[6,7], hypersensitivity to sound[4,6], and sensorineural hearing loss[8,9].

WS is associated with mild to moderate mental retardation or learning difficulties. Of central interest to research is a distinctive cognitive profile with peaks and valleys[10,11]. In particular, a severe visuospatial construction deficit is a fundamental stable phenotype in WS[11], contrasting with a relative strength in verbal short-term memory and language[11,12]. Emotionally, a particularly striking feature of children with WS is their high sociability[13,14] and empathy for others[13]. Typically, individuals with WS are socially fearless, engaging eagerly in social interaction even with strangers[13,14]. Intriguingly, this remarkable hypersociability is coupled with a strong undercurrent of anxiety that relates to non-social objects[13,15,16]. Attention deficit hyperactivity disorder (ADHD, predominantly inattentive type or combined type) is common (>50%) in children and adolescents with WS[16].

Unfortunately, the intellectual impairment characteristic of WS limits comparison of typical participants with WS to a normal-intelligence control group and reduces the ability of individuals with WS to perform consistently during testing. This can be avoided by selecting normal-intelligence participants with WS[17] (BOX 1), who can cooperate with extensive cognitive and imaging procedures and be appropriately compared with normal controls. It is likely that abnormalities found even in this high-performing group would be characteristic of the syndrome as a whole, and close to the genetic substrate of the disorder.

Because the genes involved in WS are known, and the dosage of at least some of these genes is clearly abnormal, the study of neural mechanisms in WS affords a privileged setting to understand genetic influences on complex brain functions in a 'bottom-up' way. This

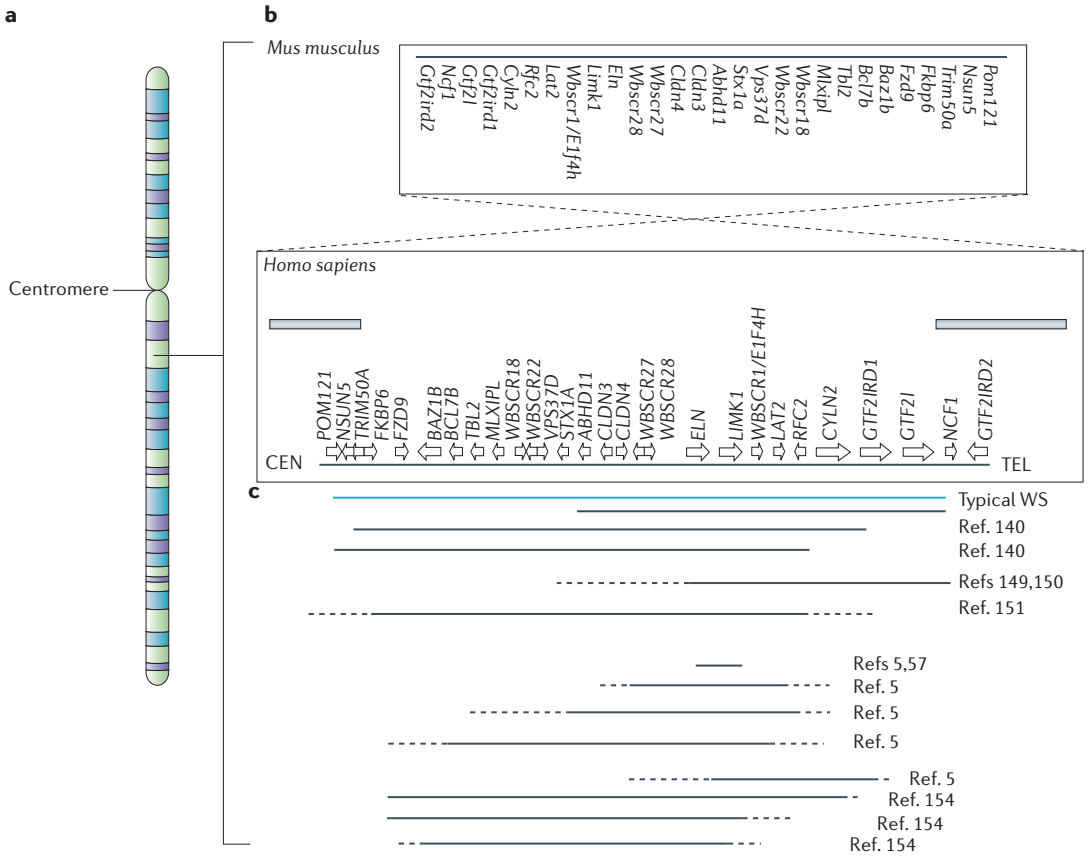

Figure 1 | **Genetics of Williams syndrome. a** | Chromosomal location of the hemideleted region. **b** | Map[140] of the region in humans (centre) and the homologous region in mice (top). Location of low copy repeat regions marked by bars. **c** | Extent of typical Williams syndrome deletion and examples of small (atypical) deletions. Dashed lines indicate uncertain extent of the deletion in that portion. Adapted, with permission, from REF. 140 © (2005) American Academy for the Advancement of Science.

extends and complements efforts to understand genetic mechanisms of behaviour in the general population, in which contributions of individual genes are small, gene–gene and gene–environment interactions are the rule, and unambiguously functional variations are uncommon and difficult to characterize.

The goal of this article is to review recent advances in defining the neural substrates of the unique neuropsychiatric features of WS and to begin to define separable neural subsystems in this syndrome, specifying mechanisms for visuospatial cognition, social behaviour and memory under genetic control. We hope that these emerging convergent results form a point of departure not only for a deeper understanding of WS, but also for the investigation of dissociable genetic contributions to complex behaviour in humans in general.

Genetics of Williams syndrome

WS is a genomic disorder in which the clinical phenotype is a consequence of abnormal gene dosage due to a hemizygous deletion that results from unequal homologous recombination during meiosis[18]. The common 1.6-Mb deletion involving 7q11.23 (FIG. 1a) is mediated by flanking groups of low copy repeat sequences causing misalignment because of high sequence homology[19–21] (FIG. 1b). Inversion of the same segment has been found as a polymorphic variant in ~7% of the general population[22] and 27–35% of transmitting parents[19,22], and has been reported in some individuals with mental retardation and features associated with WS[23]. However, these individuals did not fit either the cognitive profile or the personality profile associated with WS (C.B.M., C. A. Morris and L. R. Osborne, unpublished observations). The first case of duplication of the WS region was recently reported[24]. The phenotype, which includes severe speech and expressive language delay in the context of visuospatial construction skills at the level of other family members, contrasts strongly with the WS phenotype.

Structural abnormalities in WS

At post-mortem, reduced brain size[25], Chiari malformations[26,27], corpus callosum shape changes[28,29] and altered cell size and density in primary visual cortex[171] have been described in WS. Using structural MRI, reductions were localized to the parietal lobule[30] and occipital[31] grey matter. Cerebellar size is preserved[32,33], although the neuronal integrity marker *N*-acetyl aspartate (NAA)[34] may be reduced there.

Hyperreflexia
Exaggerated deep tendon reflexes.

Strabismus
Eye misalignment; also known as 'crossed eyes'.

Nystagmus
Involuntary and often rapid and repetitive oscillatory movements of the eyeballs.

Homologous recombination
Exchange of DNA segments of similar sequence. Occurs by breakage and reunion in paired chromosomes during meiosis.

(Arnold-)Chiari malformations
A group of disorders characterized by protrusion of the cerebellum through the large opening in the base of the skull into the spinal canal.

Box 1 | **Williams syndrome and intelligence**

Contrary to some initial reports[80], the results of recent research[10] indicate that severe mental impairment is rare in Williams syndrome (WS). Rather, the mean full scale IQ for WS is typically in the mild mental impairment range. For example, 112 8–17 year olds who had classic WS deletions and did not have autism spectrum disorder (ASD) completed the Differential Ability Scales-School Age version (DAS-School Age[155]). Because of the unusual cognitive profile associated with WS, the DAS-School Age, which provides separate standard scores for Verbal, Nonverbal Reasoning, and Spatial abilities (clusters) is a particularly useful full-scale measure of intelligence. For the general population, mean general conceptual ability (GCA, similar to IQ) and mean standard score on each of the clusters is 100, with a standard deviation of 15. For this sample of individuals with WS, mean GCA was 59.19 with a standard deviation of 11.59 (C.B.M., unpublished observations); 19% scored in the normal range (≥70). Mean cluster standard scores were 70.59 for Verbal, 67.88 for Nonverbal Reasoning, and 55.00 for Spatial. For 83% of participants, the Verbal and/or Nonverbal Reasoning standard score was significantly higher than expected for GCA, which indicates that the use of the overall standard score from an omnibus IQ measure as the determinant of intelligence level is not appropriate for most people with WS.

Most behavioural researchers studying WS report IQs from the Kaufman Brief Intelligence Test (KBIT[156]). For a sample of 374 individuals aged 5–55 years with WS who have classic deletions and do not have ASD (C.B.M., unpublished observations), mean IQ (68.46) on this test, which includes only Verbal (mean = 71.52) and Nonverbal Reasoning (mean = 70.83) subtests, is about two standard deviations below the general population mean (100); the standard deviation (14.84) is similar to that for the general population (15). Therefore, the shape of the IQ distribution for the KBIT, which does not assess spatial ability, is similar to that for the general population, but negatively displaced by about two standard deviations. The higher mean IQ for the KBIT than the DAS-School Age is primarily due to the inclusion of Spatial subtests on the DAS but not the KBIT; mean performance on the Verbal subtests of the two measures was similar, as was mean performance on the Nonverbal Reasoning subtests.

Significant advances in our understanding of the structural basis of WS have come from the application of voxel-based morphometry (VBM), which allows the study of genetic variation without restriction to anatomical boundaries. In our cohort of high-functioning participants with WS, this approach identified circumscribed symmetrical grey matter volume reductions in WS in three regions (FIG. 2a): the intraparietal sulcus, around the third ventricle, and the orbitofrontal cortex (OFC)[17]. The intraparietal sulcus finding was recently confirmed in children with WS and mental retardation[35]. Another study of typically functioning individuals with WS also found the most pronounced reduction in the intraparietal sulcus[36], but, in addition, identified relative regional density increases in the orbital and medial prefrontal cortices, the anterior cingulate, insular cortex and superior temporal gyrus[36], whereas no volume increases were found in our cohort. Recent work from these two groups suggests that methodological differences contribute to these discrepancies, such as the choice of template used to match images and the method used to map individual images into a common anatomical space.

Although the intraparietal sulcus has been implicated in the visuospatial construction deficit of WS[17], and the OFC has been linked to hypersociability[37], clear functional correlates of the structural abnormality around the third ventricle have yet to be defined. We have speculated[17] that hypothalamic abnormalities might contribute to the many poorly understood hormonal disturbances found in WS[4,38]. Thalamic abnormalities, if confirmed, could affect several sites of cortical processing.

Insights from analysis of regional volume are supplemented and extended by new analyses of cortical shape. Overall curvature of the brain is reduced in WS[39], and abnormally increased gyrification has been noted in the parietal and occipital lobes[40], and the temporoparietal zone[41]. Length reductions in the central gyrus[42,43] might be related to overall brain size reduction in WS. Convergent evidence demonstrates reductions in sulcal depth in the intraparietal sulcus (FIG. 2b–d) both in participants with WS of normal IQ[44] and those with mental retardation[45], clarifying the macroanatomical correlate of this regional volume reduction seen in VBM.

Although findings in sulcal depth and regional volume largely agree in directionality and location, a recent study on cortical thickness found increases of 5–10% in the right perisylvian and inferior temporal zone in WS[41]. This supports theoretical predictions that regional volume and cortical thickness should be subject to different maturational mechanisms[46]. It has been proposed[47] that tension along axons might explain how and why the cortex folds in a characteristic pattern. WS results would be consistent with this theory if a reduced population of neurons in the intraparietal sulcus results in a reduction in white matter connections of this area[48]. Further investigation, particularly based on diffusion tensor imaging, would be helpful. In preliminary data from a subgroup of five high-functioning participants with WS, we found abnormal white matter integrity immediately underlying the intraparietal sulcus[49].

Functional abnormalities

Sensory function. There are few reliable data to suggest abnormal primary sensory processing in WS. The results of one functional MRI (fMRI) study using noise and music stimuli in a small group of participants with WS and mental retardation suggested reduced activation in auditory cortex in WS at a lenient statistical threshold[50]. Visually, individuals with WS have a high incidence of strabismus[51,52] and reduced visual acuity[53], especially stereoacuity[54]. These primary sensory problems do not correlate with the visuospatial constructive deficit[53], which indicates that the latter has an independent neural basis. Changes in evoked potential recordings during illusory contour completion were found in participants with WS who had mental retardation, indicating possible changes

Differential Ability Scales-School Age
(DAS-School Age). A standardized assessment of general intellectual functioning designed to provide specific information about an individual's strengths and weaknesses across a wide range of intellectual abilities. It is particularly appropriate for assessing individuals with WS because it yields separate standard scores for verbal, nonverbal reasoning and spatial abilities, as well as an overall standard score (general conceptual ability (GCA), which is similar to IQ).

Voxel-based morphometry
(VBM). A widely used method for the analysis of imaging data that enables a statistically principled voxel-wise between-groups comparison of local grey matter volume, unconstrained by anatomical landmarks.

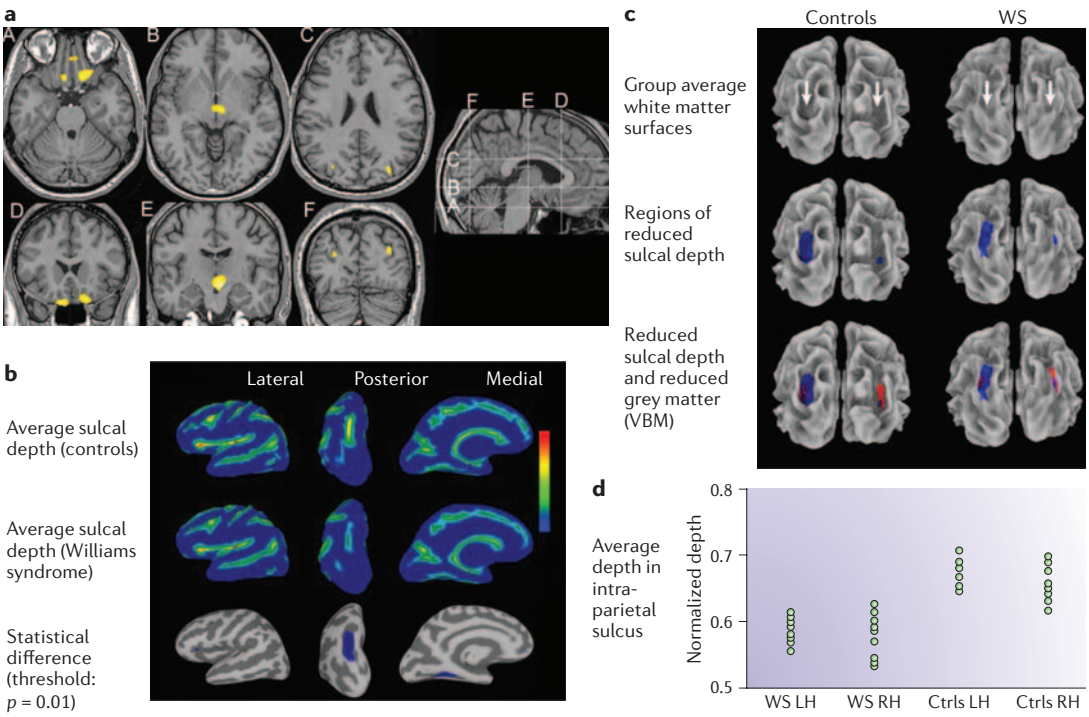

Figure 2 | **Structural abnormalities in the brains of individuals with Williams syndrome. a** | Panel graph showing regional volume reductions in the intraparietal sulcus, the hypothalamus and orbitofrontal cortex in high-functioning individuals with Williams syndrome (WS) compared with normal controls[17]. **b** | Views of average sulcal depth for the left hemisphere in normal control group (top row) and people with WS (middle row)[44]. The bottom row shows the statistical difference map, which is thresholded using a false discovery rate of $p = 0.01$. The largest regions of significant difference were found in the intraparietal sulcus and the collateral sulcus. **c** | Within-group average cortical surface models for controls and participants with WS, showing the visibly deeper sulci (indicated by arrows, top row) in the average representation of control participants' brains[44]. The middle row highlights the regions of significant group differences in normalized sulcal depth (shown in blue) on these average surface models. The bottom row overlays these with the results (shown in red) of a voxel-based morphometry (VBM) analysis for the same group of participants (thresholded at $p = 0.01$, corrected for multiple comparisons), showing regions of significant reduction in local gray matter volume. Overlapping regions are shown in purple. **d** | Plot of individual participants' sulcal depth measures within the region of interest (ROI) defined by the thresholded sulcal depth statistics (that is, the regions shown in blue) in the intraparietal sulcus region. Each point on the plot represents the average sulcal depth in the back-projected version of the ROI (using the inverse of the spherical registration transformation) on an individual participant's surface. LH, left hemisphere; RH, right hemisphere. Panel **a** reproduced, with permission, from REF. 17 © (2004) Cell Press. Panels **b**–**d** modified, with permission, from REF. 44 © (2005) Society for Neuroscience.

in low-level visual processing regions, although data from matched controls will be necessary to confirm this[55]. Most fMRI studies using visual stimuli (reviewed below) did not show primary visual abnormalities. A recent fMRI study of high-functioning individuals with WS using retinotopic mapping[56] also found no abnormalities in the extent of the functionally defined primary visual area.

Visuospatial construction. Visuospatial construction — "the ability to visualize an object (or picture) as a set of parts and construct a replica of the object from those parts"[57] — is measured clinically by pattern construction, block design tasks or drawing. Severe impairment in this domain is a neuropsychological hallmark of WS[11]. The primate visual cortex is organized into two functionally specialized, hierarchically arranged processing pathways, a ventral or 'what' stream for object processing and a dorsal or 'where' stream for spatial processing[58] (FIG. 3a). Although these two pathways interact[59], the visuospatial constructive disabilities in WS, together with relatively good face and object processing skills[60], suggest a neural processing abnormality in the dorsal stream[61–64] with relatively intact ventral stream function.

We tested this hypothesis with a series of functional imaging experiments investigating several levels of the visual processing hierarchy in high-functioning individuals with WS[17]. Ventral stream processing, as measured with fMRI during passive viewing of pictures, attention-demanding processing of the identities of pictures and a shape-matching task, was intact. However, dorsal stream function while participants attended to the spatial locales of the same pictures or performed a two-dimensional analogue of the classic block design task was abnormal (FIG. 3b). Hypofunction was observed immediately adjacent to, and anterior to, the intraparietal sulcus region in which we had identified decreased grey matter volume and sulcal depth[17,65] (FIG. 3a). Because these functional abnormalities lay distal to the structural anomaly in the

Retinotopic mapping
A functional imaging technique that can be used to delineate the extent of visual brain areas by capitalizing on the fact that they represent retinal information in a consistent spatial map.

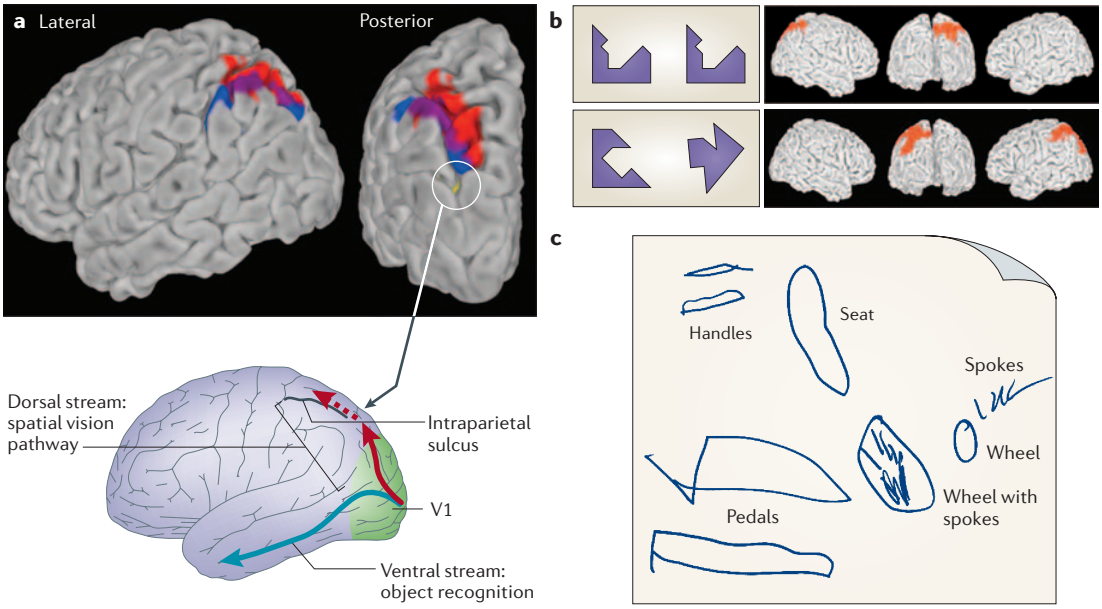

Figure 3 | **Dorsal visual stream functional deficits in Williams syndrome. a** | Spatial relationship between area found to be structurally abnormal with voxel-based morphometry (yellow), and two tasks tapping into the function of the dorsal visual stream (red and blue) in high-functioning participants with Williams syndrome (WS) compared with controls during functional MRI (fMRI)[17]. Overlapping regions in the parietal lobule are coloured purple, showing consistent functional abnormalities in the dorsal visual stream directly adjacent to the structural abnormality. Lower panel shows location of proposed functional–structural impairment in the dorsal stream at the intraparietal sulcus. V1, primary visual cortex. **b** | Left panels show examples of square completion stimuli, used for a task that tests visuoconstruction (participants check whether the two pieces can be assembled into a square). Right panels show significant hypoactivation in the parietal lobe of people with WS compared with controls in the square completion visuoconstruction task during fMRI, showing dorsal visual stream impairment. **c** | Drawing of a bicycle by a 9 year old with WS showing pronounced problems with visuospatial construction. It should be noted, however, that drawings like this are part of the sequence of learning to draw, even for typically developing children. Although people with WS usually show extreme delay in learning to draw, by adulthood most produce drawings that reflect the global aspects of the intended object[10]. Panels **a** and **b** reproduced, with permission, from REF. 17 © (2004) Cell Press. Panel **c** reproduced, with permission, from REF. 10 © (2000) John Wiley & Sons.

dorsal stream, it seemed that the latter was serving as a roadblock to the hierarchically organized dorsal stream information flow from earlier, more inferior-posterior, to later, superior-anterior visual processing areas. This was formally tested with path analysis, a method that allows statistical assessment of interactions among regional nodes in a predefined neural system model. This model was based on well-known anatomical constraints, similar to those of previous path analyses of the visual system[66], and consisted of functional data from nodes in early visual areas, in the most activated ventral stream region, in the structurally changed intraparietal sulcus region and in a dorsal stream location of pronounced hypofunction in WS. It fit well with the functional data from both participants with WS and matched controls. When each interregional path was tested for significance of contribution to the overall fit, the only difference between groups was that the path from the intraparietal sulcus to the later dorsal stream region was significant in controls but not in individuals with WS[17].

These data suggest candidate genes that might influence visuospatial constructive cognition in the general population through an impact on intraparietal sulcus function. It would, therefore, be of great interest to determine whether genetic variations in the general population have an impact on the anatomical integrity and functional activation of this region. Such findings would add a new biological dimension to the study of visuospatial construction.

Memory and hippocampal function. Although verbal short-term memory is a relative strength in WS[11], several cognitive domains linked to the hippocampal formation are severely affected, including spatial navigation[67,68], and especially long-term memory, both in the verbal[69] and spatial[70] domains.

We undertook a multimodal imaging study aimed at comprehensively characterizing the hippocampal formation (HF) in our cohort of high-functioning individuals with WS[71]. Baseline neurofunctional status, measured during rest with oxygen-15 water positron emission tomography, was profoundly reduced bilaterally in the hippocampal formation, extending into the entorhinal cortex (FIG. 4a). We also used proton magnetic resonance spectroscopy (MRS) for *in vivo* assay of NAA, a cellular integrity marker and measure of synaptic abundance[72]. Reduced NAA (as a ratio to creatine), which was more pronounced in the left hippocampal formation, was found

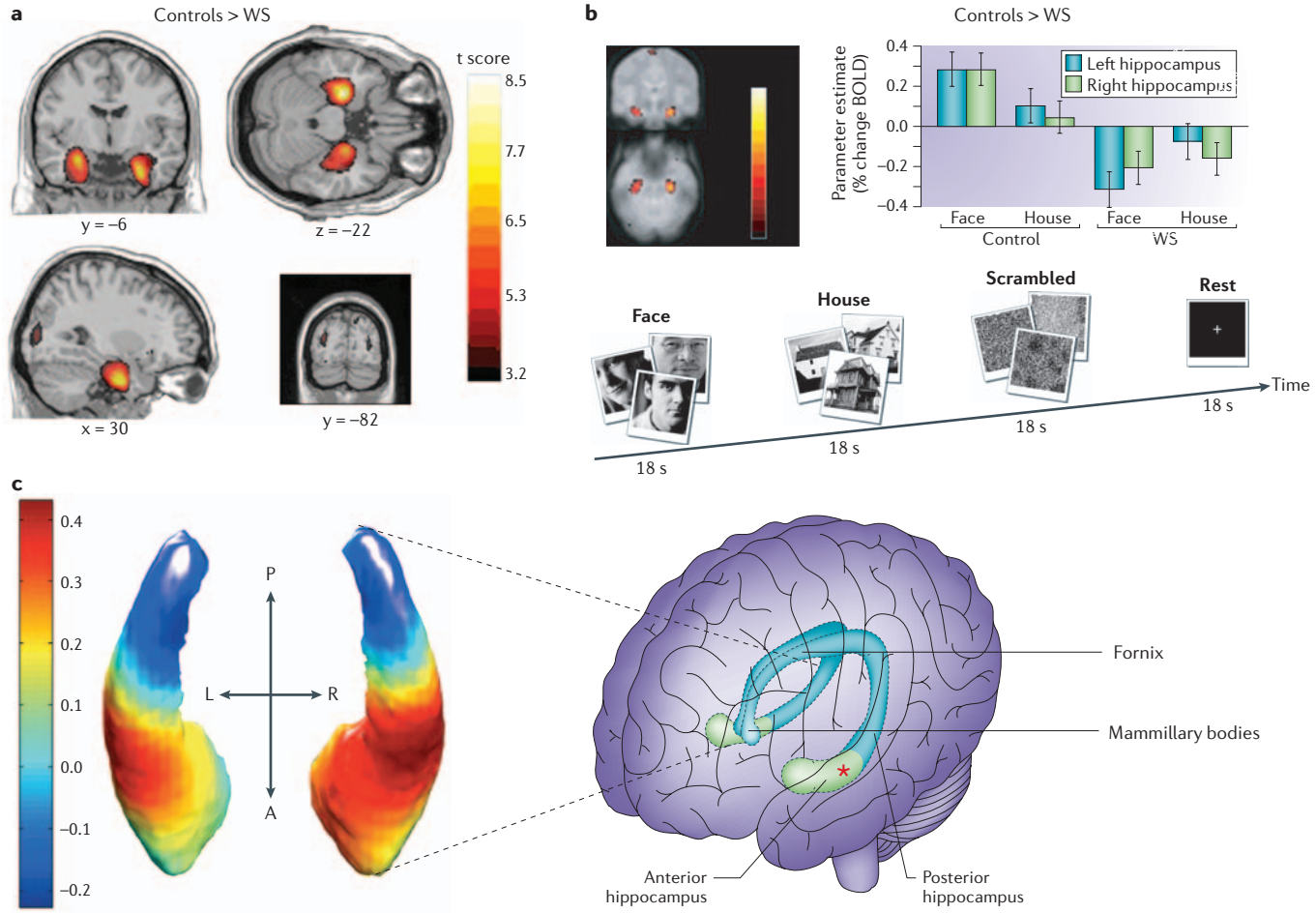

Figure 4 | **Hippocampal abnormalities in Williams syndrome. a** | Marked reduction of regional cerebral blood flow (rCBF, measured using positron emission tomography) at rest in the anterior hippocampal formation bilaterally in high-functioning participants with Williams syndrome (WS) relative to normal controls ($p < 0.05$, corrected for multiple comparisons). Bottom right panel shows reduction in rCBF in the intraparietal/occipitoparietal sulcus in WS ($p < 0.001$, uncorrected). **b** | Results of functional MRI (fMRI) experiment during the presentation of face and house stimuli, which differentially activate the hippocampal formation in normal controls. Top left: average blood oxygen level dependent (BOLD) response in participants with WS compared with that of healthy controls shows reductions in the anterior hippocampal formation bilaterally (significant at $p < 0.05$, corrected for multiple comparisons) shown superimposed on an average fMRI brain volume. Top right, parameter estimates of percentage change in BOLD response to face and house stimuli relative to baseline in both participant groups at the left and right voxels of maximum group difference, located in the hippocampus. Bottom: schema of stimuli and experimental paradigm. **c** | Map of shape change, computed using deformation-based morphometry (a variant of voxel-based morphometry), rendered on average hippocampal template (posterior view). Negative values indicate relative local volume reduction in WS relative to controls; positive values indicate relative local volume expansion in WS relative to controls. Panels **a**–**c** modified, with permission, from REF. 71 © (2005) American Society for Clinical Investigation.

in participants with WS[71]. As long-term potentiation (LTP) is highly dependent on intact oxidative metabolism[73], and hippocampal NAA levels are indicative of tissue glutamate concentration[74], these findings, together with the deficit in resting blood flow, indicate overall depression of hippocampal energy metabolism and synaptic activity in WS.

Functional reactivity of the hippocampal formation was assessed with fMRI during passive viewing of face and house stimuli, which differ in their relevance to spatial cognition[75]: faces preferentially activate the ventral stream, whereas houses are processed by both the ventral and dorsal streams[76]. If hippocampal formation activation deficits in WS were a consequence of deficient dorsal stream input (via the parahippocampal cortex, including regions of the parietal lobe[77]), hippocampal formation activation to houses should be predominantly impaired. By contrast, abnormal processing in the hippocampal formation itself should have an impact regardless of stimulus type. A group difference emerged in the bilateral anterior hippocampal formation that corresponded well with the resting blood flow reduction (FIG. 4b): the control group showed more activation for face than house stimuli, whereas no activation was seen to either stimulus in individuals with WS, suggesting primary hippocampal dysfunction rather than impaired dorsal stream input[37].

Long-term potentiation (LTP). Enduring increase in the amplitude of excitatory postsynaptic potentials as a result of high-frequency stimulation of afferent pathways; LTP has been most studied in the hippocampus.

In contrast to the marked functional changes, structural changes were subtle (FIG. 4c), similar to observations in mouse models (see below). Manual delineation of hippocampal structure on high-resolution structural MRIs showed volume to be normal in individuals with WS. This is consistent with previous data[17,36] and with the idea that the reduction in blood flow, NAA metabolism and functional responsivity of the hippocampal formation is not due to volume loss but rather to functional impairment of neurons in this region.

The strong impact on the hippocampal system observed in WS, and the remarkable similarity between observations in humans and phenotypes in mouse knockouts (discussed below) strongly suggests that the WS region contains genes that are important for hippocampal function. The study of functional variation of these genes in the general population, and their interaction with genes known to modulate function in this region in humans, such as brain-derived neurotrophic factor (BDNF)[78], is therefore a promising line of future inquiry.

Verbal and musical abilities. In the early 1990s, the prevailing view was that individuals with WS had normal language abilities despite severe mental retardation[79–81]. Recent research has provided a more nuanced picture, suggesting that the claim of normal language abilities was due to the specific comparison group initially chosen: individuals with Down syndrome (DS)[10,82,83]. Performance of individuals with WS on standardized assessments of language[84] indicates clearly that their language is below age expectations[83,84]. Initial reports that individuals with WS use unusual vocabulary[80,81,85] have not been replicated[83,86,87]. Grammatical abilities of children with WS, although superior to age- and IQ-matched children with DS[80,81,85,88], are at the same level as age- and IQ-matched children with mental retardation other than DS, or typically developing (TD) children matched for mental age[88–91]. Studies of morphological processing show children with WS at or below the level of matched younger TD children[92,93]. Although the language produced by older children and adults with WS is usually grammatical and fluent, pragmatic abilities such as turn-taking and topic maintenance are weak[83,94].

In most ways, language acquisition by children with WS is best characterized as normal but delayed[83]. The relationship between language and verbal memory ability in children with WS seems to be stronger than for TD children[88,95,96], and has been interpreted to indicate that children with WS might need to depend more on verbal memory abilities to acquire language. Karmiloff-Smith and colleagues[97] have raised the more general possibility that although language development in WS may mostly follow a normal but delayed path, the processes by which abilities are acquired may not be the same as for TD children. Unfortunately, no imaging studies have examined language function in WS, with the exception of one electrophysiological experiment that suggested altered left temporal response to semantic anomalies[98]. Further work is needed to establish or refute the assumption of a neural deficit in the language domain in individuals with WS.

It is often stated in the media that WS is associated with unusual musical talent[99], and it has been suggested[100] that this perceived aptitude in people with WS indicates that musical ability may even reflect an independent module of mind. However, although as a group individuals with WS are highly interested in music[101,102], most individuals with WS are not musically gifted[103] and their performance on standardized tests of musical ability[104,105] is the same[106] as that of a mental age-matched TD group, and below that of an age-matched TD group[107].

Social and emotional processing. The gregariousness of individuals with WS is the most immediately striking aspect of this condition. Increased interest in social interaction is evident from infancy onwards[108–110], and increased empathy[10,13], positive interpersonal bias[14], social disinhibition — even towards people they objectively do not consider approachable[111] — and overfriendliness extend into adulthood[112,113] (see BOX 2 for a comparison of WS and autism). Positive face stimuli (but not other emotions) are highly salient and rated more approachable by participants with WS[114]. Tager-Flusberg and colleagues have distinguished between social–perceptual and social–cognitive components of theory of mind[115]. Although initial studies suggested that the social–perceptual component might be relatively spared in WS, more recent studies have indicated that both the social–perceptual[116] and the social–cognitive[115] components of theory of mind are at or below the level of age- and IQ-matched controls with other forms of developmental disability, and well below the level of age-matched TD controls. Therefore, despite their social gregariousness, people with WS encounter problems in everyday interactions because of an inability to detect and respect social danger signals, and overall social adaptation and success is low[109,111,113,117,118]. Although people with WS often appear outwardly happy[119], closer observation indicates that there is considerable anxiety in this population. Individuals with WS show high rates of symptoms of generalized and anticipatory anxiety[8,15,16,117], and ~50% meet DSM-IV criteria for specific phobia[8,16].

Early on, it was proposed[14] that the social abnormality in WS could be related to abnormal amygdala function because the amygdala monitors environmental events such as danger[120]. Lesions of the amygdala and linked cortical regions, such as the OFC, impair social functioning and can lead to disinhibition[121]. However, the presence of increased non-social anxiety in WS suggests additional neural mechanisms. To investigate this question, we studied the differential response of the amygdala and its neural regulation using tasks requiring perceptual processing of threatening visual stimuli previously shown to reliably engage the amygdala[122]. The tasks involved presenting either threatening and fearful scenes, which are rarely encountered and socially less relevant, or angry and fearful facial expressions, which are commonly encountered and socially highly relevant. Amygdala reactivity in individuals with WS to threatening, socially relevant stimuli was significantly diminished (FIG. 5b). As such signalling is crucial for appropriate avoidance behaviour[120], this abnormal response might contribute

Theory of mind
The ability to interpret people's behaviour in terms of their mental states. Includes both social–perceptual (capacity to distinguish between people and objects, and to infer mental disposition from facial, prosodic and body expressions) and social–cognitive (explicit representation of and reasoning about others' beliefs and intentions) components.

Box 2 | **Williams syndrome and autism**

The neurobehavioural profile of Williams syndrome (WS), particularly in the social domain, invites comparison with another neurodevelopmental disorder, autism. In contrast to the hypersociability, increased empathy and fascination with faces seen in WS, autism is characterized by qualitative disability in social interaction, including failure to develop age-appropriate peer relationships and lack of social or emotional reciprocity[157]. Unlike the relative language strengths of WS, language in people with autism is usually relatively weak; many individuals do not develop spoken language, others have marked impairment in initiating conversation, and/or stereotyped, repetitive or idiosyncratic use of language[157].

Autism and WS have, therefore, been seen as clinical opposites. However, several cognitive domains are impaired in both: the use of non-verbal behaviours, including eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction, and judging facial expressions[111,158]. In addition, the two disorders coexist in some individuals. In a series of 128 4–16-year-olds with WS, 9 cases of autism spectrum disorder (ASD) were identified[16]; 6 other cases were previously reported[159,160]. Rather than being neuromechanistically related, such dual diagnoses might represent instances of coincident separate 'hits'.

Nevertheless, there is considerable interest in comparing the neurobiological substrates, particularly of social cognition, in these disorders. Although no formal, direct cross-diagnostic assessment of brain structure or function has been published, some inferences can be drawn. In autism, as in WS, attention has been focused on the amygdala[161], with findings of increased cell-packing density and both increased and decreased amygdala volume[162]. Amygdalar hypofunction has been reported in autism[163–165] as well as hypofunction in other key regions for face processing and social function[158], including the fusiform gyrus[164,166,167]. However, increased amygdala activity during face processing has recently been reported along with a positive correlation between duration of gaze fixation and amygdala and fusiform activation, suggesting both heightened emotional response and an explanation for previous findings of hypoactivation in autism[168]. Therefore, there is no consensus about the direction of amygdala activation to faces in autism, and attentional and cognitive bias concerns have not been adequately addressed. These concerns are mitigated in individuals with WS, who have increased interest in faces, making it behaviourally unlikely that reduced visual processing of faces accounts for reduced amygdala activation that we reported in response to threatening faces. Moreover, we observed no group difference in fusiform activation or in differential response to threatening faces versus scenes[37]. Also, in a detailed group and single-subject analysis of ventral visual stream activation to neutral expression faces[17], fusiform face area activation was normal in individuals with WS, again mitigating concerns about abnormal bottom-up control of amygdala function. Although not yet explicitly studied, it is likely that, as in WS, the neurobiology of social cognition in autism involves system-level dysregulation, is context dependent, and is best understood when viewed developmentally.

to diminished fear of strangers and consequent social disinhibition[14]. Conversely, and again in excellent agreement with the clinical profile of WS, amygdala reactivity to socially irrelevant stimuli was abnormally increased (FIG. 5b). As specific phobia has been associated with increased amygdala reactivity[123], this observation offers a potential mechanism for the high rate of non-social anxiety seen in individuals with WS[15]. Clearly, however, the proximate cause of the social behavioural abnormality in WS was not a deficit of amygdala activation, which was actually increased for non-social stimuli, pointing towards abnormal regulation of this structure.

In the same study, we observed that IQ-matched normal controls differentially activated regulatory regions in the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MPFC) and OFC in response to task difficulty, whereas high-functioning participants with WS did not (FIG. 5a). In particular, the OFC was not differentially activated in the WS group at all. Together with the structural abnormalities observed in the OFC, this provided convergent evidence for a deficiency of this region in the context of social processing. In both human and animal models, OFC activity has been associated with representation of the relative reward value of primary and secondary (learned) reinforcers[124]. In particular, OFC and OFC–amygdala interactions are crucial for stimulus-reinforcement association learning[125]. Meta-analyses of the functional imaging and lesion literature have defined a medial–lateral distinction within the OFC, with the lateral areas, where abnormalities were found, involved in evaluating the valence of reinforcers, which may change ongoing behaviour[124]. Specifically with regard to social cognition, the role of OFC–amygdala interactions has been proposed to link sensory representations of stimuli with social judgements made about them on the basis of their motivational value[126]. Lesions of the OFC are associated with social disinhibition[127] and impaired ability to detect *faux pas*[128].

In this context, a functionally abnormal OFC is in good agreement with the social disinhibition and impairments in adjusting behaviour according to social cues that are found in individuals with WS[14,111]. This was further substantiated by an analysis of functional interactions between the prefrontal cortex and amygdala, which showed that the OFC does not interact with the amygdala in WS, whereas a significant negative correlation was found in controls. This suggests a primary OFC deficiency, which would be predicted to contribute to social disinhibition, reduced reactivity to social cues and increased tendency to approach strangers, as is typical for individuals with WS. During maturation, aversive consequences of these dysfunctional social interactions would become increasingly apparent but, with a deficient OFC, could not be translated into appropriate emotional valence adjustments, rendering the amygdala signal useless to guide behaviour.

Apart from the implication of genes in the WS region in the emergence of orbitofrontal regulatory function in social cognition, these data have relevance for social neuroscience in general. They provide human data suggesting a possible dissociation between the neural substrate of social and non-social fear, supported by data from non-human primates with neonatal amygdala lesions[129], which show increased social but decreased non-social fear, the inverse of the situation in WS. In addition, these data identify a core network of prefrontal–amygdala interaction for social cognition under genetic control that can, and has, been used to investigate the impact of genetic variation on socially relevant brain function in the general human population[130].

Modularity of mind

The concept of modularity of mind has been widely discussed in the psychological, neuroscientific and philosophical literature. In the initial definition by Fodor[131], several criteria for cognitive modular systems were delineated, most importantly domain specificity (modules process only certain types of input), informational encapsulation (modules operate independently) and fixed neural architecture. The article[80] and related conference presentations of Bellugi and colleagues catapulted WS to

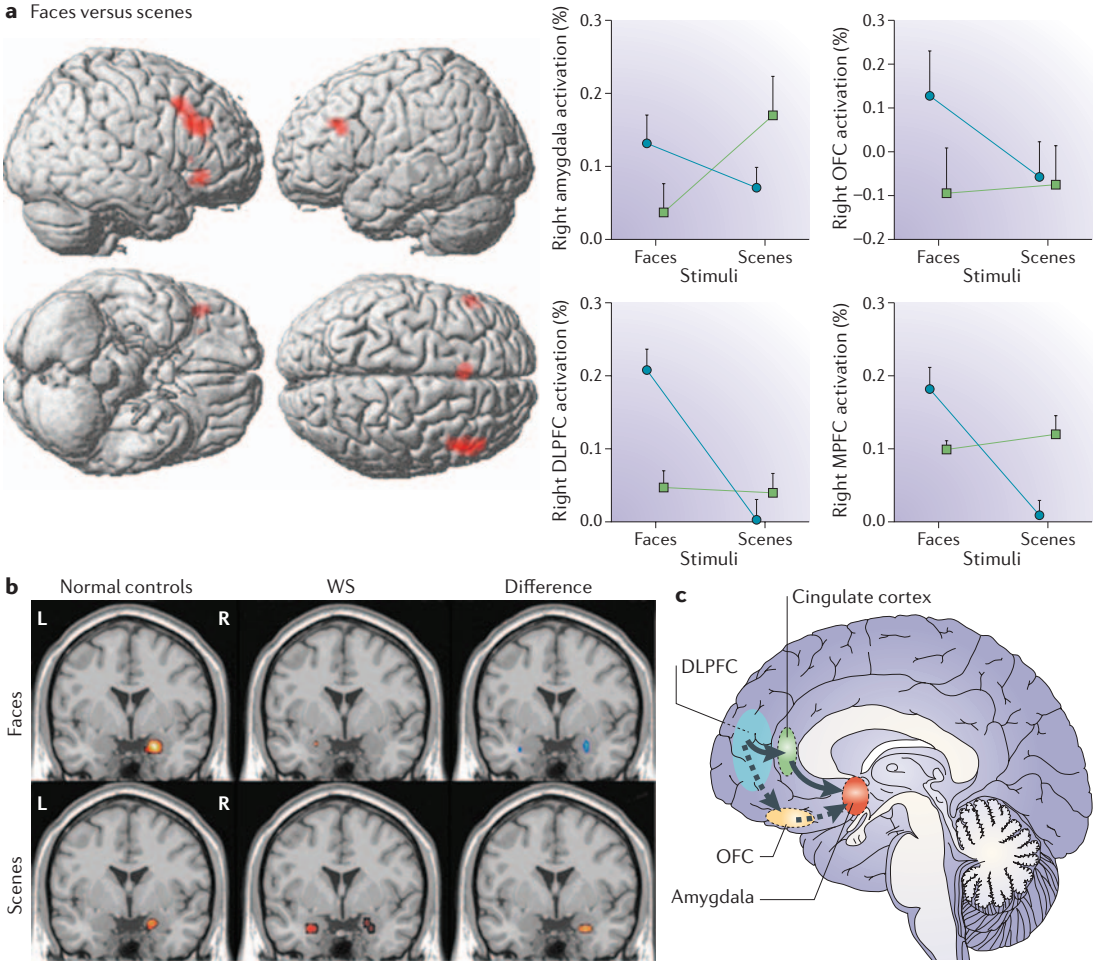

Figure 5 | **Neural mechanisms of hypersociability in Williams syndrome. a** | Regions of significant difference between normal controls (NC) and people with Williams syndrome (WS) (increases or decreases) in reactivity to a task in which a pair of fearful faces (socially relevant stimuli) or fearful scenes (socially less relevant) are matched against a third picture. Activation during functional MRI, rendered in red on standard brain surface. Statistical threshold is $p < 0.05$, corrected for multiple comparisons. Changes in blood oxygen level dependent (BOLD) response were seen in the right amygdala, dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC) and medial prefrontal cortex (MPFC). Mean ± standard error shown for each group and stimulus condition (right). **b** | Amygdala activation ($p < 0.05$, corrected for multiple comparisons) for face and scene stimuli, rendered on normal coronal MRI at ±1 mm to the anterior commissure. First column, normal controls; second column, high-functioning participants with Williams syndrome; third column, significant differences between groups (blue NC>WS, red WS>NC) in the amygdala. **c** | Schema depicting key regions for social cognition and emotional regulation affected in WS[169]: amygdala, OFC, DLPFC and cingulate cortex. Panels **a** and **b** reproduced, with permission, from REF. 37 © (2005) Macmillan Publishers Ltd. Anatomical image adapted, with permission, from REF. 170 © (1996) Appleton & Lange.

the centre of the modularity debate[85,132] with the argument that WS represents a clear dissociation between intact language abilities and severe cognitive deficits, suggesting the existence of a 'language module', and secondary sources often take WS as evidence for a strong modularity position implied in the initial statements of Bellugi *et al.*[133,134]. As reviewed here, however, subsequent work has largely challenged the research base supporting these claims: in particular, language abilities in WS, although a relative strength compared with visuospatial construction abilities, are not intact, and the cognitive impairment in WS is not severe[10]. Emphasizing interdependence, and not modularity, in people with WS, both vocabulary and grammatical abilities are strongly correlated with verbal working memory, nonverbal reasoning ability and visuospatial constructive ability[86] to an even greater degree than for the general population[95]. The modularity view has also been comprehensively criticized for lacking a developmental perspective[135].

The characterization of neural mechanisms offers a fresh view of the question of modularity. In particular, the evidence relating to the visual system suggests that the pronounced impairment in visuospatial constructive function in WS, sparing object perception and primary visual function, is a consequence of a localized structural–functional abnormality in a system that

is itself highly modular and hierarchical in design[17]. Conversely, the evidence for social cognition showed an abnormal activation profile in the amygdala that mirrored the clinical phenotype. However, the data did not suggest localized dysfunction, but rather abnormal regulation by the prefrontal cortex that was consistent with compensatory, and possibly adaptive, reorganization between cortical subregions that is consistent with a developmental phenomenon[37].

One conclusion that could be drawn from these data for the modularity debate in general is that even if Fodor's criterion of "fixed neural architecture" is accepted, there is no easy correspondence between cognitive domain specificity and independence, and the properties of neural systems in which these functions are instantiated. Whether or not a given genetic or neurodevelopmental functional impairment — even if it affects a circumscribed area of the brain — will have consequences that appear modular at the cognitive level depends on the details of neural connectivity of the systems in which this region participates.

Isolation of genetic mechanisms

With the neural endophenotype of WS coming into focus, the next major advances will come from delineating the individual and combined contribution of the ~28 genes in the WS region to these neural abnormalities. Several complementary strategies are being pursued. Mouse knockout models allow the investigation of single gene effects in animals. The detection and study of individuals with atypical (smaller) deletions — which, although rare, sometimes occur as a result of the complex genetic structure of the WS region — allows us to make inferences about contributions of single genes or groups of genes not deleted in such individuals if they show relevant differences to the common WS phenotype. At present, candidate genes for neurobehavioural abnormalities include LIM domain kinase 1 (*LIMK1*), implicated by linkage in the genesis of the visuospatial constructive deficit[57], and cytoplasmic linker 2 (*CYLN2*)[136]. Knockout mouse models for both of these genes have recently been described[136,137], as have knockouts for two other genes in the WS region, frizzled 9 (*Fz9*) (REF. 138) and *GTF2IRD1* (general transcription factor II i repeat domain-containing 1)[139,140].

Gene knockout models. In mice, the WS region is found, with considerable synteny, on chromosome 5 (REFS 141,142). Knockout methodology has opened up the possibility of studying both single and multiple gene haploinsufficiency in animal models. These studies have revealed intriguing similarities between neural systems found to be impaired in neuroimaging studies of individuals with WS, and neuropathological, neurophysiological and behavioural abnormalities in mice. Although fear conditioning abnormalities have been investigated, and tap into some of the same neural circuits, social interactions have unfortunately not been studied; this would be of great interest given the leading role of social symptoms in the WS phenotype.

The first of these knockout models concerned *Limk1*, a regulator of cofilin phosphorylation and actin dynamics that has been strongly linked to the visuospatial deficit of WS by the study of small deletion kindreds (see below). *Limk1* encodes a cytoplasmic protein kinase, which is prominently expressed in the developing brain[143] and has been implicated in the control of growth cone motility in cultured neurons[144]. As actin and its regulation are essential for cellular motility, dendrite outgrowth and synaptic regulation at mature synapses, including hippocampal LTP, hemi-insufficiency of the gene encoding LIMK1 is an attractive candidate for many of the observed structural and functional abnormalities of WS. Unfortunately, data on hemizygous knockout mice have not been reported. However, null mutants showed abnormal dendritic morphology (elongated spines) in the neocortex and hippocampus in the setting of grossly normal hippocampal volume[137]. High-frequency hippocampal LTP was also enhanced. Behaviourally, mice showed increased locomotor activity, enhanced fear conditioning to simple sound stimuli, and impairment in the Morris water maze task — although they acquired the spatial positions of the maze normally, they were impaired in altering the response when the location of the spatial cues was changed. It is intriguing to speculate that behavioural disinhibition and enhanced fear conditioning in a non-social context might be related to the abnormal hyper-reactivity of the amygdala to non-social fear-inducing stimuli observed in humans with WS; further studies focusing on amygdala function in this animal model, ideally in hemizygous mice, would be highly desirable.

The second report described mice hemi-insufficient for *Cyln2*. *Cyln2* encodes a cytoplasmic linker protein of 115 kDa (CLIP-115) that has been implicated in the local regulation of microtubule dynamics, especially in response to positional cues[136]. Brain anatomy of hemizygous knockout mice was macroscopically normal[136]. Behaviourally, mice showed no change in amount of locomotor activity, but some impairment in coordination. However, they did show decreased contextual, but not cue-conditioned, fear response, arguing for a hippocampal, but not amygdalar, abnormality in fear processing associated with this gene. This was supported by decreased hippocampal LTP in hemizygous mice.

Both *Cyln2* and *Limk1* encode proteins that regulate dynamic aspects of the cytoskeleton of the cell, either via the actin filament system (LIMK1), or through the microtubule network (CLIP-115)[144]. These alterations might lead to defects in neuronal structure and synaptic plasticity in adulthood and/or to defects during brain development, and suggest a possible convergent mechanism for structural–functional abnormalities in WS.

WNTs regulate the development of dorsal structures (including the hippocampus) in the developing mammalian CNS. Recent studies have examined the mutants of one class of WNT receptor, the frizzled genes, and found them to be involved in various phenotypes in the developing brain, including regional neurotrophic functions and regulation of major fibre tracts. *Fzd9* is selectively expressed in the hippocampus. *Fzd9*-hemizygous mice

Endophenotype
A quantitative biological trait associated with a complex genetic disorder that is hoped to more directly index the underlying pathophysiology, facilitating efforts to find or characterize contributing genes.

had generally normal gross anatomical hippocampal organization, but showed large increases in apoptotic cell death in the developing dentate gyrus, which was partly compensated by an increase in precursor cells. In a test of memory with a visuospatial component, homozygous mice lacking *Fzd9* were somewhat (though not significantly) impaired, indicating a possible functional link of the observed hippocampal abnormalities to memory and visuospatial cognition. Intriguingly, the seizure threshold in mice hemi- or homozygous for the deletion was reduced. Epilepsy has been described in individuals with WS, but is not usually of a psychomotor type.

General transcription factor II, i (*GTF2I*) and *GTF2IRD1* emerge as candidate genes from the study of individuals with WS who have small deletions. Both are ubiquitously expressed and belong to a family of transcription factors that interact promiscuously with multiple proteins and DNA, linking signal transduction to transcription, and could, therefore, influence a broad range of neural physiological and developmental processes[145,146]. *Gtf2ird1* has been knocked out in mice, but a characterization of the neural–behavioural phenotype is lacking, although no obvious behavioural problems or lifespan reductions have been observed[139,140].

Involvement of other genes in the WS region, such as *WBSCR14* (REF. 147) and syntaxin 1A (*STX1A*), which has been implicated in synaptic vesicle docking[148], has been proposed on the basis of their expression in the brain, but has not been established further. The evidence from individuals with small deletions indicates that neither of these genes is likely to have a major role in the neural–behavioural phenotype. See online Supplementary information S1 (table) for a summary of information about brain expression from public data sources for genes in the WS region not discussed further in this review.

Small deletions in the WS region. The typical WS deletion contains ~28 genes, but the complex genetic instability of the region leads to only partial deletions in some individuals. If *ELN* is affected, many come to medical attention as a result of cardiovascular abnormalities. A study of these cases is of high interest, because genes not deleted can be related to aspects of the WS phenotype not present, which helps to narrow down the list of candidate genes for neural and behavioural phenotypes of WS. Conversely, (a subset of) genes deleted in small-deletion individuals can be associated with aspects of the phenotype that are present. The extent of these deletions is indicated in FIG. 1c.

Three individuals have been described with the cognitive phenotype and mental retardation, but with atypical centromeric breakpoints resulting in smaller deletions. *STX1A* and the genes proximal to it were not deleted, but the telomeric breakpoint was consistent with the common deletion at or just beyond *GTF2I* (REFS. 149,150). These cases therefore argue against a major role of genes centromeric to *STX1A* in the neural abnormalities of WS. This is supported by data from a highly intelligent individual, lacking cognitive symptoms, with an atypical 850-kb deletion that included these genes, but not genes telomeric to replication factor C2 (*RFC2*)[151]. Unfortunately, the literature is less consistent regarding the involvement of genes telomeric to *ELN*, especially *LIMK1*. A typical cognitive profile was seen in 11 of 13 individuals from families with atypical deletions encompassing only *ELN* and *LIMK1* (REF. 57). As *ELN* mutations do not affect cognitive function and elastin is not strongly expressed in the brain, this led to the proposal that *LIMK1* hemizygosity contributes prominently to impairment in visuospatial constructive cognition. In a follow-up study of five such families, none had mental retardation, but affected family members fit the WS cognitive profile[5]. Again, all families shared a deletion of *LIMK1*. However, three individuals with similar deletions who do not fit the cognitive profile have also been described[152]. Reasons for this discrepancy have been discussed[5,151,153] and include: variable penetrance of this phenotype; gene dosage; the possibility that higher IQ in individuals with small deletions might allow them to use alternative strategies to circumvent visuospatial constructive impairment; as well as gene–gene interaction effects, such as those discussed above for *LIMK1* and *CYLN2*.

With regard to other neuropsychiatric aspects of WS, deletions in five families with the WS cognitive phenotype but no mental retardation[5] did not include FK506 binding protein 6 (*FKBP6*) or *GTF2I*, suggesting that the mental retardation typically seen in WS might be associated with deletion of either the centromeric and/or telomeric portions of the WS region. Comparison of these five families with the evidence excluding genes centromeric to *STX1A* from the neural phenotype most strongly suggests the necessity for *GTF2I* hemideletion in the mental retardation of WS. Whether *GTF2I* haploinsufficiency alone is also sufficient for the emergence of mental retardation is an open question; it is possible that deletion of additional gene(s) telomeric to *STX1A* is also required.

In these cases, as well as in three other individuals in whom *GTF2IRD1* and *GTF2I* were spared, visuospatial constructive function was less impaired compared with that seen in typical WS, but was not normal[154]. A recent case of a patient in whom *GTF2IRD1* was partially deleted, but *GTF2I* spared, also showed milder visuospatial construction difficulties[140]. At this point, although more work is clearly necessary, *LIMK1*, *CYLN2* and *GTF2I* emerge as the most promising candidate genes for the cognitive/behavioural/neural phenotype in WS, with only *LIMK1* heterozygosity being sufficient for the generation of the cognitive phenotype in at least some cases. It has been noted[151] that, apart from the cardiovascular aspects and *ELN*, no other part of the WS phenotype has been recognized as an isolated Mendelian dominant character in families with a point mutation in one of the crucial genes. This could be because the phenotype is subtle and complex, and/or because gene effects in the deleted region are additive or otherwise interacting. The convergent cellular mechanisms affected by *LIMK1* and *CYLN2* suggest such a model. In addition, the presence of a large deletion could itself contribute to the phenotype, either by a dosage effect or by interactions with adjacent (for example, silencing) elements. Delineation of the neural phenotype should enable a search for

subtle, clinically subthreshold effects of genetic variation in these candidate genes in the general population, which, if found, would greatly strengthen the implication of any such gene in the WS neural phenotype.

Conclusions and future directions

In recent years, there has been rapid progress in defining neural systems that are specifically altered in WS. Visuospatial processing associated with abnormal function and structure of parietal regions, hippocampal dysfunction, and dysregulated amygdala in the context of orbitofrontal disturbances have emerged as neural mechanisms plausibly linked to the unique behavioural phenotype of this condition. Both neuroscientific data and recent psychological evidence show that WS emerges from a complex interplay of these altered systems that needs to be viewed from a developmental perspective and is not generally consistent with cognitive or neural modularity.

These results form a point of departure for future research, which needs to move towards a detailed and mechanistic inquiry into specific genetic mechanisms for executive and social cognition. In particular, we hope that the question of whether and how individual genes, or their interactions, in the WS region contribute to the emergence of separable neural systems abnormalities will be pursued, using animal models, study of atypical participants and, potentially, the examination of variation in WS region genes in the general population. Another important requirement is for developmental studies to investigate the time course of emergence and modification of altered neural circuitry in WS. Because it relates to genetic mechanisms underlying complex behaviour in general, the potential research and clinical relevance of such work promises to reach far beyond the population of people with WS, truly making this rare condition a unique window to genetic contributions to neural function.

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Acknowledgements
This work was supported by the National Institute of Mental Health (NIMH) Intramural Research Program (IRP), a grant from the National Institute of Neurological Disorders and Stroke (C.B.M.) and a grant from the National Institute of Child Health and Human Development (C.B.M.). We thank C. Rainey for help with figure preparation, L. Kempf for preparation of the supplementary table and S. Kippenhan, P. Kohn and C. Morris for their ongoing collaboration on our neuroimaging work.

Competing interests statement
The authors declare no competing financial interests.

DATABASES
The following terms in this article are linked online to:
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At-a-glance summary

- Williams syndrome is a neurodevelopmental disorder with a prevalence of up to 1 in 7,500, caused by a hemizygous deletion of ~1.6 megabases, containing ~28 genes, on chromosome 7q11.23 through unequal homologous recombination during meiosis. Williams syndrome is characterized by typical facial features, cardiovascular abnormalities, mild to moderate mental retardation or learning difficulties, and unique neuropsychological and behavioural features that have made it a focus of research in neuroscience and genetics.
- The neuropsychological profile of Williams syndrome shows a severe weakness in visuospatial construction, combined with relative strength in verbal short-term memory and language. However, neither language production nor verbal short-term memory is typically completely normal. Behaviourally, individuals with Williams syndrome show a striking social fearlessness and gregariousness, combined with strongly increased non-social fear.
- We review recent advances made in defining the neural substrates of the unique neuropsychiatric features of Williams syndrome and define separable neural subsystems in this syndrome, specifying mechanisms for genetic influences on visuospatial cognition, social behaviour and memory. These results are discussed in the context of emerging data that link dissociable genetic contributions to these phenotypes through the study of knockout mouse models and atypi-

cal deletions in humans.

- The brains of individuals with Williams syndrome are smaller and show regions of reduced grey matter volume, and abnormal gyrus and sulcus configuration. A reduction of grey matter volume and depth has been identified in the intraparietal sulcus, a region that is important for visuospatial constructive function. In addition, functional MRI studies show activation deficits in the adjacent parietal lobe as a functional correlate of a circumscribed dorsal visual stream deficit that can be linked to the structural abnormality and may underlie the severe visuospatial constructive impairment seen in Williams syndrome.
- Convergent imaging evidence shows abnormal resting blood flow and activation of the anterior hippocampal formation together with only subtly abnormal structure. This might be linked to the severe long-term memory and visual-navigational impairments associated with Williams syndrome.
- In individuals with Williams syndrome, the amygdala is less active to threatening faces, but shows increased activity to threatening non-social stimuli, mirroring the fear profile in behaviour. Interactions between the amygdala and prefrontal regulatory regions, especially the orbitofrontal cortex, are abnormal, which suggests that the neural systems for social and non-social fear are dissociable and underlie different genetic–developmental trajectories.
- Knockout mouse models for LIM domain kinase 1 (*Limk1*) and cytoplasmic linker 2 (*Cyln2*) show similar hippocampal abnormalities to those identified in humans, implicating these genes in hippocampal function. The results of studies of human families with small deletions suggest that *LIMK1* is a promising candidate gene for involvement in the severe impairment in visuospatial construction seen in individuals with Williams syndrome, and that GTF2I (general transcription factor II i repeat domain-containing 1) hemideletion is necessary for mental retardation in this syndrome.

Toc Blurb (Max. 40 words)

Williams syndrome is a rare neurodevelopmental disorder with a distinct behavioural and neuropsychological profile. Meyer-Lindenberg *et al.* describe new research relating structural and functional differences to the underlying genetics of this disorder and their influence on cognition and behaviour.