A specific cognitive deficit within semantic cognition across a multi-generational family

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We report a study of eight members of a single family (aged 8–72 years), who all show a specific deficit in linking semantic knowledge to language. All affected members of the family had high levels of overall intelligence; however, they had profound difficulties in prose and sentence recall, listening comprehension and naming. The behavioural deficit was remarkably consistent across affected family members. Structural neuroimaging data revealed grey matter abnormalities in the left infero-temporal cortex and fusiform gyri: brain areas that have been associated with integrative semantics. This family demonstrates, to our knowledge, the first example of a heritable, highly specific abnormality affecting the interface between language and cognition in humans and has important implications for our understanding of the genetic basis of cognition.

Keywords: semantic memory; human language; phenotype

1. INTRODUCTION

Human language consists of both words and rules [1], together these components can, apparently effortlessly, convey complex thoughts, feelings and ideas. The relationship between a word and its meaning is abstract and assigned in an arbitrary way [2,3]. Our mental dictionary draws directly upon our experience of objects, associated facts and word meanings. The representation and use of this knowledge are called semantic cognition [3]. In this study, we describe a family with an isolated heritable deficit in semantic cognition. Although the family do not suffer from a progressive condition, it is helpful to draw analogy with neurologically patients, such as those with semantic dementia (SD) [4–6], to provide a better understanding of their deficits in the context of contemporary theories of semantic cognition.

Patients with SD [4–6] suffer from a selective and progressive breakdown of semantic cognition leading to an inability to represent the meanings of (previously known) words across picture naming [2], providing verbal definitions [7] or drawing objects [6,8]. Consequently, comprehension impairments are present in every modality, including words, pictures and sounds [6,7,9]. These deficits in semantic cognition occur despite preserved memory for daily events, visual perception, spatial cognition and articulate speech [6]. Even a mild breakdown of semantic cognition can lead to a difficulty in finding words during conversation [2,6]. The critical ingredients for communicating with other people are not simply the ability to find spoken words, but the ability to identify a constellation of associated meanings across different modalities, and integrate these aspects of word meaning effectively when speaking.

Contemporary theories of semantic cognition which seek to explain how and where unified conceptual representations occur in the brain [10–12] have identified a role for the anterior temporal lobes (ATL) of the brain in processing conceptual knowledge [10,12]. Within these models, the ATL has been conceptualized as a semantic ‘hub’ that binds modality-specific inputs from across a distributed network of perception, action and language-specific brain regions [12–14]. The neuro-anatomical distribution of brain damage in SD has been measured using structural and functional magnetic resonance imaging (MRI) [15–17] and positron emission tomography [18,19]. The semantic deficit in SD is linked to the deterioration of the inferolateral aspects of the ATL [12,14], and is usually bilateral, across the temporal pole and the rostral-inferior surface. This role for the ATL in the processing of conceptual knowledge is supported by evidence from a range of methods, including functional MRI in healthy adults and Transcranial Magnetic Stimulation (TMS) [13,17,20].

(a) Cognitive genomics

Our understanding of the genomics of semantic cognition lags behind the identification of gene-language associations within the spoken language systems [21,22] and gene-memory associations [23]. For example, familial studies of language impairment have located genetic variants associated with the articulation of speech sounds, i.e. in the combination of motor sequences [24], or the ability to reproduce unusual sequences of speech sounds [25], where the influence of word meaning is relatively weak. A family referred to as the JR family has been identified in which approximately half of all members, spanning four living generations, have, since childhood, reported a severe and relatively specific problem in their ability to recall verbally encoded material. Self-reported ‘verbal memory problems’ were the key presenting feature, not a psychiatric disorder or clinically led diagnosis. Unlike SD, there was no progressive element: older individuals did not report greater memory difficulties. The pattern of inheritance was
suggestive of a penetrant-dominant genetic anomaly. The primary purpose of the present investigation was to determine whether the cognitive profile of the JR family constituted a novel and stable phenotype, and to identify whether structural brain abnormalities co-occurred with their cognitive deficit.

The present study aimed to discover the extent to which the nature and severity of reported deficits in verbally encoded material was consistent across family members. The finding of consistency could serve as the basis for identifying the nature of a potential underlying inherited genetic anomaly. We used a case-control design to evaluate cognitive dysfunction in eight affected individuals (six females and two males) representing four generations of the JR family (aged 8–72 years). In order to identify whether psychometric deficits had correlates in anomalous brain structure, we conducted neuro-imaging analysis of brain structure as well as detailed probing of semantic memory.

2. METHOD

(a) Early identification of affected cases

Initial contact with the JR family arose through clinical assessment of a male child, aged 5 years, who had been referred for social communication difficulties. Probing during a clinical interview revealed self-reported verbal memory impairments that affected both the child and his mother. A family pedigree (figure 1) was collected to generate case numbers and 17 members of the extended JR family were contacted for interview to provide case descriptions (electronic supplementary material, S1). Consanguinity between grandparents was identified (first cousins) but converging reports across family members regarding the presence of memory impairments in previous generations (now deceased) implied their consanguinity could not be the origin of the putative genetic abnormality.

On presentation, affected individuals demonstrated fluent and grammatical speech, their conversational style was articulate with coherent sentences, and the content of their social conversation was engaging and mostly relevant to topic. However, their conversational style was occasionally limited by catastrophic failures of recall for word or topic, resonant of the tip-of-the-tongue phenomenon experienced by many people [26], including SD patients [2]. Their statement ‘I know what I want to say but I can’t quite get to the word’ typified this difficulty, although they did not report partial recall and were adept at masking failure. In almost all cases, visuo-spatial skills were strong and they reported using visuo-spatial strategies to support verbally mediated recall. Self-report concentrated on the severity of memory impairment with real-world examples such as a difficulty following a narrative thread while reading for pleasure or while watching television drama. Personally relevant events were remembered and discussed with occasional cueing. Despite superficially good social adjustments and an ability to engage with work, the personal impact of their difficulties had been severe with considerable impact on their ability to cope with school and work environments.

From the extended family of the presenting mother and child pair, eight individuals (six females mean age = 42.8 years; range = 15–75 years, III,7; IV,6; IV,8; IV,10; V,6 and V,8) and two males (one aged 32 years, plus the original male now aged 8 years, V,7 and V1,1, respectively), consented to neuropsychological assessment of intellectual ability ([27,28], also electronic supplementary material, S2; figure 1).
Figure 2. Per cent correct recall scores for (a)(i)(ii) immediate and delayed recall of logical story 1, (b)(i)(ii) immediate (second presentation) and delayed recall of logical story 2, and total recall of (c)(i)(ii) verbal paired associates and (d)(i)(ii) word list learning subtests, shown for six adult JR cases; with dashed lines to indicate child cases (V1,1 and V,8). Bars indicate adult group mean values. Each data point displays individual performance (each JR adult or the pooled mean of two matched controls).

(b) Intellectual ability and group-matching
All eight JR family cases were intellectually high-functioning (performance intelligence quotient (IQ) mean = 116.8, range = 104–136) although their verbal intellect varied substantially across subtests (verbal IQ mean = 88.8; range = 70–112). Their weakest scores were in the expression of knowledge of words and concepts (vocabulary mean = 6.4).

Matching across age, gender and intellect stabilized the identification of cognitive impairment. Each affected JR adult was matched with two controls on three criteria: gender, age (±1 year for all cases, except case III,7 who was matched ±4 years) and non-verbal intelligence (±7 points using the performance IQ scores). Only one control dataset was available for case IV,8. Children were similarly matched to control participants on gender, age (±six months) and intellect (performance IQ score ±7 points). Within-family controls were not used owing to the lack of a strong match for age and gender within the family, and were inappropriate owing to the absence of a priori objective diagnostic criterion (beyond self-report) on which affected cases could be classified.

3. RESULTS
To validate self-report, all affected JR cases consented to standard memory and language assessment ([29,30], see also the electronic supplementary material, S2). Memory index (MI) scores indicated visual memory performance

\[ n = 8; \text{visual immediate} = 103, \text{range} = 91–112; \text{visual delay} = 108.7, \text{range} = 94–125 \] was stronger than verbal memory \( n = 8; \text{verbal immediate} = 88.1, \text{range} = 74–105; \text{verbal delay} = 79.5, \text{range} = 50–99 \). Verbal-delayed MI scores were substantively lower than predicted from performance IQ for all eight JR cases by at least 12 points (statistically significant in seven of eight cases). Five cases had verbal-delayed MI scores at least 12 points below their MI scores predicted from verbal IQ (statistically significant in three of five cases; VI,1; III,7; V,8; electronic supplementary material, table S3a,b).

(a) Verbal memory, group-wise comparisons
To investigate the consistency of the memory profiles of affected JR family, verbal memory composites (verbal MI scores) were broken down to component subtests. Six adult JR cases were compared with a group of matched controls \( n = 13, \text{age range} = 15–79 \text{years}, \text{mean} = 44.6 \text{years} \).

As illustrated in figure 2a(i)(ii),b(i)(ii), adult JR family cases displayed weaker retrieval of story information presented immediately (story 1; \( t_s = 3.43, p = 0.001 \) and story 2; \( t_s = 4.15, p = 0.004 \)) or after a short delay (story 1; \( t_s = 3.76, p = 0.006 \) and story 2; \( t_s = 3.99, p = 0.005 \)). Cumulative recall of word pairs over four trials as in figure 2c(i)(ii), \( t_s = 3.52, p = 0.008 \), and after a delay \( t_s = 3.57, p = 0.008 \) implied weak associative
binding of known words in JR family cases. Retrieval success from word lists was weaker when words were recalled immediately \((t_f = 3.18, p = 0.01)\), or after a 10 min delay \((t_f = 2.03, p = 0.04)\), as shown in figure 2d(i)(ii).

Extended analyses implied these deficits were stable with age; these included the two child JR family cases with pro-rated raw scores for immediate \((\text{story } 1 t_f = 2.34, p = 0.02)\) and delayed subtests \((\text{story } 1 t_f = 3.40, p = 0.006)\), plus pro-rated total word list recall scores \((t_f = 4.30, p = 0.002)\) and word lists after a delay \((t_f = 3.09, p = 0.008)\). Impaired immediate verbal memory implied the fundamental problem lay in a semantic coding deficit, rather than a deficit in long-term memory consolidation. A restricted ability to learn word pairs, and poor re-telling of stories, appeared to be owing to a difficulty in extracting associated meaning from words and sentences in affected JR cases.

(b) Semantic cognition, groupwise comparisons

If poor semantic coding of verbal material reflected more general deficits in semantic cognition, then language tasks that largely depend upon the extraction of associated meaning of words and sentences were predicted to be impaired \([31]\), see the electronic supplementary material, S2). Groupwise comparisons of per cent accuracy scores on three tests of semantic processing consistently revealed group differences: (i) when required to identify a semantically associated word pair within a list \((\text{e.g. } \text{revive, resuscitate, rescue, deliver, word class}; t_f = 3.23, p = 0.009)\), (ii) when extracting meaningful relationships from short orally presented sentences \((\text{semantic relationships}; t_f = 3.58, p = 0.006)\), and (iii) when asked to report information after listening to a paragraph \((t_f = 7.5, p = 0.0001); \text{also electronic supplementary material, figure S4})\). Semantic processing deficits further characterized the deficit in the affected JR family members.

(c) Expressive language and phonological memory: groupwise comparisons

We questioned whether these deficits in semantic cognition comprised part of a broader spectrum of language impairments. Perhaps, their difficulties lay in the ability to extract meaning from the syntactical structure of sentences \((\text{e.g. from word order})\), or perhaps they were less able to grasp the sound-based \((\text{phonological})\) coding of sentences they heard. Measures of expressive language \([31]\) and sentence comprehension \([32]\) were administered to all cases and their matched controls. For three expressive language tests \([31]\), groupwise comparisons of per cent accuracy scores indicated variable levels of ability in the JR family group \((\text{also electronic supplementary material, figure S4})\). No group difference was evident when assembling sentences from a word set; \(\text{JR mean } 73.3 \text{ versus control mean } 76.9, t_f = 1.30, p = 0.12\), but formulating sentences showed a marginal group effect; \(\text{JR mean } 77.6 \text{ versus control mean } 90.3, t_f = 1.66, p = 0.07\). Repeating sentences that increased in length was challenging for the JR group; \(\text{JR mean } 61.2 \text{ versus control mean } 77.0, t_f = 5.66, p = 0.0007\). The JR family group was competent at organizing and constructing simple sentences, implying they were able to code the sound-based elements of speech, and generate a meaningful syntactical structure for simple sentences. Their problems became apparent when they repeated longer sentences that required better memory for \((\text{more content words})\). A deficit in semantic coding that became more apparent with more content words could have affected their ability to access and draw on word meaning to support recall \([33,34]\), or it could affect their ability to select the most appropriate content words during recall \([35,36]\).

All JR family cases were able to correctly identify sentence meaning from pictures, after listening to syntactically simple and complex sentences \([32]\) \((\text{age-scaled scores ranged from } 90 \text{ to } 109))\). Their good comprehension of spoken sentences further implied that the origin of their difficulties with sentence repetition did not simply reflect inadequate knowledge of syntactically complex sentence structures. An alternative hypothesis to explain their unusual difficulty was that they experienced impaired phonological memory with an inability to code and temporarily retain sequences of speech sounds \([37]\), which could have led to early expressive language delay and constrained their verbal memory performance. To address this possibility, digit recall and non-word repetition tests were administered to all cases and their matched controls \([27,28,38]\), also electronic supplementary material, figure S2). Individually, the longest digit span forward \((\text{LDSF})\) score \([27,28]\) was at least five digits for adults \((\text{LDSF}; \text{V,6 } = \text{five digits}; \text{V,7 } = \text{nine digits}; \text{IV,6 } = \text{five digits}; \text{IV,8 } = \text{six digits}; \text{IV,10 } = \text{seven digits to the oldest case III,7 } = \text{five digits})\), although both child cases achieved LDSF scores of four digits, lower than expected for their age \((\text{VI,1 } < \text{20 centile rank and V,8 } < \text{5 centile rank})\).

Strikingly, non-word repetition scores \([38]\) were comparable across groups \((F < 1, p = 0.62)\). Although non-words ranged from two, three, four and five syllables in length \((\text{JR mean } 8.50, 8.67, 5.67 \text{ and } 5.50 \text{ versus control mean } 8.58, 7.67, 6.67 \text{ and } 6.50)\), there was no syllable length by group interaction effect in a mixed ANOVA \((F_{3,45} = 1.69, p = 0.42)\). As non-word repetition is a highly sensitive test of phonological memory, the JR deficit could not be simply explained as a weakness in the coding and temporary retention of speech sound sequences.

(d) Probing semantic cognition, case-by-case analyses

To probe semantic cognition further, two tasks: associative picture matching \([9]\) and picture naming \([39,40]\) were evaluated through individual \((\text{casewise})\) profiling of six JR cases available for testing \((\text{V,8; V,6; IV,6; IV,8; IV,10 and III,7})\). Individual scores were plotted against scores of age- and performance IQ-matched controls \((n = 8 \text{ per individual case})\), with any case-control differences determined using a modified \(t\)-test \([41]\). Associative semantics was assessed by matching pictures of related concepts from two input modalities; picture matching and written word matching \((\text{e.g. does CAMEL go with CACTUS, TREE, SUNFLOWER or ROSE?})\) \([9]\). There was a stable overlap of accuracy scores of all six JR cases with eight individually matched controls in pictorial matching \((\text{case versus control mean}); \text{V,8 } = \text{62 versus } 57.7, \text{CI range } 1.8; \text{V,6 } = \text{62 versus } 61.4, \text{CI range } = 1.9;\)
IV,6 = 60 versus 62.5, CI range = 1.4; IV,8 = 62 versus 60.9, CI range = 1.5; IV,10 = 62 versus 60.3, CI range = 1.8; III,7 = 55 versus 57.9, CI range = 1.6; all p > 0.2) and written word – picture matching (case versus control mean: V,8 = 62 versus 59.2, CI range = 2.9; V,6 = 62 versus 62.1, CI range = 1.4; IV,6 = 62 versus 62.45, CI range = 1.2; IV,8 = 59 versus 61.1, CI range = 2.2; IV,10 = 62 versus 60.7, CI range = 2.6; III,7 = 62 versus 62.5, CI range = 1.6; all p > 0.2, with the exception of IV,8 > 0.05). Associated conceptual knowledge of words and pictures was well within the performance limits of controls, implying the affected JR family were unimpaired in their access and organization of non-verbal semantic cognition.

Confrontational naming of 300 object and 400 action pictures indicated all cases were within the performance of controls when naming objects and actions accurately [39] (figure 3a; all p > 0.3 for object naming accuracy, and all p > 0.1 for action naming accuracy except for case III,7 t7 = 1.71, p = 0.07). Close inspection of the pattern of errors revealed that the majority of errors in the affected JR family and their controls, involved a substitution of a related word. For example, there were errors that varied by an interchangeable label (e.g. alligator-crocodile), and errors that varied by a common feature (e.g. denture-teeth, twig-branch, beetle-ladybird) or were drawn from a superordinate category (e.g. bear-panda, animal-raccoon). Other errors included thematic (e.g. camera-tripod, moon-circle) and associative errors (e.g. tomato-can, plate-butter) in a minority of the affected JR family. In a further test of naming [40], we presented 30 pictorial items graded by difficulty (median lemma frequency = 12/1000, range = 0–152), followed by a probe of item definitions which revealed a subtle impairment of naming. As shown in figure 3b, only one case V,8 had weak retrieval of both names (V,8 = 62 versus 57.7, CI range = 1.8) and item definitions (V,8 = 62 versus 57.7, CI range = 1.8). All other JR family cases scored outside the range of control scores when retrieving item names (all p < 0.05, except V,6; t7 = –1.74, p = .06), but most were within control limits when producing item information (all p > 0.4, except III,7; t7 = –1.56, p = 0.08). Naming deficits were dissociated from providing word definitions of these low-frequency items in all cases except V,8 and three cases showed a dissociation between naming and knowing that was classical by definition (p < 0.05) [42]. Overall, variable retrieval of word names implied either diminished conceptual knowledge, or a weakness of the mapping between stored concepts and the sound based (phonological) form of words.

(e) Neuroimaging analysis of JR cases

Brain images were acquired on a 1.5 T MRI system (Siemens Avanto) using a three-dimensional T1-weighted FLASH (Fast Low Angle Shot) sequence with the following parameters: repetition time = 11 ms; echo time = 4.94 ms; flip angle = 15°; voxel size = 1.0 x 1.0 x
1.0 mm. Data were processed and analysed according to the quantitative voxel-based morphometry (VBM) method [43] implemented on SPM8 software (Wellcome Department of Imaging Neuroscience, www.fil.ion.ac.uk). VBM preprocessing was performed using a unified segmentation method that combines bias correction, image registration and tissue classification using default grey and white matter (WM) tissue probability maps. Segmented grey and WM images were smoothed using a 12 mm full-width half-maximum Gaussian kernel. Normalized grey and WM segments were modulated by their Jacobian deformation field (modulated images) to preserve the information about local tissue volumes (in comparison with local tissue density for the unmodulated images). Global grey or WM volumes and age were included in group comparisons as covariates of no interest.

All cases, except two adults (V,7 and IV,10) and all but four controls, agreed to undergo structural brain scanning. Four additional healthy participants were recruited so that each affected JR family case was compared with two age- and gender-matched controls. The mean age of the JR family cases was 41.5 years (s.d. 23.5) compared with 41.2 years (s.d. 22.6) for controls. Age range was from 10 to 78 years in both groups. As deficits within semantic cognition were found to characterize JR family cases, regional volume reductions were hypothesized in the ventral and lateral temporal lobe as well as inferior frontal cortex and anterior portion of the temporal lobes. These areas in the left hemisphere have previously been implicated in semantic cognition, by functional imaging and lesion studies [10,11,19,44]. More specifically, inferior frontal cortex has been implicated within a ‘semantic working memory’ or control system [45,46] and the anterior portion of the temporal lobe is involved in conceptual semantic processing [12,13,19]. As localization to one hemisphere is less likely in disorders of a developmental origin [47], we also anticipated changes in contra-lateral, homotopic areas of the right hemispheres of affected family members.

We found there was reduced grey matter volume in the JR family cases compared with matched controls in the following regions (at $p < 0.001$, uncorrected, cluster extent threshold $p < 0.05$, uncorrected): (a) and (b) in bilateral inferior temporal cortex and fusiform gyri, (c) cerebellar hemispheres and vermis (see also b), and a small cluster in the ventral anterior cortex, and (d) in left anterior insular cortex. The T maps are superimposed on the average grey matter segment of the control group. Left side is shown as left on the image (neurological convention).

**Figure 4.** VBM grey matter volume reductions in seven JR cases (excluding adult case V,7) compared with matched controls (height threshold $p < 0.001$, uncorrected, cluster extent threshold $p < 0.05$, uncorrected): (a) and (b) in bilateral inferior temporal cortex and fusiform gyri, (c) cerebellar hemispheres and vermis (see also b), and a small cluster in the ventral anterior cortex, and (d) in left anterior insular cortex. The T maps are superimposed on the average grey matter segment of the control group. Left side is shown as left on the image (neurological convention).
4. DISCUSSION

The JR family is a fascinating multi-generational family, possessing an unusual yet highly heritable cognitive profile and presumptive evidence for a dominant pattern of familial transmission. The phenotype was unique and not readily characterized by known phenotypes in the domain of verbal memory impairments [21,25]. The deficit was characterized by a constellation of features that were common to affected JR family cases: (i) poor memory for stories over short and long delays, (ii) impaired sentence repetition, (iii) impaired learning of words, in lists and in pairs, (iv) deficient listening comprehension, (v) poor use of conceptual knowledge in matching words across lists and using sentences, and (vi) a selective difficulty naming low-frequency items. Given the very wide variation in age, the coherence of their difficulties in semantic cognition (broadly defined) was remarkable. All JR family cases have a similar affected status according to this cluster of deficits. Evidence of left-sided bias in abnormalities of the inferior temporal cortices among affected family members implies that there had been anomalous development of a brain region that is strongly linked to semantic cognition [10,19,20,48]. Our findings have uncovered a potential causal link between anomalous neuroanatomy and semantic cognition, inherited as a potentially dominant trait.

(a) Integrative semantics

The affected individuals experienced difficulty putting words to ideas; that difficulty was more noticeable when memory demands increased. Language impairments were evident in tasks that demanded the use of conceptual knowledge, such as matching words across lists, or recalling stories, or reporting information after listening to paragraphs. They appeared unable to compensate for inefficient semantic coding of sentences and paragraphs despite their awareness of syntactical structure and their ability to code and retain speech sounds in phonological memory. This was surprising in view of their considerable intellectual and executive resources. Integrating the meaning of words, objects and factual statements with language processing was a hallmark of their deficit. According to ‘hub-and-spoke’ theory of semantic cognition ([12,14,20]; also convergence zones in [10]), stored concepts are generated by mapping distributed knowledge of words, objects and family members have a diminished ability to generate maps across distributed knowledge of words, objects and facts. Pictorial associative-matching was an important test that demonstrated their specific knowledge of associated concepts (e.g. dog–bone–hole). Their ability to access detailed representational knowledge within verbal and non-verbal domains was relatively intact. Their semantic coding deficit could not simply be characterized as a severe failure to build conceptual knowledge of the world, at least, within domains. During the early stages of SD, deficits within semantic cognition can be easier to detect from picture naming than from general semantic assessment [2,7]. Accordingly, disruption to the mappings across distributed knowledge could not be ruled out as a partial explanation for the familial phenotype.

The JR cases showed a selective pattern of deficits within the language tasks, notably when asked to make arbitrary mappings between words and their meaning, such as defining spoken words in the absence of a picture cue. Their picture naming difficulties were revealed only when asked to name usually low-frequency items: they were able to pass general tests of naming. Like controls, their labelling errors usually constituted substitution of meaning, they were not mistaking sounds. Naming low-frequency words depends more on access to stored conceptual knowledge than high-frequency words [2,12]. Despite their difficulty, most individuals were able to provide detailed knowledge of less frequent items when probed using a picture cue. The affected JR family members demonstrated an inability to pinpoint the correct word during a task that placed high demands on access to meaningful concepts. This could imply poor regulation of processes that steer access to the information that is most relevant in a task [36,49–51].

The selective pattern of difficulties within semantic cognition closely aligns the affected JR family with the milder end of a spectrum of semantic memory impairments observed in neurological patients [2,7,35,36]. The demands of mapping to meaningful concepts increase when people are required to recall longer word lists, or sentences and stories, or to draw meaningful comparisons across spoken word lists, or just to retrieve names for unfamiliar items. We contend that the key deficit was the inability to effectively draw on integrative aspects of semantic cognition, where a fragile conjunction of features that underpins stored concepts failed to supplement speech and language processing.

(b) Converging evidence from neurobiology

The structural differences in temporal cortex that we observed from neuroimaging affected JR cases could have defined a specific region that acts as a neural hub for generating and storing conceptual knowledge [12,17,20]. Classical studies of regional brain stimulation demonstrated impaired language in association with the ‘basal temporal’ language areas [52]. The cognitive consequence of stimulating the infero-temporal and fusiform gyri regions is reminiscent with the self-reported difficulties of JR cases. A putative causal relationship between the volumetric abnormalities of the JR family cases and a deficit of integrative semantics is further supported by functional MRI evidence for a potentially strategic role of the left fusiform gyrus and inferolateral temporal gyrus in verbal semantics [17,20,44,48]. Functional MRI studies with healthy adults reveal a cluster of semantic activation in the inferior temporal cortex. There are multiple activation peaks in the anterior and mid-fusiform regions in a position remarkably close to the abnormalities observed in the JR cases [17,53]. Also, left-hemisphere brain activation while making synonym judgements is suggested to occur through the fusiform gyrus, thus dorsolaterally up to the anterior inferior temporal gyrus ([17], see also evidence from repetitive TMS, [13,20]). The structural anomalies we found were slightly more lateralized, and more posterior than the anterior fusiform regions identified as neural ‘hubs’
for semantic cognition [14,20,48]. However, these (left-biased) bilateral structural anomalies observed within the anterior temporal cortex in the affected family members are similar to regions impacting on semantic cognition when disrupted in neurological patients [11,17,36].

Interestingly, the JR family showed some evidence of WM abnormalities in the frontal regions, as well as bi-parietal grey matter abnormalities. Evidence from functional MRI [49,50,54] has emphasized the role of left infero-frontal regions in processes that control and select task-relevant information. Yet, more posterior activation in temporal cortex co-occurs with frontal activation, suggesting a more extensive network of semantic control [51], also [55] using repetitive TMS. For the JR family, their difficulties could concur with dysregulation throughout a broader (executive) semantic system, similar to semantic aphasia [36,51]. Equally, reduced ability to generate thematic content from stories (also thematic naming errors, e.g. camera for tripod) concur with abnormalities of the temporoparietal cortex purported to support thematic semantic knowledge [56].

A final consideration was whether the pattern of selective deficits in verbal skills implied a difficulty specifically with knowledge of words, rather than concepts. We considered the evidence for anomalies in brain regions linked to word knowledge. Word-generation has long been associated with activation of lateral, as well as ventral, regions of the left posterior temporal cortex in healthy adults [44]. For example, the allied occipital-temporal region BA37 comprises a multi-modal language area [44,57]. This area which lies posterior to the structural anomalies in affected cases is specifically activated by words (relative to non-word strings) in blind and sighted individuals (see fig. 1d in [57]). The bilateral anomalies within the infero-temporal cortex in the affected JR family did not align with the more posterior region of the left occipital-temporal lobe that generate a sound-meaning interface for stored word knowledge [57,58]. Accordingly, our observation that the affected JR family appeared to know the meaning of words, and could pronounce individual words correctly, fitted with the more anterior localization of the neuroanatomic findings [53]. Instead of misnaming words, or substituting similar sounding but incorrect words, affected family members report substituting an associated word (e.g. ‘tripod’ for ‘stool’, or ‘evolving’ for ‘breeding’), implying a lack of precision in the mapping of word meaning to concept. We acknowledge that a conceptually driven impairment that is predominant in the left hemisphere could weaken the interface between the auditory and meaningful aspects of words during spoken language processing. The convergence of subtle and specific deficits in semantic cognition in the affected JR family, together with consistent variation in brain morphology in the anterior temporal cortex, is strong evidence that we have identified a common phenotype in this family that caused fragile mappings for the generation and use of stored concepts.

5. CONCLUSION

A novel inherited deficit in ‘integrative semantics’ has been identified in a single family that can be traced across four generations. The deficit is associated with reduced grey matter in the posterior inferior portion of the temporal lobe, a brain area known to be involved in the interaction between language and semantic systems. This family demonstrates, to our knowledge, the first example of a heritable, highly specific abnormality affecting semantic cognition in humans.

This study received favourable ethical opinion from the Institute of Child Health Research Ethics Committee, London, UK (REC no. 03BS12).

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