BRAIN
REVIEW ARTICLE

Temporopolar regions of the human brain

M.-Marsel Mesulam

Following prolonged neglect during the formative decades of behavioural neurology, the temporopolar region has become a site of vibrant research on the neurobiology of cognition and conduct. This turnaround can be attributed to increasing recognition of neurodegenerative diseases that target temporopolar regions for peak destruction. The resultant syndromes include behavioural dementia, associative agnosia, semantic forms of primary progressive aphasia and semantic dementia. Clinicopathological correlations show that object naming and word comprehension are critically dependent on the language-dominant (usually left) temporopolar region, whereas behavioural control and non-verbal object recognition display a more bilateral representation with a rightward bias. Neuroanatomical experiments in macaques and neuroimaging in humans show that the temporoparietal region sits at the confluence of auditory, visual and limbic streams of processing at the downstream (deep) pole of the 'what' pathway. The functional neuroanatomy of this region revolves around three axes, an anterograde horizontal axis from unimodal to heteromodal and paralimbic cortex; a radial axis where visual (ventral), auditory (dorsal) and paralimbic (medial) territories encircle temporopolar cortex and display hemispheric asymmetry; and a vertical depth-of-processing axis for the associative elaboration of words, objects and interoceptive states. One function of this neural matrix is to support the transformation of object and word representations from unimodal percepts to multimodal concepts. The underlying process is likely to start at canonical gateways that successively lead to generic (superordinate), specific (basic) and unique levels of recognition. A first sign of left temporopolar dysfunction takes the form of taxonomic blurring where boundaries among categories are preserved but not boundaries among exemplars of a category. Semantic paraphasias and coordinate errors in word–picture verification tests are consequences of this phenomenon. Eventually, boundaries among categories are also blurred and comprehension impairments become more profound. The medial temporopolar region belongs to the amygdalocentric component of the limbic system and stands to integrate exteroceptive information with interoceptive states underlying social interactions. Review of the pertinent literature shows that word comprehension and conduct impairments caused by temporopolar strokes and temporal lobectomy are far less severe than those seen in temporopolar atrophies. One explanation for this unexpected discrepancy invokes the miswiring of residual temporopolar neurons during the many years of indolently progressive neurodegeneration. According to this hypothesis, the temporopolar regions become not only dysfunctional but also sources of aberrant outputs that interfere with the function of areas elsewhere in the language and paralimbic networks, a juxtaposition not seen in lobectomy or stroke.

Mesulam Center for Cognitive Neurology and Alzheimer's Disease, Northwestern University Feinberg School of Medicine, Chicago, IL 60611, USA

Correspondence to: M. Mesulam
330 East Superior St, Tarry-8, Chicago, IL 60611, USA
E-mail: mmesulam@northwestern.edu

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Introduction

In 1934, Karl Kleist[1] published a detailed functional localization map where every nook and cranny of the cerebral cortex but one was assigned a consequential task. The temporopolar region was the sole exception (Fig. 1A). A similar verdict came from Bogen and Bogen,[2] who wrote: 'If you have … a cerebral lesion that produces a loss of language … it is rather unlikely that the lesion will

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be in the left occipital pole. It is even less likely that it will be in the left temporal pole.' And yet nearly 70 years later, the temporal pole became celebrated as the unique site of an amodal hub critical for all semantic knowledge.[3] The goal of this review is to explore the factors that contributed to this shift and to summarize emerging views on the behavioural neurology of this region.

The territory covered by this review will be designated 'temporopolar region' TPR rather than 'temporal pole' or 'anterior temporal lobe.' This term will refer to the 2–3 cm of cerebrum that extend from the limen insulae to the anterior tip of the temporal lobe.[4] Defined in this way, TPR encompasses a territory more circumscribed than the 'anterior temporal lobe' but larger than the 'temporal pole' [i.e. Brodmann's area (BA) 38[5] or von Economo's area TG[6]]. Accordingly, the major constituents of TPR include the temporopolar cap (BA38), anterior parts of the superior temporal, middle temporal, inferior temporal and fusiform gyri (STG, MTG, ITG and FG) and perirhinal, periamygdaloid and piriform cortices.

The lack of information on TPR during the formative century of behavioural neurology can be attributed to the reliance of traditional localization research on focal strokes (as in the case of Bogen and Bogen) and gunshot wounds (as in the case of Kleist). However, the triple blood supply from the middle cerebral, posterior cerebral and, to a lesser extent, anterior choroidal arteries make TPR resistant to focal strokes and its location makes it more than likely that penetrating injuries would prove fatal. These two factors are likely to have made TPR opaque to neurobehavioural investigations. Initial insights into TPR functionality emerged through the unexpected contribution of neurodegenerative diseases, which until then had been considered too diffuse to yield meaningful information on functional localization. To be sure, Pick,[7] Dejerine[8] and many others had reported cognitive and behavioural symptoms associated with degenerative diseases. However, the value of these cases for functional localization remained unrealized until new imaging modalities enabled the anatomy of atrophy to be visualized and quantitated in tandem with symptom progression.

This line of research gained momentum in the 1980s through the characterization of primary progressive aphasia (PPA), a syndrome which showed that focal perisylvian neurodegenerations could impact cognitive function as selectively as any stroke or gunshot wound.[9,10] Within the next decade, progressive atrophy started to be reported in TPR as well and became linked to impairments of naming, word comprehension, object recognition and conduct.[11–20] Subsequently, autopsies showed that Pick's disease and frontotemporal lobar degeneration (FTLD) with TDP-43 proteinopathy of type C (TDP-C) were the two entities responsible for the vast majority of focal TPR neurodegenerations (Fig. 1B–E). While Pick's disease rarely, if ever, causes selective TPR neurodegeneration, almost all TDP-C cases are associated with initial and peak atrophy at the TPR.[21,22]

In neurodegenerative diseases, including those that target the TPR, functional localization is commonly based on regression analyses where impairment magnitude in a given domain is correlated with the magnitude of atrophy or hypometabolism. Through a method of inference analogous to the one used in patients with stroke or penetrating injury, neural elements in areas of significant correlation are considered critical for the selected function. In support of this approach, there is good evidence that the magnitude of *in vivo* atrophy corresponds to the magnitude of neuropathology at post-mortem examination.[23–26] However, the contribution of additional areas where correlations remain shy of statistical significance and the possibility of neural reorganization within sites of atrophy cannot be ignored. Therefore, clinico-anatomical correlations in neurodegenerations need to be interpreted with particular caution and confirmed by observations obtained in other contexts.

This review will start with vignettes of six clinical cases personally seen at the Northwestern Neurobehavior Clinic, and which were chosen to illustrate prototypical TPR syndromes. The spectrum of cognitive and behavioural impairments in P1–6 will raise the question of whether TPR has commensurate neuronal connectivity patterns. As there is no rigorous information on the synaptology of the human cerebral cortex, the experimentally established neuroanatomy of the macaque will be used to guide the interpretation of imaging-based anatomical observations in the human TPR. Given the challenges facing clinico-anatomical correlations in neurodegenerations, the next part of the review will seek to determine whether the specializations attributed to TPR through P1–6 can be confirmed in cases of non-neurodegenerative lesions and functional mapping. This discussion will lead to an apparent puzzle, namely that non-degenerative TPR lesions trigger impairments of the same kind as in P1–6 but of much lesser severity. This mismatch will be addressed by a discussion of the computational anatomy underlying word comprehension and object recognition. A major goal will be to highlight the importance of top-down projections emanating from residual TPR neurons and to propose that their aberrant connectivity in neurodegeneration might trigger deficits that surpass those of acute lesions. The neuroanatomy of conduct will be subjected to a similar analysis, but from the perspective of interoceptive rather than exteroceptive neural systems.

The word 'semantic' will be used sparingly to avoid conflation of verbal semantics, non-verbal semantics and semantic memory. To quote Aristotle, 'Spoken words are symbols (*symbola*) of affections of the psyche; written words are symbols of spoken words. Like written words, spoken words are not the same for all persons. The affections of the psyche, however, of which these are primarily signs (*semeia*), are the same for all, as are also the objects (*pragmata*) of which the affections are likenesses.'[27] Therefore, descriptive terms such as 'word comprehension', 'object naming', 'person identification', 'object recognition' will be used whenever possible to deconstruct the term 'semantic'. One advantage is to avoid the confusion of object naming with object recognition, as prescribed by Aristotle. However, terms such as 'semantic paraphasia', 'semantic aphasia' and 'semantic dementia' will be maintained according to current usage because they have become part of established medical terminology.

Characteristic TPR syndromes (P1–6)

Pioneering case reports[12,13,16–18,28,29] and a review of patients personally seen at the Northwestern Neurobehavior Clinic suggested a classification of TPR syndromes into at least six patterns. Domain-specific forms include the 'behavioural syndrome' of predominantly right TPR atrophy, the 'visual associative agnosia' also of predominantly right TPR atrophy and the 'word comprehension (semantic) aphasia' of left TPR atrophy. Additional hybrid syndromes reflect combined impairments in these three domains and are generally associated with bilateral atrophy. One of these hybrid forms, the combination of semantic aphasia with associative agnosia, is known as 'semantic dementia' (SD) according to consensus

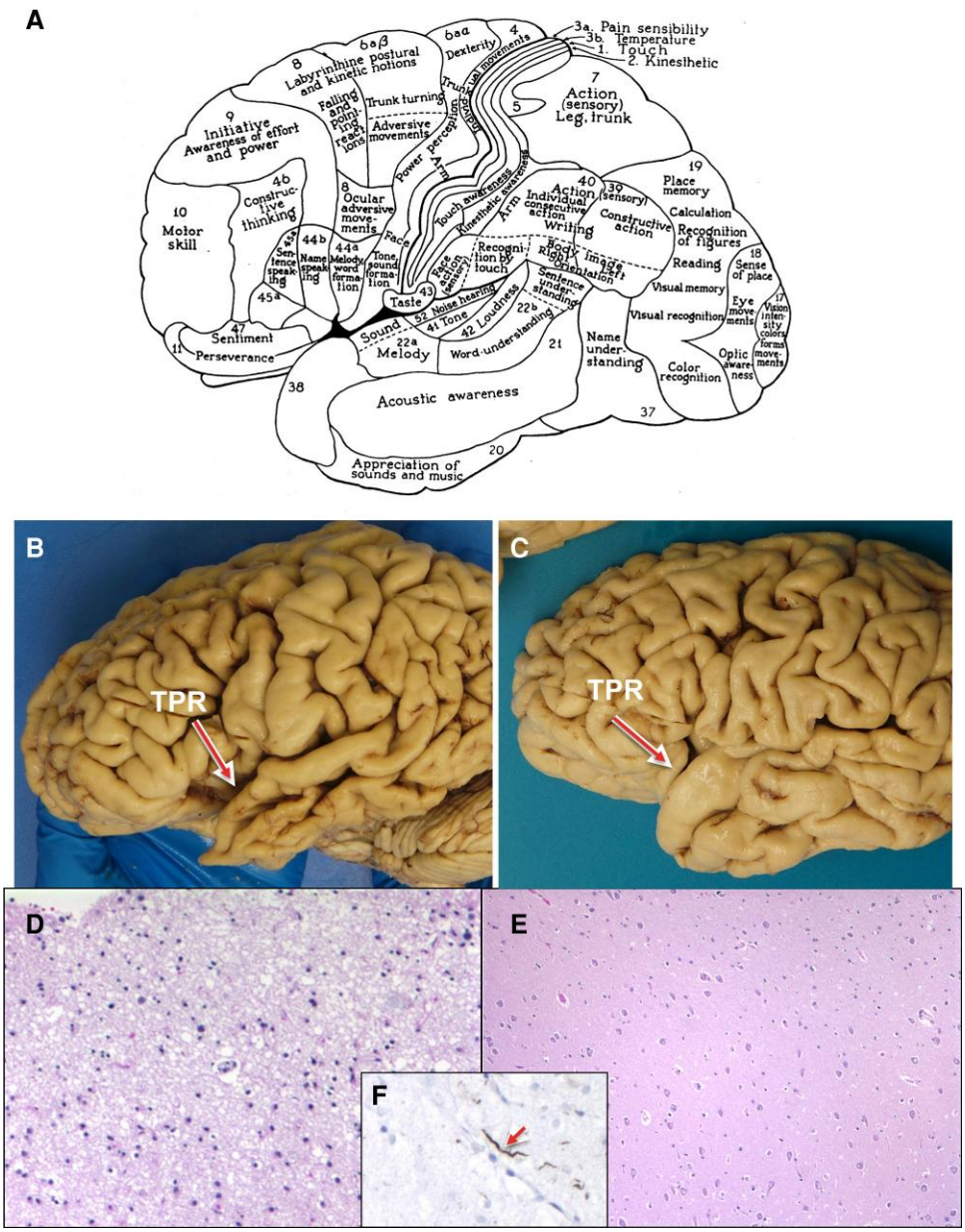

Figure 1 From silence to signal at the temporopolar region. (**A**) Karl Kleist's 1934 map[1] as published in Basil Haigh's 1973 English translation of Luria's *The Working Brain*.[229] (**B**) Post-mortem specimen of a semantic primary progressive aphasia (PPA) patient who died at the age of 64 years, 14 years after symptom onset. The neuropathological diagnosis was frontotemporal lobar degeneration with TDP-43 proteinopathy of type C (TDP-C). The arrow points to the severe but also very focal left temporopolar region (TPR) atrophy even after 14 years of disease. (**C**) Post-mortem specimen of an agrammatic PPA patient who died at the age of 69 years, 9 years after symptom onset. The arrow points to the preserved TPR. (**D**) The photomicrograph shows the severe spongioform degeneration of TPR cortex in the TDP-C patient shown in **A**. (**E**) The CA1 sector of the hippocampus from the same patient. Tissue is largely intact, illustrating the selectivity of the neurodegeneration. (**F**) The arrow points to the pathognomonic long TDP-43 neurites that are seen in TDP-C.

criteria.[30] Five of the six cases summarized below came to autopsy, four with TDP-C, one with Pick's disease. None of the six cases had known disease-causing mutations.

P1: dissolution of comportment (behavioural variant of frontotemporal dementia)

A 62-year-old right-handed man displayed changes in personality and comportment. He adhered to inflexible daily routines, ate the same type of meal day after day, became reluctant to change underwear and increased his consumption of sweets. His wife noted that he seemed to have lost his sense of humour as well as his capacity for empathy, and that he became prone to making inappropriate comments in company. Hoarding, shoplifting and filching food from other restaurant customers were also reported. Although routine activities were preserved, complex chores suffered from poor judgement. During a remodelling task, for example, he overspread the plaster into adjacent sills, so the windows were stuck shut. On examination two years after symptom onset, he was noted to be indifferent, superficial, laconic and irascible. There was no evidence of anomia, aphasia, prosopagnosia or visuospatial impairment. Working memory span was normal. Performance on declarative

memory tasks was variable but uninterpretable because of poor effort. His MRI scan at the time of the testing showed prominent atrophy in the right anterior temporal lobe, including TPR, mostly on the medial aspect (Fig. 2A and B). Additional but less extensive atrophy was present in lateral frontal cortex of the right hemisphere. The post-mortem examination revealed the pathology of Pick's disease. There were more Pick bodies and fewer neurons in the right than left TPR.

The clinical picture fits criteria for behavioural variant FTD (bvFTD).[31] This syndrome can be associated with bilateral frontal or right-sided TPR atrophy.[32,33] The predominantly TPR form (also known as the right temporal variant) has been associated with impaired social conduct, loss of empathy, blunted sensitivity to the emotion of others, inability to link interoceptive stimuli to feelings, compulsions, bizarre dietary habits, hyperreligiosity and disinhibition.[15,16,34–39] Some of these patients had relatively pure behavioural syndromes while others also had memory, face identification, object recognition and language deficits.[37,40] Many of the cases had additional involvement of neighbouring insular, orbitofrontal and amygdaloid areas.[34,41] The atrophy may spread to the contralateral TPR, although rightward asymmetry is usually maintained. Quantitative investigations have correlated disinhibition, loss of empathy, aberrant social cognition and impaired emotional recognition with the magnitude of right TPR atrophy, especially in its dorsal segment.[41–45] Additionally, diffusion tensor imaging (DTI) in PPA patients showed that abnormalities in the uncinate fasciculus correlate with overall behavioural abnormalities.[46] In a patient population that included several neurodegenerative diseases, sensitivity to the significance of emotional expressions was correlated with the strength of functional connections that link the right TPR to the orbitofrontal cortex, a connection subserved by the uncinate fasciculus.[47] In a mixed group of patients including those with bvFTD, blunted skin conductance responses were correlated with TPR atrophy, albeit on the left side.[48] The neuropathology in cases such as P1 tends to be heterogeneous,[49] but is predominantly TDP-C or Pick's disease in non-genetic cases.[22,35] Although the acronyms rtvFTD (right temporal variant FTD) and sbvFTD (semantic behavioural variant frontotemporal dementia) have been proposed,[37,49,50] the high overlap of core symptomatology suggests that it might be more parsimonious to maintain the bvFTD term as the canonical clinical designation but with the addition of an anatomical qualifier (e.g. 'bvFTD syndrome with right TPR atrophy'). At the stage of clinical assessment neighbourhood signs such as prosopagnosia and anomia would indicate that TPR rather than prefrontal atrophy is the principal culprit of the bvFTD syndrome.[50]

P2: dissolution of face and object recognition (associative visual object agnosia)

A 54-year-old left-handed woman started to experience difficulty recognizing familiar persons at work, causing her to lose her job. In addition to this prosopagnosia, her husband reported the subsequent onset of changes in memory for recent events, decision making and interest in socializing. Daily activities gradually became restricted. However, 8 years after onset she was continuing to drive herself to the beach and enjoyed backgammon and gin rummy, two games where she frequently beat her husband. At that time, no disinhibited behaviours, rituals or altered food preferences were described. Performance on the Wisconsin Card Sorting Test,[51] a test of abstract thinking and mental flexibility, was normal. In keeping with features of prosopagnosia, she could match faces that were identical and estimate their ages but could not name any of the 20 photographs of famous persons or describe their characteristics. Upon hearing the names, however, she offered relevant information in 13 of 20 cases. For example, when shown the picture of John Kennedy she could only say 'It's a him. He's got a big mouth. Dark hair.' When she heard his name, she said 'President of the United States, he was assassinated.' She had severe anomia, more for animals than tools. She was unable to choose the correct object when she heard its name and was unable to describe the nature of the object she was shown. However, she was able to define the meaning of the word that denoted the unnamed objects. Although objects could not be named by visual inspection, their characteristic sounds could be matched to their names in 9 of 12 trials.

The following transcript is from a session where figurines of a lion, elephant, alligator and cow were placed in front of her.

Examiner (E)	Are things in front of you animals or fruits?
P2	Oh, they are all animals.
E	Are any of these dangerous?
P2	[She points to the cow.]
E	Are any of these found in a farm?
P2	No.
E	What is an 'elephant'?
P2	It's an animal you find in a zoo.
E	What is a 'lion'?
P2	They are ferocious.
E	What is a 'cow'?
P2	They live on a farm.
E	What is an 'alligator'?
P2	An animal that lives on water.
E	Are they dangerous?
P2	Yes.

The features noted above fit the syndrome of 'Associative Visual Object Agnosia'. Her problem can be formulated as a deficit of iconical rather than lexical representations. Her anomia reflected a modality-specific inability to link the visual percept to multimodal associations that enable the recognition of the object and its naming. The MRI 3 years after onset of the prosopagnosia showed mild asymmetric atrophy of the right TPR with extension into the adjacent medial temporal cortex, including the FG (Fig. 2C and D). Five years later, at the time of the examination noted above, the right TPR remained the site of peak atrophy, but neurodegeneration had also progressed to encompass posterior orbitofrontal cortex, anterior insula and inferotemporal cortex. Lesser atrophy was also seen in the left TPR (Fig. 2E and F).

Progressive prosopagnosia has been reported with atrophy of the right TPR, FG, amygdala and hippocampus.[14,29,40,52–55] The atrophy tends to be bilateral but with a distinct right-sided predominance in right-handers. In contrast to cerebrovascular accidents where the critical lesion is located posteriorly in the inferior temporo-occipital part of the FG,[56,57] the TPR can be the principal and initial target of atrophy in neurodegenerative cases. It appears that prosopagnosia can be classified into upstream (posterior) and downstream (anterior) types. The posterior form displays classic modality-selective features whereas the anterior type tends to progresses into a multimodal person identification deficit.[14,58] As will be

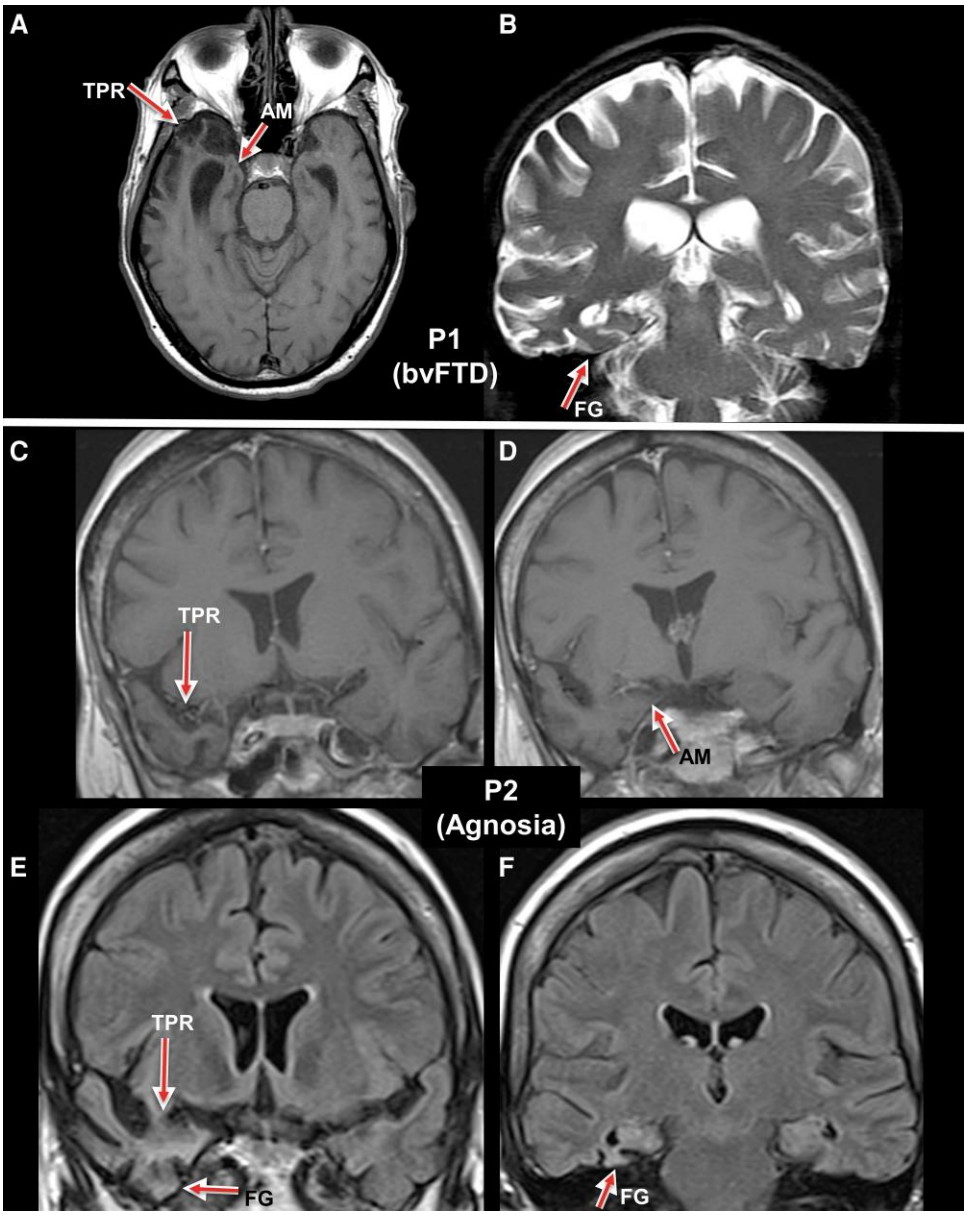

Figure 2 Right temporopolar syndromes. (**A**) Axial MRI of P1 shows the asymmetrical atrophy of the right TPR including the spread to the amygdala (AM). (**B**) Coronal MRI of P1 showing the preservation of the posterior fusiform gyrus (FG). (**C**) Initial MRI of P2 showing the asymmetric atrophy of the right TPR. (**D**) Initial MRI of P2 showing preservation of the amygdala. (**E**) Second MRI of P2 showing the progression of atrophy in the right TPR and the emergence of lesser atrophy in the left TPR. The right anterior FG is atrophic and gliotic. (**F**) Second MRI of P2 showing that the posterior FG is also atrophic and gliotic.

illustrated by P4 below, an even more extensive multimodal face and object agnosia emerges with bilateral TPR syndromes known as semantic dementia (SD). The question could be asked why P1 and P2 have such different clinical pictures even though they share predominantly right-sided TPR atrophy. One possibility is that the left-handedness of P2 somehow made the right TPR less critical for comportment. Another factor may be related to the distribution of lesser atrophy sites outside of TPR. For example, in P2 the FG, a region critically important for encoding face and object percepts, was atrophied from its temporopolar level all the way back to the occipital cortex in the right hemisphere (Fig. 2F). This was not seen in P1 (Fig. 2B). The involvement of the amygdala, more in P1 than P2, might be another factor underlying the different clinical presentations (Fig. 2A and D).

P3: dissolution of word comprehension and object naming (semantic variant PPA)

A 59-year-old right-handed man complained of word-finding lapses. He had a diagnosis of childhood dyslexia. At neuropsychological assessment 3 years after symptom onset, he performed normally in all cognitive domains except language. He had a severe object naming impairment most severe for animals and edible things. Word comprehension (tested by the Peabody Picture Vocabulary Test, PPVT[59]) was normal. He could recognize and describe the identity and nature of faces and objects he failed to name. For example, upon seeing the photograph of Einstein, he could not retrieve the name but said 'he studied everything outside of this world. Very, very smart'. Peak cortical atrophy at that time

was confined to the left temporal pole and his metabolic PET scan showed hypometabolism mostly confined to the left TPR. Over the next 4 years, the atrophy progressed posteriorly to encompass the entire TPR without major extension into the FG (Fig. 3). As the atrophy spread, he started to make pointing errors in a word–picture matching test and could no longer define the meaning of the corresponding noun. However, he could describe the nature of the object he could not name. He also obtained a perfect score on the picture version of the Pyramids and Palm Trees Test (PPTp),[60] a test of non-verbal object recognition. The naming errors therefore appeared to be caused by an inability to understand the meaning of the word that denoted the object, a distortion of lexical rather than iconical representations. His word–picture matching errors usually targeted objects of the same category (e.g. jacket–shirt, pear–strawberry, pliers–screwdriver), a phenomenon also known as taxonomic interference or coordinate verification errors.[61] Objects that could not be named at the specific level were named generically (e.g. pear was called 'a fruit') or triggered semantic paraphasias (e.g. escalator was called 'elevator').

At the initial visit, he failed to name the hippopotamus figurine but could choose it from among foils upon hearing the noun (i.e. one-way naming error). When asked to define the word 'hippopotamus' he said 'large, heavy, African, land and water animal, somewhat aggressive, dark grey'. At the third visit (7 years after onset), he could not name the object, could not match the object to the word (i.e. two-way naming error) and could no longer define the word 'hippopotamus'. Upon seeing the picture, however, he said 'I remember that one is not in the USA either. It's to the South, mostly they are in the water'. So, at this stage recognition of the nature of the object was relatively preserved. Other aspects of language (grammar and repetition) declined moderately but not as severely as naming and comprehension. Comportment, judgement, insight and reasoning were mostly preserved and there was no prosopagnosia. Memory for non-verbal items remained intact throughout the 7 years of follow-up. At around 7 years into the disease, he started to display obsessive perseveration on trivial daily matters (e.g. how to handle the fireplace), loss of empathy, excessive conviviality, rigid adherence to set routines and self-centred volubility. At the same time, however, he was writing a book that was eventually published and he painted pictures, including a very competent cityscape in oil, which now hangs in our offices. The autopsy revealed TDP-C.

P4: combined dissolution of word comprehension and object recognition (semantic dementia)

At the age of 64 a left-handed woman started to have difficulty following conversations, understanding the gist of jokes and recognizing familiar faces. She could match photographs of the same person, even from different perspectives, but could neither name them nor surmise their identity. Judgement, insight, attention span, reasoning, episodic memory and response inhibition were intact. Visuospatial functions were preserved and she had no simultanagnosia. Language repetition and grammar were preserved. She could understand syntactically complex sentences if the constituent words were familiar (e.g. boy, girl, kiss). In addition to the prosopagnosia, she also had a severe object naming deficit with semantic paraphasias and failure to match the noun to the object. Single word comprehension was also impaired. She was unable to answer yes–no questions related to the nature of the objects she could not name. The impairments therefore encompassed iconical as well as lexical representations and her object recognition deficit (agnosia) was multimodal. Despite these difficulties, she lived independently and maintained her customary daily living activities. She died 6 years later from lung cancer. The MRI initially showed right TPR atrophy which eventually became bilateral. The metabolic PET scan showed right-predominant bilateral hypometabolism mostly confined to TPR. The FG was atrophied; the amygdala appeared less affected. The autopsy revealed TDP-C.

P5: combined dissolution of word comprehension and conduct

A 52-year-old woman started to show poor judgement and insight together with word-finding failures and inability to understand names of common objects (e.g. 'grass'). She was oriented to time and did not appear to have difficulty recalling recent experiences. She could recognize familiar persons but could not recall their names. She became fixated on religious icons, spent a great deal of time and money trading them online and brought her evangelical exhortations boldly written in red ink to the examination. She held to a rigid and repetitive diet. Interpersonal conduct and empathy were severely undermined. Although household chores were not performed as meticulously as in the past, she continued to pay family bills, prepare meals, drive and shop. Speech was voluble and self-centred but not agrammatic. Naming was severely impaired, especially for animals. She could not match the noun to the object but could surmise the nature of the unnamed object when queried by multiple questions. At that time, the MRI and metabolic PET scan showed bilateral TPR atrophy and hypometabolism, slightly more on the left. The amygdala was gliotic bilaterally. P4 died 10 years later. The autopsy revealed TDP-C.

P6: combined dissolution of word comprehension, object recognition and conduct

A 56-year-old right-handed woman started to experience face recognition problems. On examination 5 years later, she had severe impairments of object naming, word comprehension (assessed by the PPVT) and non-verbal object recognition assessed by the PPTp. Her deficits were so severe that errors did not respect semantic boundaries. When shown the picture of the current Pope, for example, she thought it was the face of a 'tennis player', and when asked to define the word 'scissors' she asked if it was the name of an animal. Memory for recent events was preserved, and mental flexibility tested by the Wisconsin Card Sorting Test was intact. Conduct underwent progressive impairment. She became obsessed with cleanliness, repetitively blew her nose to the point of bleeding, attempted to clean a sharp knife by licking it, developed excessive religiosity and overindulged in alcohol. Nonetheless, she continued to travel with her husband and enjoyed tennis and golf. Basic daily living activities were preserved, and she successfully managed her finances. The initial MRI 2 years after onset reported right 'temporal lobe' atrophy. The quantitative scan 9 years after onset showed right-predominant but bilateral TPR atrophy extending into the FG (Fig. 4A). She died 17 years after onset. The autopsy revealed TDP-C.

Among the syndromes illustrated by P1–6 (Fig. 4B), P3 is the only one that fits the diagnosis of PPA, a diagnosis which requires the language disorder to emerge and progress in relative isolation, without comparable impairments of explicit memory, non-verbal object recognition or conduct.[62] The combination of severe anomia and word comprehension impairment in P3 further classify his PPA as the 'semantic variant' (svPPA, PPA-S).[63] Behavioural components

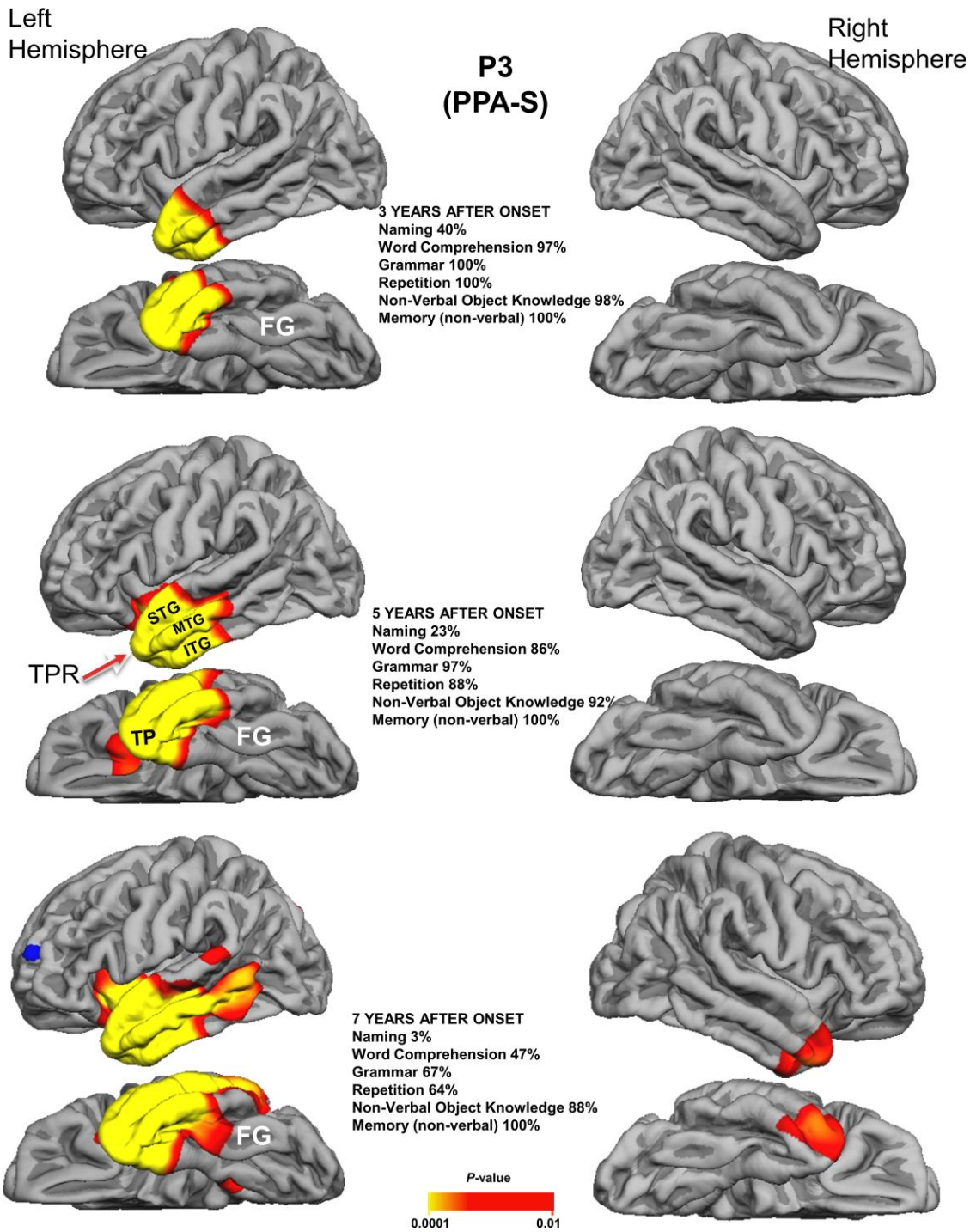

Figure 3 Evolution of left temporopolar atrophy. Longitudinal assessments of P3. The FreeSurfer software was used to detect atrophy in comparison to controls as described elsewhere.[21] The yellow and red areas show regions of significant peak atrophy. The heat bar shows the *P*-values at False Discovery Rate = 0.05. Naming was assessed with the Boston Naming Test,[230] word comprehension with the Peabody Picture Vocabulary Test,[59] Grammar with Northwestern Assessment batteries as previously described[21,231–233]; repetition with the six most difficult items of the Western Aphasia Battery—Revised,[234] Non-Verbal Object Knowledge with the picture format of the Pyramids and Palm Trees Test[60] and Memory with the Rivermead Behavioral Memory Test.[235] Test results are reported as a percentage of control performance. In each pair of cortical maps, the top represents a lateral view and the bottom a ventral view. FG = fusiform gyrus; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; STG = superior temporal gyrus; TP = temporal pole. Modified from Mesulam *et al.*[21]

such as self-centredness, obsessive preoccupations, addictive interest in SUDOKU (or other puzzles) are common in PPA-S but rarely disrupt customary activities, which can continue to be performed at high levels of complexity. The history of dyslexia in P3 is interesting because it has been identified as a potential risk factor for PPA in a subset of cases.[64] It has been suggested that artistic skills such as those of P3 may actually be accentuated in some cases of FTLD.[65] The clinical picture in P3 would not fulfil the 1998

consensus criteria of SD, which require the presence of both word comprehension and object recognition impairments.[30] However, the distinction has often been overlooked and PPA-S patients have frequently been incorporated into investigations of SD without differentiation.[66] To make matters even more confusing, the 2011 consensus guidelines do not include 'SD' among the three principal diagnostic labels and subsume it under the PPA-S classification. Consequently, patients with characteristics of PPA-S, as exemplified by P3, have commonly been designated 'SD' in the pre-2011 literature,[12,13] whereas SD has been designated PPA-S (or svPPA) in many reports published since then.

Depending on local preferences, each of the cases P3–6 could have received a diagnosis of SD, the common denominator being prominent word and object recognition impairments on a background of variable behavioural abnormality.[30] The distinction of PPA-S from SD revolves around the observation that naming and word comprehension are critically dependent on the language-dominant (usually left) TPR whereas the experiential recognition of persons and objects has a more bilateral representation.[67,68] In some cases, the left TPR atrophy of PPA-S spreads to the right and the clinical picture takes on the features of SD. In others, as in P4, the combination of semantic aphasia with associative agnosia fits the SD designation even at initial stages. In contrast to P2, the object and face recognition impairments in SD tend to be multimodal. They are always associated with severe naming deficits because it is not possible to name an entity that is not recognized. Although the distinction of PPA-S from SD is not always clear-cut, clinical presentations, potential symptomatic interventions, anatomical substrates and cognitive mechanisms can be quite different in prototypical forms of the two syndromes. For example, the mechanism of anomia is based on poor noun comprehension in PPA-S, while it may also reflect poor object recognition in SD (Table 1). Despite the challenges of nomenclature, the SD and PPA-S literatures have jointly offered fundamental insights into the nature of word and object knowledge by showing that TPR damage selectively increases the confusability of concepts, impairs the ability to make fine-grained discriminations within categories and undermines the recognition of words and objects, particularly at specific (subordinate) levels of categorization. Notable themes generated by this prolific literature include the conceptualization of TPR as a universal amodal 'semantic' hub and the demonstration that word comprehension is critically dependent on far more anterior parts of the temporal lobe than Wernicke's area, which is traditionally located at the temporoparietal junction.[3,12,13,61,66,69–105]

Neuroanatomy of the macaque temporal lobe

The symptomatology of P1–6 encompasses multiple realms of neural function. Does TPR display concordant patterns of neural connectivity? In addressing this question, it is important to keep in mind that methods for studying synaptic connectivity in the human brain have serious limitations. Tractography with DTI reveals the heading of white matter fascicles but not their synaptic targets, cellular origins, or directionality; task-based functional MRI (tbfMRI) cannot distinguish critical from corollary activation sites or their structural interconnections; resting state functional MRI (rsfMRI) infers connectivity through inter-areal coherence but cannot distinguish monosynaptic from polysynaptic linkages; neuronal recordings through implanted electrodes offer very limited coverage and scant information on synaptic architecture. These are some of the reasons why animal models of cortico-cortical connectivity remain invaluable for guiding the interpretation of DTI, rsfMRI, tbfMRI and electrophysiological data in the human brain. This is especially relevant to TPR, which is also highly susceptible to signal distortion in functional MRI studies.

The neuroanatomy of the primate temporal lobe can be approached through the perspectives of brain evolution and information processing hierarchies. In the brain of the frog, the retinal image of a fly is one synapse away from the decision to snap at the prey. This arrangement, favouring proven results over innovation, has prospered for 190 million years. Primate evolution, with a more modest track record, has opted for greater choice and improvisation through multiple nodes of convergence and divergence inserted between sensation and action.[106] A major component of this process unfolds along two sensory–fugal streams. The dorsal one (also known as the 'where' pathway[107]) computes the spatial location of an event and how to target it for action. The ventral one (also known as the 'what' pathway) is further divided into an inferior segment for the recognition of objects and faces and a somewhat less clearly established lateral segment for decoding dynamic aspects of social perception such as eye-gaze, facial expression, body movement and intention.[108,109]

The 'what' pathway permeates the neural space of the macaque temporal lobe. It is dominated by hierarchically organized visual and auditory pathways. At the first synaptic stage, primary sensory areas project to corresponding unimodal association areas, each of which is selectively tuned to specific patterns of incoming information.[106,110–113] Unimodal areas have upstream (parasensory) and downstream (metasensory) components that occupy the second and third levels of the synaptic hierarchy. Upstream areas are tuned to basic constituents of sensory experience (e.g. pitch, tone, shape, colour, movement, location), whereas the downstream areas implement the rapid encoding and gating of behaviourally relevant percepts such as faces, vocal calls and objects.[106] In the visual modality, upstream unimodal areas of the macaque include BA18 and 19 of peristriate cortex, while downstream visual association areas include BA20–21 of inferotemporal cortex and probably parts of BA35–36.[112,114] In the auditory modality, posterior STG (BA22) displays properties of upstream association cortex whereas more anterior parts of the gyrus fit the designation of downstream association cortex.[112] A fourth neuronal stage is located within heteromodal association areas of the superior temporal sulcus, where auditory and visual percepts interact and mediate the formation of multimodal concepts.[106,112,113] At a fifth synaptic stage, paralimbic areas link association cortex with core limbic areas in the amygdala, hippocampus and hypothalamus. The limbic and paralimbic components regulate the memorability of experiences, their hedonic valuation and their linkage to interoceptive states underlying social behaviours. Each pathway is reciprocal so that feedback projections from deeper levels can modulate the interpretation of incoming data and their linkage to action.[115–117] One outcome of this arrangement is to allow behaviour to be controlled by the significance rather than appearance of sensory experience. Compared to the brain of the frog, this organization offers additional degrees of freedom so that appetitive urges can potentially be delayed if the moment does not seem particularly propitious.

The TPR of the macaque is embedded within this synaptic matrix. Its lateral components display the cytoarchitecture of association granular isocortex whereas the medial components display predominantly paralimbic dysgranular characteristics, except for the small region of direct continuity with the temporal limb of piriform olfactory cortex.[118] Visual unimodal input into TPR comes

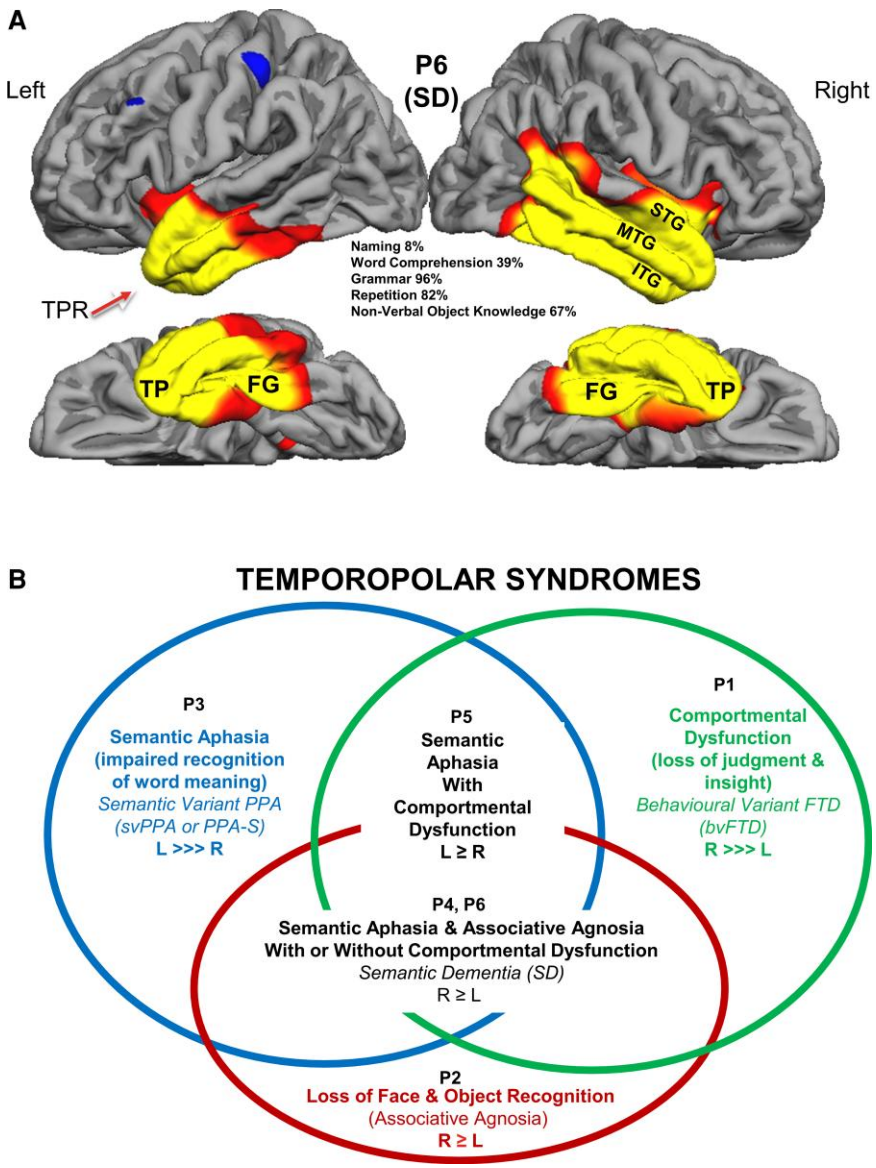

Figure 4 Temporopolar syndromes. (**A**) Atrophy map and test performance in P6. Tests are the same as in P3. FG = fusiform gyrus; ITG = inferior temporal gyrus; MTG = middle temporal gyrus; SD = semantic dementia; STG = superior temporal gyrus; TP = temporal pole. (**B**) Temporopolar syndromes.

from anterior inferotemporal cortex (BA20–21, 35–36), and auditory unimodal input from anterior STG (BA22), both representing downstream unimodal areas. The heteromodal contingent of cortical input comes from the dorsal and ventral banks of the STS and dorsolateral prefrontal cortex. There are also connections with the frontal operculum (PrCO) and the mid-to-posterior STS, areas which could be considered remotely analogous to Broca's and Wernicke's areas, respectively.[119,120] In addition to the visual and auditory projections of the 'what' pathway, input from the insula establishes a likely route for somatosensory, gustatory and visceral information.[121] Other paralimbic inputs come from rhinal cortices, parolfactory gyrus of Broca (i.e. subcallosal cingulate, BA25) and posterior orbitofrontal cortex. Monosynaptic projections are established with core limbic areas in the anterior (uncal) hippocampus, subiculum, amygdala (cortical, accessory basal and lateral nuclei) and hypothalamus.[118,122] Amygdaloid connections are far more prominent than hippocampal connections. Through this pattern of connectivity, the medial TPR can be included within the anterior (amygdalocentric) component of the limbic system.[123] This is the part of the limbic system where the emphasis is on mood, motivation, autonomic tone, affiliative behaviours and visceral sensation rather than episodic memory, which is dependent on more posterior (hippocampocentric) parts of the limbic system.[124]

The electrophysiology and behavioural affiliations of the macaque TPR are consistent with this anatomic account. For example, single unit recordings show that ventral TPR neurons have longer latencies and larger receptive fields than BA20–21 neurons, supporting the view that TPR lies at a downstream node of visual sensory–fugal pathways.[125] In the auditory modality, downstream and heteromodal association areas that project to TPR were found to contain neurons preferentially responsive to broad-band complex sounds and species-specific calls.[126,127] In ventral TPR, where visual processing predominates, neurons fire during a delay period of a visual matching-to-sample paradigm, indicating involvement in visual working memory.[128] Furthermore, heteromodal STS cortex projecting to TPR contains highly selective face-responsive

Table 1 Characteristics of anomias in four syndromes

	Anomic aphasia including PPA-L	Semantic aphasia including PPA-S	Associative visual object agnosia	Semantic dementia
Oral naming of object picture	No	No	No	No
Pointing to the object named by the examiner	Yes	No	No	No
Recognizing the nature of the pictured object	Yes	Yes	No	No
Defining the noun that is the name of the object	Yes	No	Yes	No
Recognizing the object by its sound	Yes	Yes	Yes	No

neurons.[129] In one experiment, approximately 600 neurons were recorded in inferotemporal areas likely to project to TPR as macaques viewed over 1000 natural and artificial objects. The results revealed that animate and inanimate objects created distinguishable clusters and that the animate category was further divided into clusters for bodies, hands and faces.[130] The categorical representation was organized in the form of distributed population activity, suggesting that the same neuron responds to multiple stimuli and that one stimulus activates multiple neurons, the specificity presumably being determined by differential patterns of activation across clusters.[106,129,131] The STS also contains neurons that participate in social cognition by being responsive to the change of facial expressions and the sound and action of conspecifics.[108,109]

The behavioural affiliations of the macaque TPR reflect the dual influence of limbic and association cortices. The classic Klüver and Bucy paper of 1938, for example, was based on a female rhesus monkey with bilateral excision of the temporal lobe.[132] The animal recovered from surgery without consequential impairment of vison, hearing, taste or movement. However, she had lost the ability to recognize the meaning of objects by visual inspection and showed no emotional responses indicative of conviviality, resentment, anger, fear or pleasure. She remained placid if a male mounted her and did not hesitate to approach a snake held in front of her. Subsequent experiments showed that lesions more restricted to the TPR could also trigger bizarre food preferences, disruption of affiliative behaviours and insensitivity to social signals.[133–136] In summary, and in keeping with the symptomatology of P1–6, the macaque TPR receives extensively refined sensory information related to behaviourally relevant events, provides a site for their integration into multimodal concepts, mediates their interactions with the internal milieu and modulates their influence on complex social behaviours.[110,113,118–120,125,137,138]

Comparative structural neuroanatomy of the human TPR

From a structural perspective, the human TPR has a vastly more complex topography.[139–144] In contrast to the monkey, where only minor dimples of the rhinal and superior temporal sulci can be identified, the human TPR is deeply invaginated by the superior, inferior and occipitotemporal sulci (Fig. 5). The lateral TPR contains forward extensions of the superior (STG-BA22), middle (MTG-BA21), inferior (ITG-BA20), and fusiform (FG-BA20/35) gyri. The posterior and medial parts of TPR contain periamygdaloid, piriform and perirhinal (BA35–36) cortices. Anterior to the limen insulae, the medial TPR becomes the planum polare (PP) where 2–3 sulci delimit the polar gyri of Schwalbe.[140] The dorsal PP appears continuous with the anterior planum temporale and the ventral PP with perirhinal cortex. At the anterior tip, BA38 ('polar cortex' in the strict sense) covers the TPR. The medial TPR displays a dysgranular paralimbic architecture whereas the lateral TPR maintains a six-layered homotypical structure, a distinction that that is also seen in the monkey.[118]

By analogy to the macaque, the human TPR is embedded within the 'what' pathway. It is reasonable to assume that it contains downstream nodes of auditory pathways dorsally in STG, downstream nodes of visual pathways ventrally in ITG and FG and heteromodal areas in between, in MTG. The dorsal TPR is likely to include or be interconnected with the auditory word-form area in the STG while the ventral TPR is likely to be interconnected with the face, word and object encoding areas of the ITG and FG. This organization is supported by multiple DTI and rsfMRI experiments.[105,145–148,103,149] Probabilistic DTI additionally suggests that cross-modal auditory–visual associations are graded from the posterior to the anterior temporal lobe and that they reach the highest level of integration in TPR.[146] The TPR also appears to constitute a convergence site for the arcuate (AF), uncinate (UF) and inferior longitudinal (ILF) fasciculi.[150,151] The ILF and probably also the inferior fronto-occipital fasciculus (IFOF) are likely to convey visual and heteromodal inputs from object, face and word areas of FG and ITG into TPR; the AF is a likely conduit for interactions with frontal and temporoparietal components of the language network; and the UF is likely to mediate interactions with orbitofrontal cortex and adjacent areas. Based on the anatomy of the macaque, the medial TPR is likely to provide synaptic links to the visceral, autonomic and endocrine systems of the amygdala and hypothalamus principally through insular, periamygdaloid and perirhinal cortices. Olfactory inputs have direct access to TPR through the piriform cortex, whereas gustatory and visceral inputs are likely to come from orbitofrontal and insular cortices. In addition, experiments based on rsfMRI have identified TPR connections with dorsolateral prefrontal cortex, connections that are also present in the macaque.[118,147,152]

Convergent evidence from non-degenerative lesions, imaging and depth electrodes

The human TPR anatomy summarized above is highly concordant with the cognitive and behavioural domains impaired in P1–6. Given the complexity of clinico-anatomical correlations in neurodegenerative diseases, however, the inference that TPR plays such a key role in word comprehension, object recognition and conduct would be considerably strengthened if these affiliations could also be confirmed in non-neurodegenerative contexts. One line of evidence comes from the demonstration that temporal lobectomy and stroke involving the left (but not right) TPR lead to face- and object-naming deficits, but without impairment in the ability to recognize the identity of the person or object.[153–155,156] Furthermore, the ability to produce nouns in a given taxonomic category (e.g. animals, fruits, tools) was diminished in the majority of left lobectomy cases but was mostly preserved in the group of right

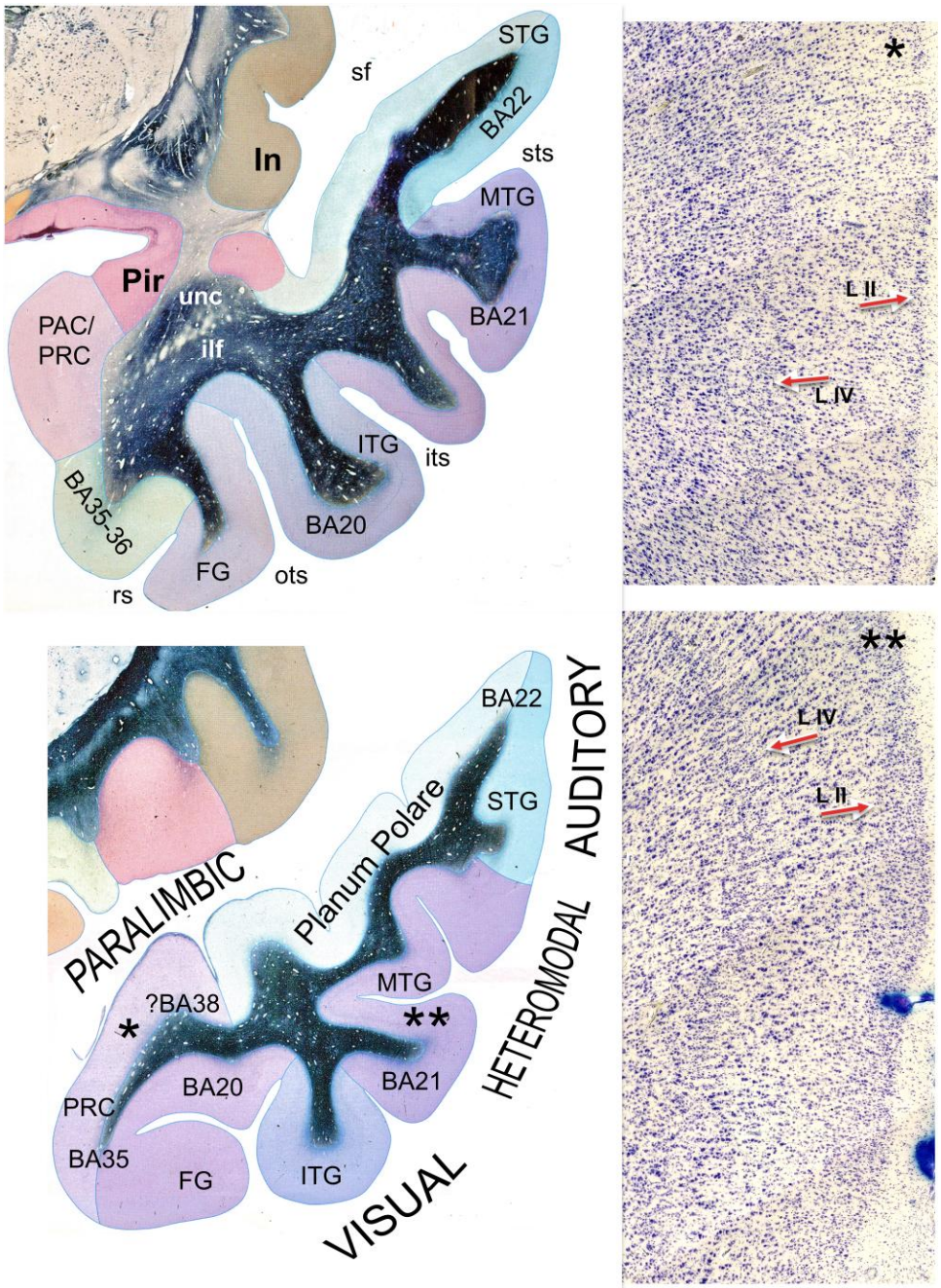

Figure 5 Temporopolar anatomy. *Top and bottom left*: Coronal sections through TPR at the limen insulae, close to the posterior boundary of TPR (*top*) and at a more anterior level (*bottom*). *Top and bottom right*: Temporal pole sections stained with cresyl violet were scanned at 10×. The section on *top* is from the ventromedial part shown with a single asterisk in the *bottom left* panel. Layer II is hyperchromic with no continuous granular lamination. Layer IV has a thin and discontinuous granular band. These features are characteristic of paralimbic transitional cortex. The section on the bottom right is from the MTG area shown with the double asterisk. Layers II and IV have continuous granular lamination. Layer II is hypochromic and the pyramidal neurons have columnar organization. These are characteristics of homotypical isocortex. *Left top and bottom* are from Mai *et al.*[4] with permission from Elsevier. They have been relabelled to maintain consistency with the text of the review. BA = Brodmann areas; FG = fusiform gyrus; ilf = inferior longitudinal fasciculus; In = Insula; ITG = inferior temporal gyrus; its = inferior temporal sulcus; MTG = middle temporal gyrus; ots = occipitotemporal sulcus; PAC = periamygdaloid cortex; Pir = olfactory piriform cortex; PRC = perirhinal cortex; rs = rhinal sulcus; sf = sylvian fissure; STG = superior temporal gyrus; sts = superior temporal sulcus; unc = uncinate fasciculus.

lobectomies.[157] In addition to anomia, left (but not right) temporal lobectomy has also been shown to trigger word comprehension impairments as indicated by the inability to detect synonyms or to access conceptual information related to an object, landmark or person upon seeing its name.[155,158–160] Semantic paraphasias have also been associated with left TPR strokes.[161] Object recognition deficits (always accompanied by naming deficits for the corresponding entity) tend to emerge with bilateral TPR lesions.[162] In keeping with these lesion data, tbfMRI and PET in neurologically intact participants have shown left TPR activations in tasks of face, object and olfactory naming.[153,163–167] Functional mapping with magnetoencephalography and tbfMRI showed that

the anteromedial TPR, including the perirhinal area, is more sensitive to taxonomic than thematic relationships of nouns,[168] that it is more engaged by tasks that require word recognition and object naming at the specific than generic level of categorization[169,170] and that it is preferentially activated by tasks that require the comprehension of abstract words rather than concrete nouns.[171]

As could have been predicted from the synaptology in the macaque, functional imaging and electrophysiological investigations revealed an anterograde auditory processing hierarchy in STG starting with phoneme encoding, proceeding anteriorly to auditory word-form representations and leading to areas abutting dorsal TPR selectively tuned to word meaning.[172,173] Interestingly, the accuracy of speaker identification by voice patterns and the ability to identify animals upon hearing their characteristic sounds was also correlated with STG and dorsal TPR activation, left-sided for the former and bilateral for the latter.[174,175] Implanted electrodes in presurgical epilepsy patients had revealed a basal region in the anterior FG sensitive to the meaning rather than shapes of written words.[176] Neurons with these properties tended to be more common in the left hemisphere.[177] This word-sensitive area is likely to overlap with the fusiform 'basal temporal language area', located 3–4 cm posterior to the left temporal tip, where electrical stimulation caused severe alexia and anomia but spared object recognition.[178] Consistent with the left hemisphere dominance for language, DTI-based investigations reported that TPR connections with the inferior frontal gyrus (Broca's area) through the arcuate fasciculus had greater consistency in the left than right hemisphere.[151] Furthermore, rsfMRI also showed that TPR is interconnected with the other two major epicentres on the language network in the inferior frontal gyrus (Broca's area) and temporoparietal junction (Wernicke's area) and that these connections are stronger in the language-dominant left hemisphere.[179]

The recognition of faces displays a somewhat greater but not complete dependence on the right TPR.[153–155,159,162,180] Intracranial recordings show that the anterior fusiform region of each hemisphere contains an area sensitive to the identity rather than surface properties of faces.[177,181] Face-responsive neurons in this area show priming effects when preceded by the name of the person, indicative of multimodal integration at the concept level.[181] Although found in both hemispheres, these neurons are more frequent in the right.[177] More posterior parts of FG contain partially overlapping areas bilaterally sensitive to faces, houses and chairs.[182] These areas show a high level of experience-based plasticity, being relatively more responsive to birds in bird watchers and to cars in car fanciers.[183] These posterior FG and ITG areas enable the rapid identification of entities for which the individual has expert knowledge and are part of the hierarchically organized pathways directed to TPR. Remarkably, anterior entorhinal and hippocampal areas in each hemisphere also contain neurons that selectively respond to particular persons or places upon seeing the picture, reading the corresponding name or in the case of persons, hearing the voice.[184,185] Because the monkey's TPR appears to be synaptically 'upstream' of entorhinal and hippocampal areas,[125] it is reasonable to assume that TPR is a source of multimodal information for these highly integrative concept neurons.

With respect to more 'behavioural' affiliations, categorization of concepts describing social behaviour were associated with functional activation of the dorsal TPR on the right.[45] In keeping with this finding, diminished capacity for affective empathy in right hemisphere strokes was correlated with infarcts that extended into the dorsal TPR.[186] However, the insula was frequently also involved so that none of the patients had lesions confined to TPR. Additional investigations with tbfMRI, rsfMRI and transcranial magnetic stimulation have identified anterior STG, STS and FG regions that are sensitive to affiliative cues such as dynamic changes of face expression, eye gaze and intention.[105,108,187] Functional activations of TPR were also detected during the retrieval of words with high social and affiliative valence,[103] and in tasks that manipulated emotion, mentalization, empathy, guilt and hedonic value of sensory stimuli.[149,188–190] Furthermore, marked emotional detachment from family members was reported after right lobectomy in a left-hander[191] and secondary mania in brain-injured individuals was most closely associated with right TPR lesions.[192,193] Although a dramatic Klüver–Bucy syndrome was reported following left temporal lobectomy for tumour removal,[194] such instances are so rare that they are difficult to interpret. With respect to the physiology of emotion, stimulation of the human TPR causes major changes of autonomic function, probably through hypothalamic and amygdaloid projections.[195] Despite its intimate relationship to rhinal cortices and the hippocampus, TPR (i.e. the part of the temporal lobe anterior to the limen insulae) does not seem to play an important role in episodic memory for recent experiences.[102]

Harmonizing convergent clinico-anatomical linkages: match and mismatch

Non-neurodegenerative lesions and functional mapping data summarized above reveal affiliations of the TPR that are quite concordant with the behavioural and cognitive symptomatology of P1–6. However, while the themes are concordant, the magnitude of impairment is not. For one, large *en bloc* temporal lobectomies on the right or strokes in the right TPR, rarely, if ever, cause major aberrations of conduct. Even bilateral medial temporal lobectomies that sever the limbic parts of TPR fail to trigger consequential deviations of comportment. For example, the MRI of the paradigmatic lobectomy case, H.M., showed destruction of medial TPR bilaterally although H.M. displayed no known conduct abnormality.[196] With respect to the left TPR, stroke and lobectomy appear to undermine mostly object naming rather than word comprehension.[153,154,156,161,162] When word comprehension is undermined, the deficit is mild and emerges only in more challenging tasks.[197] In contrast, neither the behavioural abnormalities of right TPR atrophy nor the word comprehension deficits of left TPR atrophy in PPA-S and SD are subtle. The following interview with a 52-year-old man with left TPR atrophy (TDP-C at autopsy) illustrates the almost unimaginable severity and specificity of the comprehension impairment, in this case, for words denoting natural kinds but not artefacts, and for a word when it designates a concrete entity but not an abstract concept.

E What do you do on holidays?
P7 I golf.
E What is a pumpkin?
P7 A pumpkin?
E What do you do with a pumpkin?
P7 A pumpkin or what … It is a game isn't it?
E What is a hammer?
P7 (He accurately pantomimes the use of a hammer)
E What is a battery?
P7 I have two huge ones in my boat. (Accurately shows how to carry one by the handle)

E What is an orange?
P7 Orange?
E What do you do with an orange?
P7 I don't do oranges.
E What colour is this (examiner shows a green pencil)?
P7 Green.
E What colour is this (examiner shows an orange pencil)?
P7 Yellow … no … no. Orange.

Word recognition impairments of this severity are never seen after stroke or lobectomy. How to account for the apparent mismatch in the magnitude of deficits? One possibility is that the neurodegeneration in P1–6 extends beyond TPR. This possibility cannot be dismissed. However, TPR did constitute the site of initial and peak atrophy in P1–6 and PET scans have generally supported the overlap of hypometabolism with peak atrophy on MRI.[198] A more speculative but potentially far-reaching explanation invokes distinctive features of neurodegeneration, namely the aberrant rewiring of residual neurons in areas of atrophy.[199] Instead of alleviating the impact of the neurodegeneration these residual neurons may paradoxically exacerbate it. Lobectomy, gunshot wounds and cerebrovascular lesions cause the sudden and complete unplugging of the damaged areas from cerebral circuitry followed by potentially restorative neuroplasticity outside the lesion site.[200] In contrast, the effect of neurodegeneration can be likened to an ongoing short circuit that is propagated throughout the relevant network. The intricate computational neuroanatomy of object and word recognition lends itself to an exploration of this putative phenomenon.

Words and objects—asymmetry and taxonomic blurring

As noted by Aristotle, objects (pragmata) are universal, words (symbola) are arbitrary. Pragmata do not depend on verbal labelling to be recognized experientially. Research on prelinguistic primates gives every indication that object recognition systems have a bilaterally symmetrical organization in the temporal lobes. In the human, the relative superiority of the right hemisphere may reflect the co-option of ancestral object recognition resources of the left temporal lobe by emergent verbal functions. The resultant rightward asymmetry for non-verbal object recognition is therefore relative rather than absolute.[124,201] Consequently, multimodal non-verbal object recognition is more resistant to TPR damage and is rarely impaired without bilateral TPR involvement. In fact, even SD patients who show multimodal abnormalities of object recognition during formal testing can adaptively interact with objects of all kinds during daily life, at least until the end stages of disease (e.g. P4). What is being lost appears to be the declarative knowledge of objects, especially those that are unfamiliar, not necessarily their experiential impact. In contrast to object recognition, word comprehension and naming are strongly lateralized and selectively sensitive to left TPR damage.[67,68,71,81,95,98,101,161,202]

At initial stages of left TPR atrophy, patients produce superordinate (generic) instead of subordinate (specific) labels during object naming and make within-category (coordinate) pointing errors during word–picture matching.[12] These manifestations of aberrant taxonomic mapping are key features of SD and PPA-S and have been linked to the degeneration of the TPR, including its STG, perirhinal and fusiform components.[3,61,81,84,95,97] The neurophysiological correlates of taxonomic blurring have been explored through an experiment based on N400 event-related potentials (ERP). In this experiment, PPA-S patients with left TPR neurodegeneration and mild disease were given verbal and non-verbal verification tasks. In the verbal condition, an object picture was followed, 200 ms later, by a noun that could represent a match (i.e. name of the object), a taxonomically related mismatch (e.g. name of an object of the same category) or an unrelated mismatch (e.g. name of an object of a different category). In the non-verbal condition, a picture was followed by another picture depicting a different view of the same object (i.e. match), a picture of an object belonging to the same category (i.e. related mismatch) or a picture of an object belonging to a different category (i.e. unrelated mismatch). The participants were asked to push one button for a match and another for a mismatch.

In controls, the N400 incongruity potentials evoked by either type of mismatch were significantly different from those elicited by the match, providing physiological evidence that intra- and intercategory taxonomic boundaries were maintained. In the verbal format, the PPA-S group generated N400 responses that significantly differentiated the match from the unrelated mismatch but not from the related mismatch, indicating that intracategory boundaries had become blurred (Fig. 6A and B). This physiological index of blurring was predictive of behaviour. To wit, response accuracy was impaired in detecting the match (because the noun that denotes the object is not recognized) and in detecting the related mismatches (because exemplars of the same category cannot be differentiated) but not in detecting the unrelated mismatch (because intercategory boundaries are preserved). In the non-verbal format, the PPA-S group showed no abnormality either in the N400 or in the behavioural task. This dissociation indicates that the abnormality in the verbal format could not be attributed to a loss of object recognition and that the taxonomic blurring associated with the left TPR atrophy in PPA-S selectively disrupted the mapping of word meaning, not object representations.[61,99,101]

At a figurative level, the taxonomic blurring revealed by this experiment could reflect either insufficient predictive activation of the corresponding noun or insufficient inhibition of activation spread to congeners. One consequence is to promote semantic paraphasias, which arise when words that denote similar abstract or concrete categories are confused with each other. Another manifestation emerges during word–picture verification tasks. When asked to point to the 'frog' the patient may point to the snake but not the artichoke, indicating that the word is being understood at the generic but not specific level of meaning. As the disease progresses, intercategory distinctions are also undermined and the word comprehension impairment becomes more severe as shown in the example above when the patient wondered whether the word 'pumpkin' denoted a game.[70] The naming of animals, fruits and vegetables is usually the most susceptible to taxonomic blurring and words denoting these entities are the most difficult to define in SD and PPA-S, probably because these categories are more crowded, making exemplars more confusable.[203]

Of particular interest to this review is a computational account[117,204–206] of word and object recognition that highlights the importance of feed-back (top-down) connections from TPR into posterior temporal areas. The dynamics of the cerebral cortex, according to one version of this model, are poised to minimize the uncertainty (free energy, ambiguity, entropy) triggered by a sensory input.[117] Accordingly, a word or object gated through the relevant upstream unimodal auditory or visual canonical percept area would trigger a state of uncertainty as to its nature. If it is familiar and expected, the process of multimodal recognition would be

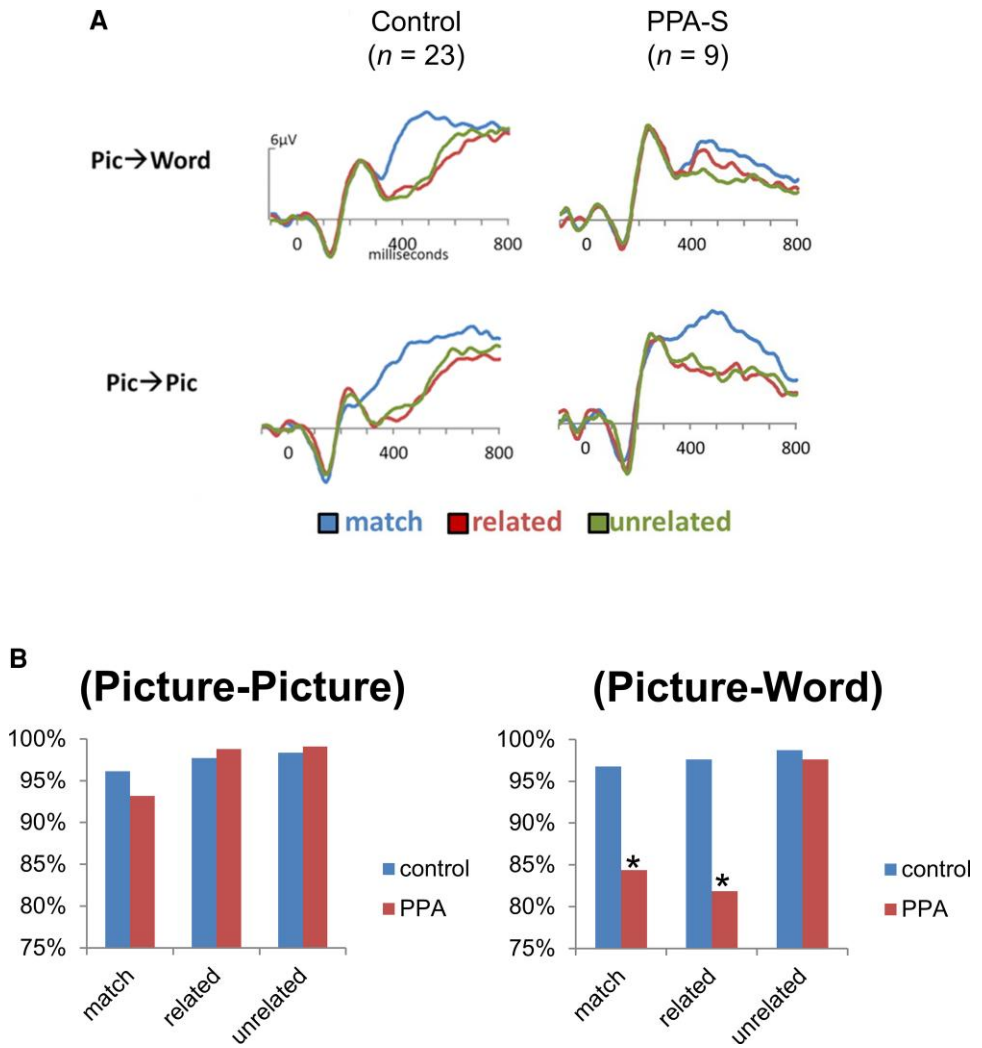

Figure 6 Blurring of word meaning. (**A**) Event-related N400 potentials in response to verbal (picture–word) and non-verbal (picture–picture) matching tasks. In controls, the N400 to the match is significantly different from the N400 triggered by both the taxonomically related and unrelated mismatches, indicating the preservation of both intra- and intercategory distinctions. In PPA-S with left TPR atrophy, the N400 triggered by the related mismatch is no longer significantly different from the match, indicating that intercategory boundaries are blurred. This abnormality is seen only in the verbal format. (**B**) In the behavioural test PPA-S makes errors only in the verbal format. The errors are in detecting a match (because the patient cannot recognize the noun that denotes the object) and in detecting a taxonomically related mismatch (because the boundaries among exemplars of the same category are blurred). Modified from Hurley *et al.*[61]

accomplished rapidly along downstream synaptic pathways already strengthened by a long record of coincident firing according to Hebbian mechanisms.[207] If the input is unfamiliar or unexpected, the continuing state of uncertainty (free energy) would promote the spread of neuronal engagement into deeper levels of the hierarchy, including TPR (Fig. 7, top). These deeper levels would then generate inferences, based on empirical Bayes, through feed-back connections. When the inference is insufficient for reaching closure, error signals are generated through forward connections until a settlement into a state of least conflict is iteratively achieved.[117] Through this process, the decoding of words and object percepts proceeds from the canonical (living) to the generic (bird), specific (pigeon) and eventually unique levels of multimodal recognition. Along this process, experiential associations are also evoked, probably involving TPR interactions with amygdaloid and hippocampal systems.[208,209] The TPR sits at the downstream pole of this process and serves a dual role as a site of multimodal convergence for word and object processing streams and also as a hub for binding the distributed information at different levels of the hierarchy through efferent top-down projections.

It would be simplistic to assume that each successive depth of representation is instantiated at a delineable patch of cortex. The process is more likely to take the form of dynamic activation waves travelling between unimodal areas and TPR. Greater depth or representation would be achieved not only by the location of the crest but also by its amplitude, reflecting the number and type of neurons recruited at that site. In the monkey, for example, neurons in a given column may respond preferentially to generic features of an object or face while activities of individual cells within the column may help to encode distinguishing features of individual exemplars.[210] In response to an object, for example, a small subset of low threshold neurons in a column can fire maximally and set constraints to guide the recruitment and interpretation of higher threshold neurons that encode more specific levels of representation.[211] The neuronal mass activated for successful recognition is likely to be inversely proportional to the set of probable solutions. There can

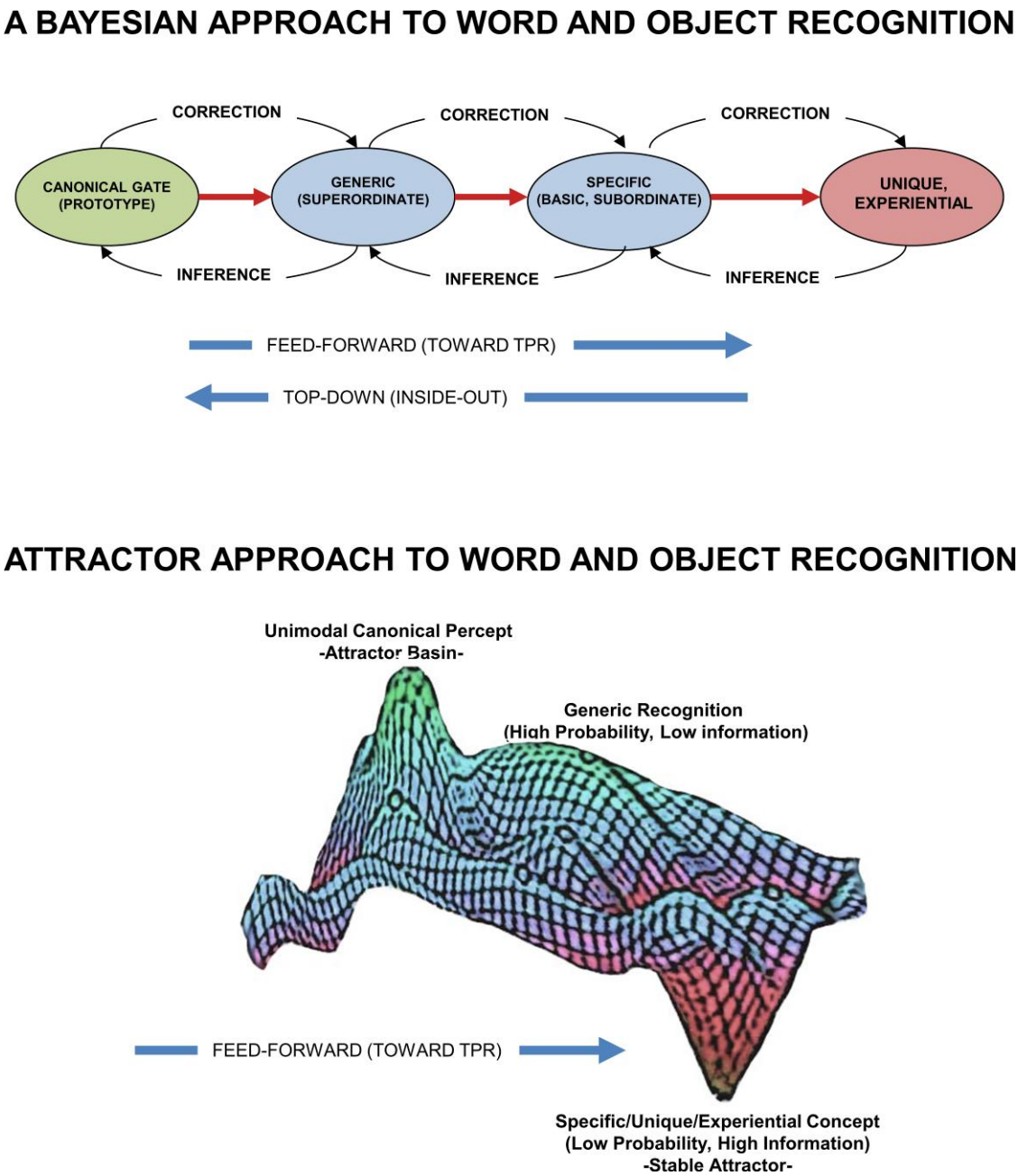

Figure 7 Anatomy of meaning. *Top*: A model based on empirical Bayes for the iterative recognition of words and objects. Green denotes unimodal cortex where specialized percepts are gated, red denotes heteromodal and paralimbic cortex where percepts are transformed into concepts. The separate stages are not necessarily located in different regions but may also represent the recruitment of more neurons at a given location. *Bottom*: A conceptualization of the process from the vantage point of attractors where unimodal percepts (green part of the colour palette) gravitate toward heteromodal concepts (red part of the colour palette) so that the uncertainty as to their nature is reduced by settling into a state of least conflict among options and constraints.

only be one correct answer to the naming of a person or landmark, making error signals more probable and therefore engaging more neuronal resources. In comparison, there are many exemplars that can be called 'hat', and many more that can be called 'stuff' so that the naming of an entity at a generic or nondescript level can be achieved with fewer neural resources. Consequently, retrieving names of relatively unfamiliar persons and landmarks is the most vulnerable to TPR degeneration,[166] followed by object naming at subordinate (specific) levels and finally naming and recognition at superordinate (generic) levels. When the process cannot proceed forward as effectively as necessary, as happens at early stages of TPR neurodegeneration, words and objects become stuck at superordinate (generic) levels of recognition so that concepts of the same category become more confusable, less fine-grained. With advanced TPR damage, words are reduced to percepts, as if belonging to an unknown language, because they fail to reach the associative depth required for recognition as a multimodal concept. As shown in Fig. 7 (bottom) the settling into a state of least conflict among competing options and constraints underlying recognition could follow the principles of attractor networks where percepts of words and

objects constitute basins of attraction that gravitate toward increasingly more stable multimodal attractors representing a best fit.[212]

Within this frame of reference, the widespread impact of TPR degeneration on word and object recognition may reflect the prominence of its feedback (or inside-out) connections to other parts of the temporal lobe. It is interesting to note that feedback connections have more diffuse axonal projections, more divergent topographies and slower time constants.[117,213] There is also suggestive evidence, at least in the context of amygdalo-cortical connections of the macaque, that feedback projections are more widespread and less confined to hierarchical synaptic stages than forward sensory–fugal connections.[214] Considering its location at one of the deepest synaptic levels of sensory–fugal pathways, the feedback signals from TPR are likely to encompass several synaptic levels.[152] In lobectomies, all neuronal activity emanating from TPR would disappear acutely and permanently, but other parts of the language network could undergo compensatory reorganization. In fact, the acute anomia after left temporal lobectomy is quite transient.[156,215] The situation is different in neurodegenerations where numerous residual neurons at peak atrophy sites are likely to undergo rewiring of their excitatory and inhibitory synapses.[199,216] Interestingly, spectral dynamic causal modelling showed that TPR atrophy leads to reduced inhibition within the temporal lobe and increased excitatory linkage with frontal cortex.[96] Therefore, the atrophic TPR is not only unable to function properly but is also likely to generate aberrant local and top-down signals that stand to perturb word and object recognition throughout the relevant networks.[217–220] Naturally, if this reasoning is carried too far, it might lead to the unsettling prospect that further destruction of TPR may be therapeutic. This possibility is easily dismissed because the aberrant functioning of TPR in SD and PPA-S emerges on a background of expanding neurodegenerative disease where restorative neuroplasticity is improbable, whereas the putative compensatory reorganization in lobectomy occurs in an otherwise relatively healthy brain.

Accounting for the behavioural variants—the amygdalocentric limbic system

As noted above, the medial TPR belongs to the amygdalocentric sphere of influence, a part of the limbic system that includes the insula, posterior orbitofrontal cortex, the anterior cingulate and the parolfactory gyrus.[123] By analogy to the synaptic pathways described in the macaque temporal lobe, the human medial TPR is positioned to mediate the gating of words, faces, objects and other exteroceptive experiences into the amygdala and hypothalamus.[106,124] This gating enables incoming concepts and events to evoke interoceptive responses and hedonic valuations that resonate with past encounters, ambient context and current expectations.[221–224] Feedback projections from medial TPR and from the amygdala could potentially serve computational functions analogous to those shown in Fig. 7 (top), namely, to infer the potential valence of incoming information and to modulate its interoceptive impact through error signals generated by upstream synaptic stages. A disruption of this circuitry through TPR neurodegeneration would compromise interoceptive guidance[225] of social behaviour and sensitivity to markers of emotion. By the same token, the control of interoceptive urges by heteromodal association cortices such as prefrontal cortex would be disrupted. Ingestive preferences would become more stereotypical and repetition would be promoted over change and flexibility, as can be seen in bvFTD syndromes associated with right TPR damage.[39,42,48] The discrepancy between the florid conduct abnormalities of P1 and their absence in patients with bilateral temporal lobectomy, as in the case of H.M., might then be attributed to the dual effect of abnormal TPR functionality superimposed upon aberrant signals emanating from its residual neurons.

Conclusions

Three axes of organization define TPR functionality, a horizontal axis that runs from unimodal to heteromodal and paralimbic cortex in an anterograde direction but with strong feedback modulation; a radial axis where visual (ventral), auditory (dorsal) and limbic (medial) territories encircle TPR and display hemispheric asymmetry; and a vertical depth-of-processing axis reflecting the magnitude of neuronal recruitment at any given site for the associative elaboration of words and objects and the interoceptive guidance of social interactions (Figs 5 and 7). Perturbations in this matrix underlie the syndromes illustrated by P1–6. Given the complexity of these syndromes, it is no surprise that the literature on TPR syndromes keeps expanding.[142,149] Through this research, the TPR has been transformed from *terra incognita* of behavioural neurology to a Mecca for cognitive neuroscience. Indeed, nowhere else in the brain can focal neurodegeneration in such a small region of cortex undermine the conceptualization of percepts and trigger the almost unimaginable failure to understand words as familiar as ‘orange’ or ‘grass’. Had Descartes known about the TPR, he might have chosen it over the pineal gland.

The story of TPR cannot be complete without mention of TDP-C. Of all known neuropathological entities, TDP-C is the only one with a selective predilection for TPR as the initial site of peak atrophy.[21,22,50] For the behavioural neurologist, a coronal MRI of the type seen in Fig. 2E would be sufficient to rule out Alzheimer’s disease and predict TDP-C as the most probable aetiology. Although autosomal dominant forms of TDP-C are exceedingly rare,[226] 64 risk genes interacting with TDP-43 have been linked to PPA-S and SD.[227] Equally interesting is the finding that heterogeneous ribonuclear protein E2 antibodies recognize abnormal TDP-43 precipitates in TDP-C but not in other forms of FTLD-TDP.[228] This finding leads to the conclusion that the abnormal TDP-43 in TDP-C has distinct immunological and probably conformational properties that selectively target TPR. It would appear therefore that TPR is unique not only in its neurobehavioural attributes but also in cellular and molecular properties that make it the selective target of TDP-C. In the future, transcriptomic investigations of TPR could be integrated with molecular and immunological correlates of TDP-C to identify which proteomic network or cell type is the preferred target. Progress along these lines could have considerable implications for therapeutic interventions. While such lines of research proceed, TPR syndromes will continue to stimulate fundamental investigations on the computational architecture of language, object recognition and conduct at a pace that will undoubtedly more than make up for the decades of initial neglect.

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Competing interests

The author reports no competing interests.

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