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REVIEW

Clinical Manifestations and Neural Basis of Semantic Dementia: Converging Evidences From Brain Imaging Studies

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Abstract: Semantic dementia (SD) is a progressive neurodegenerative disorder primarily characterized by core linguistic deficits, notably impaired confrontation naming and single-word comprehension. Associated features include surface dyslexia, prosopagnosia, relatively preserved speech production, and emotional or behavioral abnormalities. Neuroimaging reveals initial asymmetrical atrophy of the anterior temporal pole, with subsequent progression posteriorly and contralaterally. Early detection is challenging due to initial presentation often manifesting as mild word-finding difficulties, furthermore, comorbid behavioral-emotional symptoms and distinct clinical profiles associated with right- versus left-sided atrophy complicate diagnosis. Therefore, this paper comprehensively delineates the principal clinical features of SD, encompassing language deficits, emotional impairment, behavioral disturbances, and other domains. It also reviews structural and functional imaging findings and investigates the relationship between clinical manifestations and patterns of brain injury. To advance understanding of SD's clinical manifestation, the paper introduces the controlled semantic and social-semantic frameworks.

Keywords: semantic dementia, primary progressive aphasia, clinical manifestation, neuroimaging

Introduction

Semantic dementia (SD) is a progressive neurodegenerative disease characterized by impaired confrontation naming, receptive vocabulary deterioration and impaired single-word comprehension as core clinical manifestations. Individuals manifest multimodal semantic deficits, frequently accompanied by emotional and behavioral disturbances, facial agnosia and other nonverbal impairments. Early disease stages typically present with isolated semantic impairment, while executive, visuospatial, and motor functions remain relatively preserved. First described by Pick and Serieux in the 1890s,[1] this progressive language disorder was later termed "semantic dementia" by Snowden et al.[2] Hodges et al subsequently provided a comprehensive description in the early 1990s.[3] The consensus criteria established in the early 2000s proposed the designation "semantic variant primary progressive aphasia (svPPA)"[4] to distinguish it from other PPA subtypes.

SD is characterized by predominantly left-lateralized brain atrophy, particularly within the anterior temporal lobe (ATL). Nonetheless, approximately 30% of cases initially exhibit more severe right-hemisphere atrophy.[5] Here, we designate patients with predominant left ATL atrophy as "left-SD" and those with a predominant right ATL atrophy as "right-SD". Left-SD individuals experience greater difficulties in naming and word comprehension than right-SD individuals. Conversely, right-SD patients are more likely to encounter social, emotional, and behavioral challenges.[6] Facial agnosia and emotional-behavioral problems (such as irritability, impulsivity, egocentrism and diminished empathy) are relatively prominent, but symptom profiles increasingly overlap with disease progression.[7]

The unique clinical profiles of SD provide a basis for investigating human semantic concept formation. This review comprehensively discusses the clinical manifestations of SD, encompassing language deficits, emotional impairment, behavioral disturbances, and other domains, and examines the corresponding imaging evidence. It provides a detailed

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synthesis of SD's clinical profiles, and analyzes potential neural mechanisms underlying these manifestations using clinical neuroimaging data, these insights advance our understanding of SD and help identify useful targets.

Imaging Features

Structural Atrophy Pattern

SD typically shows bilateral atrophy with left ATL predominance. Voxel-based morphometry analysis shows bilateral temporal pole involvement (particularly left-sided).[8] Atrophy follows an anterior-to-posterior gradient within the temporal lobe, most pronounced in the ATL.[9] Additional atrophy affects the ventromedial frontal cortex,[10] amygdala (left>right), insular lobe, left inferior lateral temporal lobe, and fusiform gyrus.[11,12] Cerebellar atrophy (primarily Crus I/II) is also observed bilaterally.[13,14] Emerging evidence suggests amygdala atrophy may precede involvement of other brain regions, indicating its potential as a prodromal marker.[15] Circumscribed anterior hippocampus atrophy occurs,[16] more severe in right-SD versus left-SD.[17] The retention of the corpus and tail of the hippocampus also explains intact episodic memory. Atrophy and hypometabolism progress from the ATL to posterior temporal lobe and/or inferior frontal lobe[18] and may extend to orbitofrontal cortex and contralateral parietal lobe.[19]

White Matter Integrity Impairment

SD patients demonstrate impaired white matter integrity, exhibiting a laterality characterization,[20] mainly in the corpus callosum, fornix, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus, which are related to frontotemporal pathways.[21,22] Mean diffusivity changes exceed cortical thinning regions.[21] Additionally, radial diffusivity demonstrates greater sensitivity than other diffusion tensor imaging (DTI) metrics.[23] A 12-month follow-up of SD patients revealed white matter degeneration extended progressing from left temporal tracts to bilateral ATL tracts.[24] Recent evidence exhibits increased periventricular and left temporal white matter hyperintensities and reduced DTI-ALPS index (reflecting glymphatic dysfunction) in SD. This may lead to a decrease in the clearance efficiency of pathological proteins such as tau and TDP-43, thereby exacerbating neurodegeneration and cognitive decline in svPPA patients.[25]

Metabolic-Functional Connectivity Decoupling

^{18}F-FDG PET reveals the hypometabolism concentrated in the left temporal lobe (pole and hippocampus), extending contralaterally with disease progression, mirroring atrophy patterns.[19] Functional imaging studies demonstrates widespread disrupted connectivity between ATL and a wide range of brain regions in the temporal, frontal, parietal, and occipital lobes,[26] with increased connectivity in the left hippocampus, amygdala, fusiform gyrus, para hippocampal gyrus, and inferior and middle temporal gyri.[27] Graph-theoretic paradigm reveals declining global and local efficiency in temporal and frontal networks.[28] Patients with SD show increased temporoparietal network clustering, suggesting functional isolation.[29] Stepwise Functional Connectivity analysis demonstrates a reduced functional connectivity in regions directly linked to the left inferior temporal gyrus and an augmentation in cerebellar regions within the indirect connection.[30] Patients with SD in the functional magnetic resonance imaging (fMRI) task state exhibits decreased activity in the middle temporal gyrus and superior temporal gyrus and increased activity in the intraparietal sulcus, inferior frontal gyrus, and left superior temporal gyrus during the semantic processing task.[31] It signifies a diminution in ventral network connectivity, which is associated with semantic processing, and an augmentation in dorsal network connectivity, which is linked to motor speech and phonological processing. The clinical manifestations of SD may be due to the disconnection between the ATL and other language areas.

In terms of the distribution of brain atrophy, right-SD not only have more atrophy in bilateral temporal lobe regions but also in the bilateral cingulate gyrus and orbitofrontal cortex.[32] In a PET study, right-SD had more extensive metabolic reduction than left-SD.[33] Key imaging observations are tabulated in Table 1.

Language-Related Deficits in SD Patients

SD is mainly manifested as reduced expressive vocabulary and receptive vocabulary.[34]

Table 1 Key Neuroimaging Findings in SD

Modality	Primary Observations
Structural MRI	Atrophy originates in the left ATL (temporal pole, anterior fusiform gyrus)
	Atrophy progressively extends bilaterally to the right anterior temporal cortex, orbitofrontal cortex, amygdala, and anterior hippocampus, with an anterior-to-posterior gradient in temporal regions.
DTI	Reduced FA in uncinate/inferior longitudinal fasciculi
	Increased MD/RD with left hemispheric predominance
	Progressive bilateral extension
18F-FDG PET	Left ATL hypometabolism progressing to right hemisphere
	Metabolic deficits exceed atrophy extent
fMRI	Disrupted ATL connectivity to default mode/salience networks
	Dorsal attention network hyperactivity
Multimodal	Right-SD: broader atrophy involving cingulate/orbitofrontal cortices
	Left-SD: focal anterior temporal deficits

Abbreviations: SD, semantic dementia; R, right; L, left; MD, mean diffusivity; RD, radial diffusivity; Dax, axial diffusivity; Dra, radial diffusivity; DTI, diffusion tensor imaging; FA, fractional anisotropy; ATL, anterior temporal lobe.

Verbal Emptiness in Spontaneous Speech

Spontaneous speech features lexical impoverishment with overreliance on high-frequency, abstract words replacing low-frequency, concrete vocabulary.[35] This type of speech is meaningless and verbose. Furthermore, the task performance of patients is related to word frequency.[36]

Impaired Confrontation Naming

Impaired confrontation naming typically constitutes the earliest clinical manifestation in SD. Initially, misnaming of the same category of words may occur. The misnamed words are usually more archetypal. With disease progresses, generic term usage emerges. Patients increasingly use general words to describe items and sometimes may metaphorically state certain characteristics, ultimately becoming completely unable to name the item, responding with "do not know". Even though an individual retain conceptual knowledge of items but exhibit word-finding failures, resulting in circumlocutory speech characterized by imprecise definitions. Naming deficits are primarily associated with damage to temporal lobe structures. The fusiform gyrus is believed to be closely associated with naming deficits, while the superior temporal gyrus and middle temporal gyrus are associated with noun production and extraction.[37,38]

Category fluency is more impaired than letter fluency in these individuals.[39] Patients exhibit a remarkable superiority in numerical-verbal working memory performance compared to word-based tasks.[40] Significant dissociations exist in naming performance across lexical categories. Specifically, Patients are found to demonstrate a significantly weaker capacity for naming nouns than verbs,[41] biological nouns than nonbiological nouns,[6] concrete words (either nouns or verbs) than abstract words.[42] These discrepancies may be attributed to the fact that nouns (especially those denoting concrete entities) or concrete words rely more heavily on sensory and visual areas connected to the ATL, whereas the processing of verbs or nonbiological words engages more extensive motor, functional, and auditory areas.[43,44] Verb naming impairment correlates with atrophy in left inferior frontal, inferior parietal, and posterior temporal lobe regions, whereas noun naming deficits are associated with cortical atrophy in left ATL regions specifically. These findings align with the patient's neuroimaging profiles showing left ATL atrophy with relative preservation of the left inferior frontal and inferior parietal lobes.[41,45] In contrast, abstract words stems from their lack of direct perceptual association, absence of concrete attributes, and lower lexical frequency compared to concrete words, resulting in less robust semantic memory representations.[42]

Naming errors profiles in SD patients exhibit distinct characteristics correlating with lateralized atrophy patterns. Left-SD tend to be unable to name (ie, responding with "do not know") or only describe the function or circumlocutory responses featuring functional descriptions or semantic associations. Conversely, right-SD patients tend to make semantic paraphasia. Left-SD patients have greater deficits in object naming, whereas right-SD display greater impairment on the image-based semantic association tasks.[46] Performance on word-picture matching tasks shows no significant intergroup difference, attributed to its comparatively lower cognitive demands relative to naming and nonverbal semantic tests.[47]

Superficial Dyslexia

SD patients may exhibit superficial dyslexia, committing errors when reading irregular or inconsistent words. This learning process reflects reliance on phoneme-grapheme conversion rules due to semantic degradation, analogous to pseudoword reading.[48] This impairment stems from compromised access to lexical-semantic representations within the atrophied left ATL, hindering irregular word pronunciation. Reading engages two partially independent neural pathways: a ventral (temporally-based) lexico-semantic route and a dorsal (parietally-based) sublexical/phonological route. Increased neural activity in dorsal parietal regions during irregular words reading suggests compensatory reliance on the sublexical route when the lexical-semantic route is impaired.[49] Conversely, grammatical competence and motor speech are usually preserved. Phonological fluency and sublexical processing correlate with intact activation in the inferior parietal lobule and preserved integrity of the superior longitudinal fasciculus. Preservation of grammatical function may relate to left frontal lobe integrity and relatively preserved posterior temporal gyrus.[50,51]

Nonverbal Semantic Deficits

Patients exhibit nonverbal semantic impairment. Performance on nonverbal semantic assessments correlates strongly with scores on tests of naming and word understanding tests.[52] Both temporal lobes contribute to semantic representation but demonstrate functional specialization: the left temporal lobe primarily subserves language-related functions, while the right temporal lobe predominantly engages in processing visual or sensory aspects of conceptual knowledge.[53] Fiber bundle-based analysis indicate that semantic impairments are primarily associated with the disruption of short-range white matter fibers, such as the left uncinate fasciculus, inferior longitudinal fasciculus, and inferior fronto-occipital fasciculus.[22]

Emotional Abnormalities in SD Patients

Apathy and Anhedonia

Apathy represents the most prevalent neuropsychiatric symptom in SD.[54] Defined as diminished motivation and goal-directed behavior,[55] apathy is recognized as a multidimensional syndrome[56] comprising executive, emotional and initiation subtypes. Executive apathy manifests as impaired goal maintenance and organization, affective apathy as emotional blunting and indifference, and initiation apathy as reduced self-generated thought or action.[57] SD patients exhibit global apathy across all dimensions relative to other primary progressive aphasia variants.[58] fMRI reveals decreased anterior thalamic connectivity and increased prefrontal cortical connectivity in SD—regions pivotal for behavioral and emotional regulation. Disruption of their connectivity may underlie observed socioemotional cognitive deficits.[59] In a study of patients with frontotemporal lobe dementia using an atrophic network mapping approach, apathy-specific networks were identified in the orbitofrontal cortex and ventral striatum.[60] Another study of patients with affective apathy, including SD, demonstrate impaired social reward learning, suggesting a shared neurobiological substrate.[61] Apathy severity may serve as a prognostic indicator of disease progression.[62]

Concomitant anhedonia—the diminished capacity to experience pleasure from typically rewarding activities—is also observed. This symptom correlates with atrophy within an extended prefrontal-striatal network, encompassing the orbitofrontal and medial prefrontal lobes, anterior cingulate gyrus, insular cortex, and nucleus accumbens.[63] Anhedonia is more pronounced in right-SD, indicating that right temporal lobe degeneration distinctively compromises neural networks subserving emotion, reward processing, and motivational regulation, thereby diminishing hedonic capacity.[64]

In conclusion, apathy and pleasure deficits in SD primarily associate with frontal, striatal, and insular atrophy, with the right temporal lobe playing a distinctive role in the pathophysiology of anhedonia.

Recognizing Emotional Difficulties

Social dysfunction is also prominent in SD, characterized by deficits in recognizing others' emotions.[65] Emotion recognition, the cognitive process of discerning emotional states via cues like facial expressions, vocal prosody, and body language, is impaired. Debate exists regarding the preservation of emotional valence recognition (the positive/negative dimension).[66,67] Patients exhibit impaired recognition of positive emotions, potentially attributable to valence inconsistencies between negative and positive emotions in prior paradigms. Emotion recognition deficits persist irrespective of emotional intensity[68] or contextual cues.[69] This suggests a primary emotional processing deficit where semantic knowledge critically guides both emotion identification and valence processing.[70,71] Impairments correlate with atrophy in the orbitofrontal cortex, temporal lobe, amygdala, and insula,[72,73] with the right hemisphere often showing a stronger association.[32,67] Different categories of emotion recognition disorders can correspond to the damage of specific brain areas.[74] Beyond basic emotions, self-conscious emotions, such as shame, pride, embarrassment, and guilt, are also impaired,[75,76] potentially linked to right anterior cingulate gyrus.[77] Deficits extend to musical emotion recognition, associated with left anterior and inferior temporal lobes, overlapping with semantic regions.[72] DTI studies implicate the uncinate fasciculus, inferior longitudinal fasciculus, and anterior thalamic radiation.[78,79] A resting-state fMRI study reveals correlations between emotion recognition accuracy and functional connectivity with the semantic appraisal network (SAN) and the salience network (SN).[80]

Theory of Mind Impairments

The theory of mind (ToM) is the ability to infer others' mental states, thoughts, and feelings, that is, the ability to "read others".[81] Patients exhibit deficits in emotion perception, compromising social context comprehension and interpretation of complex interactions (eg, persuasion, metaphors, or deception). ToM comprises two domains: cognitive ToM (inferring beliefs, intentions) and affective ToM (inferring emotional states).[82,83] Both domains are impaired in SD, with deficits persisting after controlling for semantic factors.[84] Cognitive ToM impairment correlates with hypometabolism in the left temporal lobe and medial prefrontal cortex (mPFC), while affective ToM impairment is related to the ATL and amygdala dysfunction.[83] fMRI reveals that the impairment of ToM may be related to the decrease in functional connectivity between the mPFC and other brain regions,[85] and the right ATL also plays an important role.[84,86] The ATL likely facilitates implicit meaning comprehension through generalized and social-conceptual knowledge integration,[86] whereas the mPFC mediates reasoning about others' mental states.[87]

Empathic Dysfunction

Empathy conceptually overlaps with ToM, and its dysfunction of the right ATL and the medial frontal lobe.[88,89] SD patients have a tendency to underestimate their empathic capacity, correlating with anterior inferolateral temporal atrophy.[90] It is postulated that the lower baseline activity levels of the peripheral autonomic nervous system in SD patients may be a contributing factor to the absence of socio-emotional experience in SD patients, which is associated with left insular cortical atrophy.[91] Collectively, emotion recognition, empathy and social interaction critically depend on the integrated operations of the ATL, orbitofrontal cortex, insula, and amygdala.

Behavioral Disturbance in SD Patients

SD patients manifest behavioral abnormalities resembling behavioral variant frontotemporal dementia (FTD) at an early stage[92] and right temporal variant FTD.[93] A long-term follow-up study indicate that 44% of patients may develop behavioral variant frontotemporal lobe dementia at a later stage,[94] suggesting a strong link between the two disorders. Disinhibition,[95] obsessive behavior,[96] and stereotyped behavior[97] are common in SD patients. Patients may like counting, sudoku, performing the same leisure activities (such as jigsaws, word searches, and clock watching), eating the same food repeatedly, and strictly following rules, potentially reflecting altered reward processing[98] and motivational dysfunction.[99] Patients may exhibit abnormal egocentric behavior,[100] which may be due to impaired social cognition

and reduced mental state inference.[83] Right temporal pole pathology associates with motivational deficits and stereotypic behaviors.[32]

At present, there are few studies on the neural mechanism of disinhibition in patients with SD. The definition of disinhibition refers to the manifestation of socially destructive or morally unacceptable behaviors.[101] Heterogeneous cohort studies implicate atrophy in the orbitofrontal cortex, anterior cingulate, and temporal regions,[102,103] right medial and lateral temporal hypometabolism,[18] and decreased left insular-prefrontal connectivity.[59] Intrinsic connectivity networks (SAN, SN, task control networks) show significant involvement.[104,105] The mPFC dysfunction may underlie impaired self-conscious emotion generation, contributing to characteristic social transgressions.[75]

Binge Eating

SD patients frequently develop alimentary stereotypies (eg, rigid meal schedules, sweet food preferences, dietary perseveration)[106] or pica.[107] Reduced hypothalamic volume may precipitate aberrant eating behaviors.[108] Correlation analyses reveal that both semantic deficits and alimentary alterations associate with temporal lobe atrophy and degradation of temporal-frontal white matter tracts—particularly the superior longitudinal fasciculus, corpus callosum, and inferior longitudinal fasciculus, suggesting a shared neural substrate for these behavioral manifestations.[109]

Hyper-Creativity

Before and during early stages of the disease, SD patients often show heightened artistic creativity.[110] This paradoxical functional facilitation may reflect disinhibition of right parietal-temporal cortices secondary to left fronto-temporal damage.[111] Comparative neuroimaging suggests enhanced artistic aptitude correlates with strengthened dorsal attention network-visual association network connectivity and reduced DMN integration, likely reflecting ATL neurodegeneration triggering functional reorganization within visuospatial networks.[112]

Other Manifestations in SD Patients

Prosopagnosia

Prosopagnosia also occurs in approximately one-third of patients with SD,[113] particularly in patients with R> L.[114] This deficit reflects impaired person-specific semantic knowledge rather than perceptual dysfunction, manifesting as an inability to name familiar individuals or access biographical information.[115,116] Prevailing models propose dual hemispheric pathways for facial processing: facial naming depends on left-hemisphere language networks, while facial identification engages bilateral (predominantly right-hemisphere) visual recognition networks mediating person knowledge.[117,118]

Apraxia

As the disease progresses, apraxia may occur. At first, caregivers are not aware of patients' apraxia of objects because they initially retain some understanding of the objects they are familiar with. Preserved perceptual abilities (such as visual affordances and mechanical problem-solving skills) may facilitate compensatory object-purpose inference.[119] Furthermore, patients demonstrate tool overuse—using a single tool for multiple different tasks.[120]

Impaired Long-Term Autobiographical Memory

Patients perform well in traditional episodic memory tasks, with relatively preserved short-term autobiographical memory, but perform poorly in tasks related to long-term autobiographical memory (ie, reverse time gradient).[121]

Impaired Future Episodic Thinking

Concurrently, future episodic thinking—the capacity to mentally simulate prospective scenarios using current/past experiences—is compromised.[122] This impairment likely reflects the critical role of semantic conceptual knowledge in supporting episodic memory reconstruction, scene construction, and self-referential processing.[123]

The clinical manifestations of SD are comprehensively presented in Figure 1. And the correspondence between clinical manifestations and imaging features is presented in Table 2.

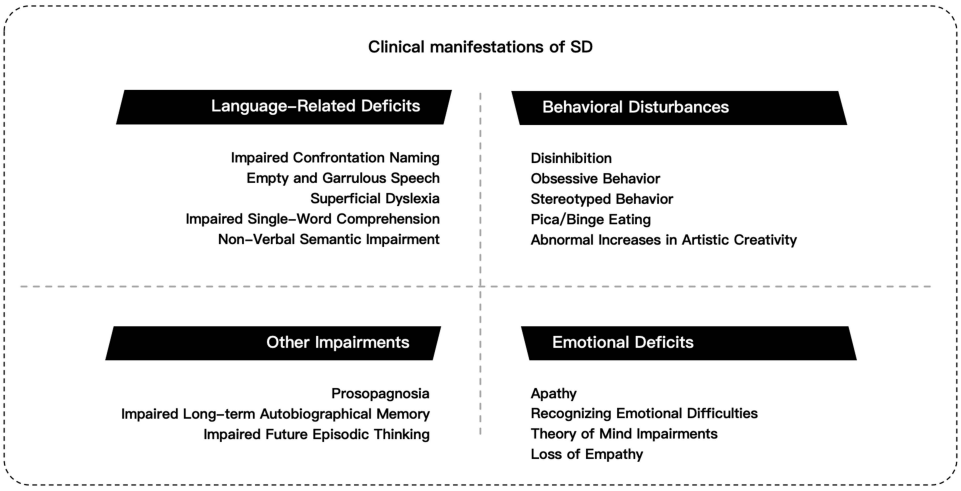

Figure 1 Clinical manifestations of SD. The clinical characteristics of patients with SD will be described in terms of four aspects of its language, behavioral, emotional and other disorders.

Theoretical Model of Semantic Dementia

The semantic hub-and-spoke model provides a robust framework for understanding language deficits in SD. In this model, the ATLs integrate multimodal inputs from distributed cortical sensory-motor regions, facilitating the extraction of distinctive semantic features when required.[124,125] As semantic cognition develops, the model demonstrates progressive functional specialization. Current evidence indicates that the semantic transmodal semantic hub is located in the

Table 2 Correspondence Between Clinical Manifestations and Imaging Features in SD

Clinical Manifestation	Core Imaging Features	Neurobiological Mechanism Explanation
Language Impairment		
Naming Impairment	Left ATLatrophy; Left fusiform gyrus volume reduction	Damage to the conceptual knowledge storage hub
Vocabulary Comprehension Difficulty	Left uncinate fasciculus/inferior longitudinal fasciculus white matter damage	Disruption of the temporal-frontal semantic pathway
Empty Speech	Bilateral temporal lobe hypometabolism; Reduced ATL-frontal functional connectivity	Dissociation between semantic networks and language production systems
Surface Dyslexia	Left middle temporal gyrus atrophy; Dorsal pathway (intraparietal sulcus) compensatory activation	Ventral semantic pathway damage; Dorsal phonological pathway compensation
Emotional Cognitive Impairment		
Emotion Recognition Difficulty	Right amygdala atrophy; Right insular hypometabolism	Damage to core emotion processing regions
Theory of Mind Deficit	Right anterior temporal pole atrophy; Reduced medial prefrontal functional connectivity	Impairment in social concept integration and intention reasoning
Empathy Reduction	Right orbitofrontal cortex thinning; Anterior cingulate volume reduction	Damage to social-emotional judgment networks
Behavioral Disturbance		
Behavioral Disinhibition	Orbitofrontal cortex atrophy; Right temporal hypometabolism	Loss of function in behavioral inhibition centers
Stereotyped Behavior	Right caudate nucleus atrophy; Anterior thalamic radiation white matter damage	Dysfunction in reward-motivation circuits
Hyperphagia/ Eating Stereotypy	Hypothalamus volume reduction; Inferior longitudinal fasciculus/ arcuate fasciculus microstructural damage	Impaired integration of hunger-satiety signals

(*Continued*)

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Table 2 (Continued).

Clinical Manifestation	Core Imaging Features	Neurobiological Mechanism Explanation
Other Manifestations		
Prosopagnosia	Right fusiform face area atrophy; Bilateral temporo-occipital connection damage	Disruption of dedicated face recognition pathways
Loss of Autobiographical Memory	Anterior hippocampal atrophy; Posterior hippocampal relative preservation	Episodic memory retrieval dependent on semantic frameworks
Future Episodic Thinking Impairment	Default mode network functional dissociation; Angular gyrus hypometabolism	Loss of semantic basis for episodic simulation

ventral ATL,[126,127] while peripheral ATL subregions process modality-specific signals. For example, the superior temporal gyrus is sensitive to auditory-verbal stimuli,[128] polar and dorsal ATLs are sensitive to social signals,[86] and the medial ATL region responds greatly to visual and conceptual information.[129] In contrast, the ventral ATL is equally sensitive to various information sources.[130,131] This hierarchical organization, characterized by progressive convergence from modality-specific peripheral regions to amodal central hubs, constitutes the "graded" hub-and-spoke model. The controlled semantic framework further elaborates this semantic network architecture. This network comprises two principal subsystems: (1) the semantic representation system, which acquires and integrates multimodal information from sensory, motor, linguistic, and affective domains to establish coherent semantic representations; and (2) the semantic control system, which regulates cognitive processes by modulating semantic information in accordance with specific task demands and contextual constraints.[132] In this system, the angular gyrus mediates automatic semantic retrieval, facilitating rapid, effortless access to stored semantic knowledge. In contrast, the posterior middle temporal gyrus forms a functional network with prefrontal regions (particularly the left inferior frontal gyrus) to constitute the semantic control network. This system becomes engaged when situations require dynamic adaptation and top-down regulation of semantic information. The coordinated interaction between these systems enables efficient information retrieval and integration during complex semantic operations.[133]

Emerging evidence indicates that the ATL plays a pivotal role in both emotional processing and social cognition.[134] Recent theoretical advances have integrated controlled semantic cognition with social cognition, leading to the development of a novel social-semantic framework.[132,135] This framework elucidates two fundamental aspects: (1) the ATL's collaborative function with other cortical regions in social information processing, and (2) the conceptualization of social information processing as a specialized mechanism for environmental meaning extraction. Importantly, this perspective suggests that social cognition shares core neural and cognitive mechanisms with semantic cognition. Neuroanatomical studies reveal significant hemispheric specialization within the ATL. Specifically, the right ATL demonstrates greater receptivity to emotionally salient sensory inputs compared to the left ATL, suggesting its predominant involvement in emotional semantic processing and cross-modal information integration.[136] Furthermore, the ATL and medial temporal lobe form functional connections with the frontal insula, facilitating contextual information processing.[137] The neural architecture supporting these functions comprises several key components: The orbitofrontal cortex is the primary hub for cognitive-affective decoding;[138] the anterior insula acts as the interface between processing emotional sensations and affective and cognitive brain systems, integrating affective and visceral information into the current situation;[139] the posterior insula integrates interoceptive information[140] and key acoustic cues for communicating affective content during behavioral preparation;[141,142] and the amygdala specializes in processing emotionally and socially stimuli, particularly in facial emotion recognition and emotional arousal monitoring.[143] Structural connectivity within this network is maintained through the uncinate fasciculus, which establishes white matter pathways linking the orbitofrontal cortex, ATL, and amygdala. This anatomical configuration supports complex cognitive functions by facilitating the synergistic integration of semantic knowledge and emotional information during social interactions and affective decision-making processes.[134,144]

Therapy

There is no specific treatment for SD currently. Previous treatment primarily involved pharmacotherapy, such as cholinesterase inhibitors and NMDA receptor antagonists,[145] although therapeutic benefits have been limited. Some language and other cognitive function training, such as speech-language therapy and cognitive stimulation therapy[146] demonstrate efficacy in ameliorating communication abilities, daily living skills, and potentially slowing symptom progression. Advances in understanding functional connectivity network alterations in SD brains suggest connectomics may yield novel therapeutic targets. Modulation of cortical excitability via non-invasive brain stimulation techniques—specifically repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS)—represents an emerging approach. tDCS applies weak direct current (1–2 mA) to the scalp via electrodes, altering neuronal membrane potential to increase (anodal) or decrease (cathodal) excitability.[147] rTMS employs a figure-8 coil to deliver a strong magnetic field, inducing currents that enhance excitability with high-frequency (10–20 Hz) or reduce it with low-frequency (1 Hz) stimulation.[148] However, optimal stimulation sites and parameters require further elucidation. Clinically, both techniques commonly target the left dorsolateral prefrontal cortex (DLPFC) and left ATL, with site selection guided by underlying pathology and desired outcomes. And they have demonstrated potential benefits in improving language functions, particularly for trained items, with effects generally being more pronounced in the short term. Nevertheless, treatment response exhibits substantial heterogeneity, and long-term efficacy remains uncertain. For instance, tDCS combined with language training has shown some improvement in word retrieval for trained items, but its impact on untrained items and overall language function is less consistent.[149,150] Similarly, rTMS targeting specific brain regions, such as the left ATL shows promise for enhancing language performance, but results are often heterogeneous and dependent on individual patient characteristics and stimulation parameters.[151] Consequently, while tDCS and rTMS offer potential therapeutic avenues for SD, further research is needed to optimize treatment protocols and establish their long-term efficacy.

Conclusion

SD features initial asymmetric atrophy of the anterior ATL, progressing to involve the contralateral hemisphere. Clinically, it is clinically characterized by prominent semantic impairments, with accumulating evidence identifying emotional and behavioral disturbances as common features. The insidious onset of the initial naming difficulties that precede significant personality and behavioral changes, underscores the necessity for vigilance in identifying SD. Understanding SD's clinical profiles and neural mechanisms is critical for advancing diagnosis and therapeutic development.

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