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Toward a functional neuroanatomy of semantic aphasia: A history and ten new cases

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ABSTRACT

Almost 70 years ago, Alexander Luria incorporated semantic aphasia among his aphasia classifications by demonstrating that deficits in linking the logical relationships of words in a sentence could co-occur with non-linguistic disorders of calculation, spatial gnosis and praxis deficits. In line with his comprehensive approach to the assessment of language and other cognitive functions, he argued that deficits in understanding semantically reversible sentences and prepositional phrases, for example, were in line with a single neuropsychological factor of impaired spatial analysis and synthesis, since understanding such grammatical relationships would also draw on their spatial relationships. Critically, Luria demonstrated the neural underpinnings of this syndrome with the critical implication of the cortex of the left temporal-parietal-occipital (TPO) junction. In this study, we report neuropsychological and lesion profiles of 10 new cases of semantic aphasia. Modern neuroimaging techniques provide support for the relevance of the left TPO area for semantic aphasia, but also extend Luria's neuroanatomical model by taking into account white matter pathways. Our findings suggest that tracts with parietal connectivity – the arcuate fasciculus (long and posterior segments), the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, the superior longitudinal fasciculus II and III, and the corpus callosum – are implicated in the linguistic and non-linguistic deficits of patients with semantic aphasia.

1. Introduction

Semantic aphasia is regularly diagnosed in clinical settings that utilize Alexander Luria's neuropsychological approach. It is a syndrome that features a specific sentence comprehension impairment and is conceptualized as a disorder of a spatial nature grounded in the temporal-parietal-occipital (TPO) regions of the brain (Luria, 1947/1970, 1962/1966, 1973).

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Patients with semantic aphasia have difficulty in spatial orientation, mental rotation, and assembling the individual parts of a picture into a whole. Similarly, they cannot comprehend sentences in which the grammar specifies a binding relationship between two parts (e.g., *Put the circle above the square*, or *does March come before May?*). While currently semantic aphasia is not included in standard aphasia classification systems such as the Boston Diagnostic Aphasia Exam (Goodglass & Kaplan, 1983) or the Western Aphasia Battery (Kertesz, 1982, 2006), it is nevertheless widely used in Russia, and in Nordic and Spanish-speaking countries in Europe and South America (Ardila, 1999; Ardila, Ostrosky, & Canseco, 1981; Christensen, 1975; Christensen & Caetano, 1999; Peña-Casanova, 1991). In addition to formal clinical descriptions, Luria (1971/1987) documented a case of semantic aphasia in the book *The Man with a Shattered World: The History of a Brain Wound* based on the diary of his patient, Lev Zasetsky, who struggled with severe semantic aphasia after a penetrating bullet wound in the left parietal-occipital area.

As a topic of research discussions, semantic impairment in brain-damaged individuals is a critical component to understanding language processes. However, the term 'semantic' is often applied to different clinical profiles and their underlying disorders. Luria (1947/1970, 1962/1966, 1973) referred to the term as the ultimate integrated meaning of a phrase or a sentence, while other clinical and experimental studies have shown that brain injury may cause a specific impairment in understanding grammatically-expressed relations between referents and events (Ardila, Concha, & Rosselli, 2000; Dragoy et al., 2016; Hier, Mogil, Rubin, & Komros, 1980). While able to understand the meaning of single components of a sentence, such patients experience difficulty in relating them to one another and synthesizing the overall meaning of the utterance, especially in semantically-reversible sentences (e.g., *The boy is putting the bag into the box*). Such descriptions of 'semantic' disorders clearly relate the deficit to the sentence level and imply a lack of obvious lexical-semantic difficulties at the word level in these patients.

Another conceptualization of the term 'semantic' characterizes a large body of contemporary works, which introduced a division among several aspects of semantic cognition that could be independently impaired by brain pathology (Gainotti, 2014; Lambon Ralph, 2014; Lambon Ralph, Lowe, & Rogers, 2007; Rogers, Patterson, Jefferies, & Lambon Ralph, 2015; Whitney, Jefferies, & Kircher, 2011). These authors distinguish between the ability to understand the meanings of multimodal stimuli and the ability to manipulate this knowledge. Disturbance of the former aspect of semantic cognition results in degraded semantic representations and is typically caused by anterior temporal lobe neurodegeneration, bilaterally. Known as "semantic dementia", this clinical profile is characterized by progressive impairment of semantic memory affecting all modalities (Coccia, Bartolini, Luzzi, Provinciali, & Lambon Ralph, 2004; Luzzi et al., 2007). In contrast, disrupted executive regulation of semantic representations is reported for individuals with aphasia caused by stroke in the prefrontal or posterior temporal/inferior parietal regions of the left hemisphere (Corbett, Jefferies, Ehsan, & Lambon Ralph, 2009; Jefferies & Lambon Ralph, 2006; Robson, Sage, & Lambon Ralph, 2012). Also referred to as "semantic aphasia", this clinical profile features semantic retrieval problems under conditions of high semantic control demands rather than impaired access to semantic representations, per se (Noonan, Jefferies, Corbett, & Lambon Ralph, 2010). Notably, both types of semantic cognition disorders are manifested at the word level as far as language is concerned.

Although the two outlined semantic deficits – at the sentence level (Luria, 1947/1970, 1962/1966, 1973), and at the word level (Lambon Ralph, 2014) – are both derived from Henry Head's (1920, 1923) notion of semantic aphasia, at present the methods used to support these two accounts (theoretical models, testing materials, clinical groups) are too different to consistently integrate them. To shed more light on at least one side of the syndrome, this paper describes the history of semantic aphasia, with an emphasis on Luria's interpretation of the syndrome as a deficit in spatial analysis and synthesis, and reviews modern neuroimaging data supporting Luria's findings concerning the neuroanatomical underpinnings of this syndrome. Next, we provide 10 new cases of semantic aphasia with both their neuropsychological profiles and lesion neuroimaging data including the extent of white matter involvement, data that were not available to Luria at the time of his historical reports. Finally, our discussion, along with recognizing the great relevance of Luria's work for modern neuroscience, emphasizes the contribution of new evidence in the revision of the functional neuroanatomical model of semantic aphasia by also taking into account white matter pathways.

1.1. *Historical cases of semantic aphasia*

The history of semantic aphasia goes back to the clinical observations of Bonhoeffer (1923) who reported cases of aphasia associated with left-right confusion due to post–central lesions of the left cerebral hemisphere. Head (1920) was the first to introduce the syndrome in detail and coined the term "semantic aphasia" linking it to an "inability to appreciate and retain the full significance of words and phrases" (p. 142). He characterized this syndrome by patients' spared pronunciation, syntax, intonation, naming and comprehension of single words, along with undisturbed memory and spared intelligence, and viewed it as an impairment in the domain of "symbolic thinking" (p. 143) going well beyond the language domain. Patients with such deficits experienced significant difficulty in describing a picture (not able to appreciate its whole meaning, but pointing out one single detail after another); in drawing (especially a highly structured picture, e.g., a room plan); or when playing chess and cards or putting together puzzles (as one patient reported, "I can see the bits, but I cannot see any relation between the bits"; Head, 1920, p. 145). Head also observed problems with the "clock-test" (not setting the clock hands correctly in response to a command); in "hand, eye, and ear probes" (showing left-right confusion when asked, e.g., to touch the left ear with the right index finger); when asked to identify the relative spatial position of objects in the room (e.g., to say where the fireplace is in relation to the door); in daily-life spatial orientation; and even with simple arithmetical operations. Regarding language, such patients could not produce a coherent narrative when

asked to reproduce a heard or read story, omitting many essential elements; failed to comprehend jokes; and made writing errors originating from difficulty in pulling the letters together. Head (1920) conceptualized this complex disorder as a general impairment in recognizing the integrated meaning (overall semantics) of an event, be it at the level of words and phrases or expressed in other cognitive modalities. Further in the course of history, similar patients were reported in other classic works (e.g., Goldstein, 1927, 1934; Nielsen, 1936).

Luria (1947/1970) also adopted the notion of semantic aphasia proposed by Head (1920), but he further elaborated upon it from two perspectives. First, he identified in greater detail the major language-related characteristics of the disorder and suggested a comprehensive neuropsychological explanation of its linguistic and accompanying non-linguistic symptoms. Like Head (1920), Luria also reported a lack of problems with respect to speech fluency, auditory comprehension, reading and repetition of single words or simple phrases. But, Luria showed that impaired comprehension of particular types of linguistic constructions represented a characteristic feature of semantic aphasia. This would include several types of sentences, specifically: prepositional (*Draw a triangle above a circle*), instrumental (*Point to the key with the pencil*), comparative (*Sonja is taller than Katja*), genitive (*Father's brother*), passive (*Kolja-NOM is hit by Petja-INSTR*), inverted (*Kolja-ACC hit Petja-NOM*), temporal (*I had breakfast after I read the newspaper*), double negation (*I am not accustomed to not obeying rules*), and embedded clauses (*The worker came from the factory to the school, where Dunya studied, to give a talk*). Luria collectively referred to these as "logical-grammatical constructions" as they required the extraction of the logical relationship between the mentioned persons, objects or events from the grammatical markers within the sentence. He also highlighted their semantic reversibility as the main source of difficulty, arguing that persons with semantic aphasia could not extract the direction of the relationship.

Following the general ideas of Head (1920), Luria also conceptualized this distinctive linguistic deficit as an inability to integrate distinct linguistically-mediated elements into a unified, simultaneous, mental representation. He argued, for example, that phrases like *father's brother* do not refer to either of the mentioned persons, but rather to their relationship that produces a new referent – *the uncle*. Similar reasoning could be applied with respect to other logical-grammatical constructions, as well as to another frequently observed sign of semantic aphasia – impaired appreciation of figurative language, such as metaphors and set expressions like proverbs and humor. Non-literal linguistic expressions of the latter kind also require capturing the overall sense of the phrase, which is different from the additive meaning of its component parts. Finally, the unusual reading and writing profiles of individuals with semantic aphasia reflect their tendency to focus on groups of individual letters and their strategy to move from one such letter group to another, carrying the same characteristic features of an inability to recognize or produce a word as a whole.

Furthermore, similar to Head (1920), Luria integrated semantic aphasia into a broader neuropsychological context and linked these linguistic deficits (impairment of logical-grammatical constructions comprehension and figurative language appreciation, specific reading and writing profiles) to other cognitive disorders. Constructional apraxia (an inability to reproduce or rotate geometrical figures), body schema disorder (left-right confusion), as well as spatial agnosia (difficulty in integrating visual representations), frequently co-occur with semantic aphasia (Luria, 1947/1970). Calculations are also often impaired, with operations over ten being highly problematic. Patients do not recognize the difference between symmetrically-built numerals (such as 17 and 71, IV and VI) and experience difficulty with multi-digit numbers, erroneously breaking them into smaller parts. However, as compared to Head's clinical descriptions, Luria made a critical step forward in the explanation of the syndrome. He proposed that the underlying impairment of spatial analysis and synthesis caused deficient gnostic and praxic operations in real physical space, but was also responsible for the disturbance of abstract operations in mental quasi-space, mediating the comprehension of logical-grammatical constructions and figurative language, as well as manipulations with numbers (Luria, 1947/1970, 1962/1966). From this perspective, the same spatial component, i.e., a defect in the building and perception of simultaneous spatial structures, is represented across multiple cognitive domains and is responsible for all observed symptoms (Luria, 1973), including semantic aphasia and the other spatial disorders typically accompanying it. This exemplifies the essence of Luria's systemic approach to higher cognitive functions, according to which a single factor can lead to impairment of the various functions in which it is involved.

Although not widely recognized, the co-occurrence of semantic aphasia and specific non-linguistic symptoms highlighted by Head (1920) and Luria (1947/1970) was employed in more modern research. Hier et al. (1980) documented three English-speaking patients with impaired comprehension of characteristic syntactic constructions (comparative, temporal, passive, spatial) and concomitant complex spatial impairments (constructional apraxia, spatial agnosia, dyscalculia, and dysgraphia) due to lesions to the TPO junction of the left hemisphere. Ardila et al. (2000) reported a patient with Gerstmann's syndrome (including finger agnosia, left-right confusion, dyscalculia in this case, but minimal writing difficulties, which otherwise complete the clinical tetrad of Gerstmann's syndrome; Gerstmann, 1940) and linguistic deficit compatible with semantic aphasia (difficulties in understanding logical-grammatical relations, comparison, spatial and time adverbs). Seghier (2012) attributed a similar aggregation of cross-domain symptoms to the function of convergence of multisensory information and manipulation with mental representations, which echoes Luria's ideas. Finally, Ardila (2014) has recently made a further step in suggesting a unifying mechanism of semantic aphasia and the incomplete version of Gerstmann's syndrome (without agraphia), proposing that both result from the disturbance of verbally-mediated spatial knowledge. Although this proposal differs from Luria's original explanation, which referred to the spatial factor of a multi-modal nature, it is within the same vein of conceptualizing semantic aphasia and other concomitant cognitive impairments as space-related disorders.

The second contribution that Luria made with respect to semantic aphasia was the lesion analysis of patients. Although Head (1923) was the first who plotted the lesions of

his four semantic aphasia patients on the brain surface, Luria observed and carefully documented many more cases. Luria (1947/1970) extensively reviewed the functions of anterior occipital (Brodmann's areas, BA, 18 and 19), inferior parietal and TPO regions (BA 39 and 37) of the left hemisphere, suggesting them as the cortical areas responsible for the integration of isolated stimuli into simultaneous structures. In accordance with the state of knowledge at the time, Luria (1947/1970) associated these regions with gaze regulation, potentially driven by simultaneous schema, mechanisms of vestibular projections creating spatial coordinates, integration of optic and deep kinaesthetic representations, and bonding visual perception to speech acoustic traces. Referring to these functions of the affected brain structures, Luria later emphasized the role of spatial perception disturbances, and especially those of asymmetrical schemata, in semantic aphasia (Luria, 1965). At the same time, Luria noted that focal damage to visual cortex involving BA 18 and 19, or to regions bordering the anterior and superior parts of the inferior parietal lobule (BA 7, 40 and upper portions of BA 39) might cause minor or no impairment of logical-grammatical organization of speech, which only becomes prominent when the lesion is more extensive or encompasses the parietal cortex adjacent to the temporal and occipital areas (Luria, 1947/1970).

The original study by Luria (1947/1970) included 55 patients with traumatic injury to TPO areas; focal brain damage to other areas did not cause semantic aphasia. Luria presented a sample overlay of 12 patients' injury sites (see Fig. 1), to illustrate the relationship of semantic aphasia and the whole syndrome of a (quasi) spatial disorder to the TPO cortical region, and suggested these regions as their neuroanatomical substrate.

1.2. *Modern neuroimaging evidence*

Since Luria's time, the neural correlates of semantic aphasia as a part of an integral neuropsychological syndrome have rarely been investigated. However, modern neuroimaging research has confirmed the involvement of the left TPO area in specific aspects of linguistic and non-linguistic processing impaired in semantic aphasia (semantically complex syntactic constructions similar to Luria's logical-grammatical constructions – Richardson, Thomas, & Price, 2010; Thothathiri, Kimberg, & Schwartz, 2012; Wu, Waller, & Chatterjee, 2007; Yokoyama et al., 2007; locative constructions – Amorapanth et al., 2012; Amorapanth, Widick, & Chatterjee, 2010; Noordzij, Neggers, Ramsey, & Postma, 2008; Tranel & Kemmerer, 2004; Wu et al., 2007; non-literal language – Benedek et al., 2014; Bohrn, Altmann, & Jacobs, 2012; Chen, Widick, & Chatterjee, 2009; Rapp, Mutschler, & Erb, 2012; calculations – Arsalidou & Taylor, 2011; Baldo & Dronkers, 2007; Dehaene, Piazza, Pinel, & Cohen, 2003). In addition, a multimodal or integration role of this region is also supported by recent studies (Baldo, Bunge, Wilson, & Dronkers, 2010; Binder, Desai, Graves, & Conant, 2009; Hasson, Yang, Vallines, Heeger, & Rubin, 2008; Hinton, Dymond, von Hecker, & Evans, 2010; Humphreys, Hoffman, Visser, Binney, & Lambon Ralph, 2015; Humphreys & Lambon Ralph, 2015; Lerner, Honey, Silbert, & Hasson, 2011).

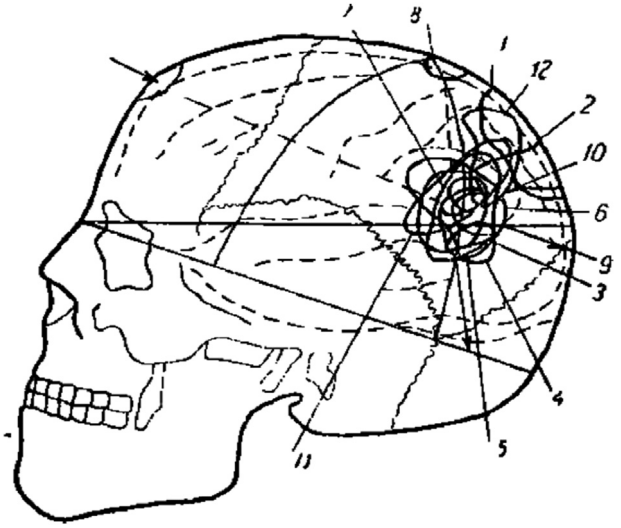

Fig. 1 – Lesion overlay of 12 patients with semantic aphasia (Luria, 1947). Reprinted from "*Travmaticheskaya afaziya*" [Traumatic aphasia], A. R. Luria, Chapter 7, p.164. © 1947, Editing House of Academy of Medical Sciences, with permission of E. G. Radkovskaya.

Regarding specific linguistic components relevant to semantic aphasia, an fMRI study by Yokoyama et al. (2007) showed that in healthy people, processing of passive sentences elicited greater activation than active sentences in the left frontal operculum and the inferior parietal lobule. Left temporal-parietal activation was found for reversible versus non-reversible sentence comprehension by Richardson et al. (2010), which was related to the subarticulatory component of phonological working memory heavily involved in processing reversible sentences, since the same area was also found active in the repetition task. Converging with these results, Thothathiri et al. (2012) investigated impaired reversible sentence comprehension in patients using voxel-based lesion-symptom mapping (VLSM) and revealed significant voxels at the border of the left temporal and parietal lobes (BA 21/22 and BA 39/40). However, in contrast to Richardson et al., (2010) findings, they showed that the role of these regions in reversible sentence processing was not reduced to supporting phonological memory functioning: when phonological memory tasks (rhyme probe spans and repetition scores) were added as covariates in the VLSM analysis, it also yielded significant voxels in the same temporal-parietal areas. Comprehension of locative constructions and thematic role assignment was tested in another VLSM study by Wu et al. (2007), who found that behavioral scores on both tasks correlated, along with the overlapping neural substrate for both deficits in the anterior superior temporal gyrus and the inferior prefrontal cortex of the left hemisphere. In this study, specific lesion sites associated with impaired comprehension of locative constructions were identified in the left inferior fronto-parietal cortex and the posterior temporal–parietal junction, while the thematic role assignment deficit correlated with damage to the mid-portion of the left middle temporal and superior temporal gyri.

A number of other studies focused on the comparison of linguistically-mediated and non-linguistic spatial processing. Tranel and Kemmerer (2004) performed a lesion subtraction analysis in patients with focal brain damage and showed that

impaired knowledge of locative prepositions (tested in production, comprehension and semantic analysis tasks) was associated with the left frontal operculum, the supramarginal gyrus and the underlying white matter. An fMRI study of neural correlates of locative constructions such as *to the left of* or *to the right of* (Noordzij et al., 2008) only revealed a significant increase of activation in the left supramarginal gyrus (BA 40), independent of the context (visual or verbal) in which prepositions were presented; the involvement of the left frontal operculum was not found. Amorapanth et al., (2010) showed greater activation in the superior and inferior parietal cortices (especially on the left) and the posterior middle frontal cortices bilaterally specific to judging categorical spatial relations between objects. An accompanying VLSM study confirmed that impairment of categorical spatial judgment corresponded to the damage to the left inferior frontal, supramarginal, and angular gyri. Amorapanth et al. (2012) performed another VLSM study testing spatial processing in different modalities (words, pictures, and schemas) in patients with focal left and right hemisphere damage: verbal spatial processing was found associated with the left middle frontal, posterior and superior temporal gyri, premotor and primary motor cortex, and the white matter underlying the supramarginal gyrus; the pure spatial representation deficit was hardly distinguishable from the deficit of labelling these relations verbally.

The left TPO region was also reportedly involved in non-literal language processing. Bohrn et al. (2012) reviewed available fMRI evidence and reported peak activations in portions of the left temporal lobe, as well as the left and right inferior frontal gyri, bilateral medial frontal gyri for non-literal versus literal language comprehension, and the left amygdala region as far as specifically figurative versus literal language was concerned (Rapp et al., 2012). Unlike the majority of findings on comprehension of non-literal language, a recent fMRI study (Benedek et al., 2014) investigating metaphor production reported focal activity in the left angular gyrus extending to posterior parts of the middle temporal gyrus and adjacent occipital regions, in the dorsal-medial middle frontal gyrus and the dorsal superior frontal gyrus, in bilateral parahippocampal and fusiform gyri, as well as in the left lingual gyrus and the right posterior cerebellum, when contrasting metaphor to literal language production tasks.

Yet another component of semantic aphasia, number processing, was conceptualized by Dehaene et al. (2003) within a tripartite model, where the horizontal segment of the intraparietal sulcus was associated with domain-specific number processing, the bilateral superior posterior parietal system related to attentional orientation of mental number line, and the left angular gyrus area supported verbal forms of number manipulations (such as precise calculation compared to approximation). A meta-analysis of fMRI studies investigating the neural basis of calculation (Arsalidou & Taylor, 2011) revealed that for both number and calculation tasks, left inferior and superior parietal regions were relevant, together with prefrontal regions involved in calculation tasks. The investigation of the relationship between arithmetical ability and language processing using VLSM (Baldo & Dronkers, 2007) showed that arithmetic operations were associated with the left inferior parietal areas (supramarginal and angular gyri), while language comprehension of reversible active and passive sentences revealed a number of foci mainly in the left middle and superior temporal gyri. The common regions between comprehension and arithmetic maps included portions of the left middle and superior temporal gyri and the inferior frontal gyrus.

In addition to the contribution of regions at the intersection of the temporal, parietal and occipital lobes to specific aspects of language and spatial processing relevant to semantic aphasia, some modern neuroimaging evidence also supports an integrative role of these regions. The left posterior inferior parietal lobule and the lateral temporal cortex (middle and parts of the inferior temporal gyri) are acknowledged to be a part of a domain-general semantic system of the human brain (Binder et al., 2009). Damage to posterior temporal/inferior parietal regions of the left hemisphere (Corbett et al., 2009) were also associated with disrupted executive regulation of semantic representations by some authors (Jefferies, 2013; Noonan et al., 2010). Reviewing fMRI evidence and converging it with lesion studies, Binder et al. (2009), in agreement with Geschwind (1965), suggested that the left angular gyrus located at the junction of visual, spatial, auditory, and somatosensory association regions can perform a function of supramodal integration, which is important for behaviors requiring rapid conceptual combination, such as sentence comprehension and discourse, in particular. In the same vein, Baldo et al. (2010) showed that impaired relational reasoning was associated with the damage to the left middle and superior temporal gyri and the inferior parietal cortex; Hinton et al. (2010), using a relation processing task, found a symbolic distance effect in the left inferior frontal, dorsolateral prefrontal and bilateral parietal cortices. The fMRI studies of temporal receptive windows mapping during nonverbal visual (Hasson et al., 2008) and verbal auditory (Lerner, et al., 2011) narrative perception showed that higher-order information (forward, but not backward or piece-wise scrambled silent films; and intact paragraphs and entire stories, but not backward, word- or sentence-scrambled stories) revealed the longest temporal receptive windows that mapped to cortical regions overlapping in BA 39 and 40, lateral BA 7 and posterior BA 22 (Lerner, et al., 2011). In a meta-analysis of functional neuroimaging studies focusing on the parietal cortex, Humphreys and Lambon Ralph (2015) demonstrated that overlapping regions in the left angular gyrus were engaged for automatic semantics, episodic retrieval, numerical fact retrieval, and sentence-level tasks; and overlapping areas in the left supramarginal gyrus were involved in phonological and bottom-up attention processes. The authors concluded that ventral parietal regions support verbal and non-verbal, domain-general stimulus-driven automatic processes (in contrast to the dorsal parietal engagement for goal-directed executively demanding tasks). Some studies (e,g., Humphreys et al., 2015, that focused on the role of the anterior temporal lobe and angular gyrus within the default mode and semantic networks) claim that unlike the anterior temporal lobe, there is little evidence that the angular gyrus is involved in semantic representation, and emphasized its multimodal domain-general function.

Taken together, modern neuroimaging findings generally support Luria's claims about involvement of the left inferior

parietal cortex and adjacent temporal-occipital areas in deficits characteristic of semantic aphasia. However, very often the involvement was not restricted to those areas and extended to the left frontal cortex (Amorapanth et al., 2012; Arsalidou & Taylor, 2011; Baldo & Dronkers, 2007; Benedek et al., 2014; Bohrn et al., 2012; Wu et al., 2007), subcortical areas (Amorapanth et al., 2012; Tranel & Kemmerer, 2004) or right hemisphere structures (Amorapanth et al., 2010; Benedek et al., 2014; Bohrn et al., 2012). With the goal of investigating the neuroanatomy of semantic aphasia in more detail, using modern neuroimaging techniques not available to Luria, we retrospectively studied 10 contemporary patients with semantic aphasia. In the following sections, we describe their neuropsychological profiles and structural brain images providing new data on the brain–behavior relationship of semantic aphasia to the left cortical TPO junction and structures beyond these classical regions proposed by Luria.

2. Material and methods

2.1. Participants

All patients included in the study were native speakers of Russian, premorbidly right-handed except one patient who reported herself left-handed in childhood but forced to use her right hand. Their mean age (and range) was 57 years (33–71), education – 13 years (8–15), months post-onset – 22 (2–61); seven were females. Seven of them became aphasic due to a single left-hemisphere stroke, two had multiple left-hemisphere strokes, and one patient had a stroke in the right hemisphere. Table 1 summarizes patients' demographic and clinical information.

The patients were admitted to the Center for Speech Pathology and Neurorehabilitation in Moscow, Russia, between 2012 and 2015, where they received a six-week intensive rehabilitation course targeting language (at least 3 h of speech therapy per day), cognitive and motor functions. The patients signed informed consent for using their clinical profiles and demographic information for statistical and research purposes. The study was approved by the Committee on Interuniversity Surveys and Ethical Assess of Empirical Research of the National Research University Higher School of Economics.

2.2. Neuropsychological assessment

To guide their rehabilitation, within a few days after admission to the Center for Speech Pathology and Neurorehabilitation, all patients went through an extensive neuropsychological examination of the major cognitive domains (praxis, gnosis, memory, arithmetic, intellect, speech, reading and writing) performed by clinical neuropsychologists and speech-language pathologists of the Center. Neuropsychological status (including aphasia type) was determined using Luria's classification system (Akhutina, 2015; Luria, 1962/1966). All patients included in the current study were diagnosed with semantic aphasia. Because of the rarity of this syndrome in isolation, we did not exclude cases whose

Table 1 – Demographic and clinical information about patients.

Patients	Age	Sex	Handedness	Education, years	Number of strokes	Type of stroke	Post onset, months	Diagnosed aphasias	Aphasia severity	Other diagnosed deficits	Scans obtained, months post onset
1	57	M	Right handed	12	1	Ischemic	61	Semantic, acoustic-mnestic, sensory	3	Kinetic manual apraxia, apractagnosia, discalculia	36
2	56	M	Right handed	15	3	1st – hemorrhagic, others - ischemic	28	Semantic, acoustic-mnestic	1	Kinetic and kinesthetic manual apraxia, spatial contructional apraxia, spatial apractagnosia	4
3	70	M	Right handed	8	1	Ischemic	48	Semantic, acoustic-mnestic, efferent motor	2	Kinesthetic apraxia, dynamic apraxia, spatial contructional apraxia, optico-spatial agnosia	48
4	71	F	Right handed	15	1	Ischemic	14	Semantic, acoustic-mnestic	2	–	26
5	61	F	Right handed	8	2	Ischemic	6	Semantic, efferent motor	1	Spatial contructional apraxia	35
6	52	F	Right handed	12	1	Hemorrhagic	4	Semantic, acoustic-mnestic	3	–	4
7	43	F	Right handed	15	1	Ischemic	29	Semantic, acoustic-mnestic, sensory	1	Spastic-rigid disarthria; dynamic apraxia, somato-spatial apractagnosia	29
8	33	F	Right handed	15	1	Ischemic	7	Semantic	2	Apractagnosia	7
9	64	F	Born left handed, forced to relearn	15	1	Hemorrhagic	18	Semantic, efferent motor	3	Manual dynamic apraxia, modality-non-specific memory disorder	15
10	66	F	Right handed	12	1	Ischemic	2	Semantic	1	Spatial apractagnosia, acalculia, disrithmia	3

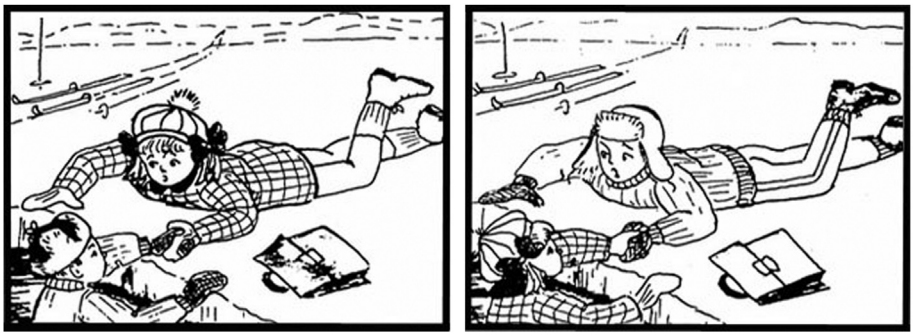

Fig. 2 – Picture stimuli for the probe "*The boy-ACC rescued the girl-NOM*" (Tsvetkova et al., 1981).

semantic aphasia was combined with other linguistic deficits.[1] Aphasia severity ranged in this group from 1 to 3 on a 1–5 scale, with 1 representing mild impairment and 5 representing severe disability, as measured by the Assessment of Speech in Aphasia (Tsvetkova, Akhutina, & Pylaeva, 1981), a standardized tool for quantitative speech and language assessment in Russian. The test includes 8 subtests targeting speech production (object and action naming, sentence production, speech production in a dialogue, narrative production) and speech comprehension (object and action picture matching, comprehension of instructions, complex syntactic constructions and speech in a dialogue) and provides a generalized measure of linguistic impairment.

In accordance with Luria's guidelines (1962/1966), the testing of multimodal sensory and symbolic spatial analysis and synthesis can identify difficulty in (quasi) spatial processing. Several tests included in modern neuropsychological investigations used in Russian clinical institutions are the most revealing in this regard. These probe the comprehension of logical-grammatical constructions and figurative linguistic expressions, reading and writing, spatial constructional praxis, visual spatial gnosis, somatospatial praxis, and calculation. In all tests, no time limit is imposed, and breaks are made whenever a patient needs one. Detailed rationales behind each type of probe and guidelines for their evaluation are explained in Chapter 3 of the seminal volume *Higher Cortical Functions in Man* by Luria (1962/1966).

In brief, comprehension of logical-grammatical constructions was tested in a sentence-picture matching task using reversible passive sentences like *The car is carried by the tractor*, inverted active sentences like *The boy-ACC rescued the girl-NOM*, and prepositional phrases like *The box is on the barrel* (see Fig. 2 for an example); in a drawing task using reversible instructions with prepositions (e.g., *Draw a circle in a square*); and in a sentence interpretation task using comparative (*Tanya is younger than Marina. Who is older?*), inverted (*Vova-ACC overtook Sasha-NOM. Who arrived first?*) and temporal (*Breakfast after lunch. Can that happen?*) constructions.

Non-literal language appreciation was probed in a metaphor (e.g., *Lion's share*) and proverb (e.g., *Don't count your chickens before they're hatched*) interpretation task. Automatized writing (patient's name), copying a sentence and writing to dictation were used to assess the status of writing. Reading was probed with single words, phrases and a text.

In the non-linguistic domains, spatial constructional praxis was assessed in several tasks: copying a cube and a table with some hidden edges (Fig. 3a), setting time-blind clocks to different times (4:30, 8:20, 2:50, 20:45), and mirror reflection of complex figures (Fig. 3b).

Probes for visual spatial gnosis included telling the time from the blind clocks, matching spatial schemes with prepositions (see Fig. 4) and orienting within a geographical map. Somatospatial praxis was assessed using the Head probes (imitation of hand movements).

Calculation probes required simple arithmetic operations (e.g., 5 + 3=…), comparison of numbers (e.g., *1740* and *1704*) and more extended math tasks (e.g., *The housewife uses 15 L of milk in five days. How much milk does she use per week?*).

2.3. *Brain imaging*

The structural MRI data were used to assess the involvement of different cortical and white matter structures in each patient. MRI images were acquired on the Center's 1.5 T S Magnetom Avanto scanner. Scans may have occurred at different time points in relation to the neuropsychological assessment (either preceding or following it), but in no case did any additional neurological accident occur between the MRI acquisition and the assessment. Also, all MRI data were obtained at least three months post onset, which assured the stability of the lesion (see Table 1 for precise scanning time). For all patients, high-resolution T1 images were obtained using an MPRAGE sequence [repetition time = 1900 msec, echo time = 3.37 msec, field of view = 192 × 256 mm (Patients 1–2) or 256 × 256 mm (Patients 3–10), slice thickness = 1 mm, 176 axial slices]. T2 images [repetition time = 5000 msec (4000 msec in Patient 10), echo time = 93 msec, field of view = 208 × 230 mm (230 × 230 mm in Patient 4), slice thickness = 5 mm (4 mm in Patient 8), 22 axial slices (28 in Patient 8)] and FLAIR [repetition time = 9000 msec, echo time = 89 msec, field of view = 201 × 230 mm, slice thickness = 5 mm (4 mm in Patient 8), 22 axial slices (28 in Patient 8)] were also available for all patients except Patient 5. During the preprocessing stage, the images were manually oriented to the AC-PC plane, the T1 was co-registered and resliced to the MNI152 T1 1 mm template using 4-th degree B-spline transformation, and T2 and FLAIR images were co-

[1] Luria's neuropsychological approach allows the diagnosis of multiple aphasia types if several distinct underlying neuropsychological factors are identified.

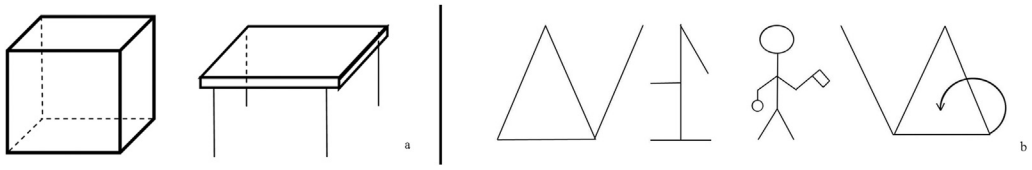

Fig. 3 – Picture stimuli for copying (a) and mirror reflection (b).

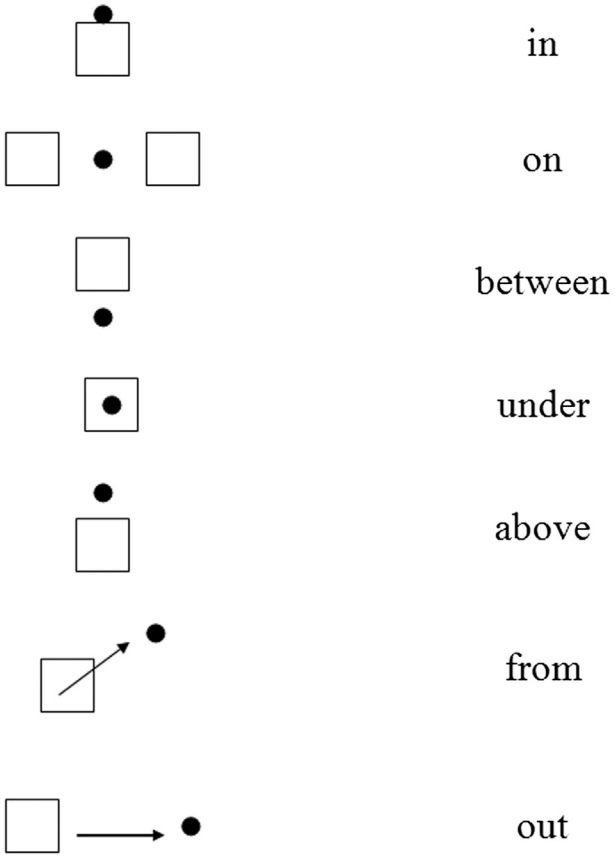

Fig. 4 – Stimuli for matching spatial schemes (items in the left column) with prepositions (written in the right column).

registered and resliced to the new T1 using trilinear transformation in the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm).

The lesions were manually delineated in MRIcron by visually assessing the preprocessed native anatomical T1 images. When available, preprocessed T2 and FLAIR images were used to verify the lesion, and also to extend its borders by including the surrounding visible gliosis and hemosiderin. In the two cases of multiple strokes, the lesions related to all cerebrovascular accidents were delineated (all three strokes of Patient 2 affected the same left parietal-occipital region and thus could be similarly symptomatic; Patient 5 had a small frontal and a larger parietal lesion). Lesioned tissue that was not related to the major cerebrovascular accident (e.g., white matter disease, small lacunar infarctions, etc.) was not delineated. The lesion masks were then normalized to MNI152 T1 1 mm space using a modified SPM8 script. Cost function masking was used to avoid distortions due to the presence of the lesion (Brett, Leff, Rorden, & Ashburner, 2001). The normalized scans were visually assessed after the normalization procedure and compared to the lesion on the native scan. The most frequent incongruity between the native and normalized lesions was the degree of damaged tissue around the enlarged posterior horns of the ventricles. This normalization error was corrected manually by a colleague experienced in lesion reconstruction, but blind to the purpose of the study, using ITK-snap software (Yushkevich et al., 2006; www.itksnap.org).

The lesion overlay of the ten patients' 1 mm normalized images over the MNI152 T1 1 mm template was generated in MRIcron. To determine which cortical areas were affected, the masks of lesion overlays were created using the *ImCalc* function in SPM8. The involvement of specific cortical structures in the overlay masks, as well as in individual lesion masks, was analyzed in MRIcron (https://www.nitrc.org/projects/mricron; *Version 1 June 2015*) applying the function *Batch Descriptives* with the Automated Anatomical Labeling (AAL) built-in template using 1 mm thick images. In view of increasing evidence of the involvement of different white matter pathways in language processing (e.g., Dick, Bernal, & Tremblay, 2014; Dick & Tremblay, 2012; Turken & Dronkers, 2011), damage to individual fiber tracts was also investigated. For this purpose, maps of white matter pathways derived from a group of healthy controls (Rojkova et al., 2015) were used to quantify the probability of a tract being disconnected (Thiebaut De Schotten et al., 2014) using Tractotron software as part of the BCBtoolkit v2.0 (http://www.brainconnectivitybehaviour.eu).

To identify the cortical regions critical for semantic aphasia as predicted by Luria (BA 18, 19, 37 and 39), we used the Online Brain Atlas Reconciliation Tool (http://qnl.bu.edu/obart/; Bohland, Bokil, Allen, & Mitra, 2009). These Brodmann's areas were selected in the Talairach Daemon cell-level Atlas (TALc) and laid over the AAL map; an overlap of more than 5% (either by the %Contained in or %Contains measure) was included. This procedure resulted in the following list of left hemisphere cortical structures, according to the AAL atlas: angular gyrus, calcarine sulcus, cuneus, fusiform and lingual gyri; inferior, middle and superior occipital gyri; inferior parietal lobule; inferior and middle temporal gyri. To keep to the formal analysis, we did not distinguish between the different subcomponents of gross anatomical structures that Luria referred to (e.g., the anterior and posterior portions of the occipital regions); nevertheless, for reasons of convenience, we will further refer to the list of AAL structures mentioned above as "Luria's list".

3. Results

3.1. Neuropsychological profiles

Individual patients' performance on tests, which are critical for diagnosing difficulty with (quasi) spatial analysis and synthesis, are summarized in Table 2.

All 10 patients were impaired in the comprehension of logical-grammatical constructions. They made errors in tasks of matching reversible sentences to one of two presented pictures depicting reversed events, drawing to reversible instructions containing prepositions, and the interpretation of other types of logical-grammatical constructions (comparative, inverted and temporal). Interpretation of metaphors and proverbs was problematic for six patients only. Seven patients had impaired writing; in most cases it was accompanied by a facilitating strategy to speak words out by sounds or syllables. Reading was basically spared in all patients, but Patients 3, 5, 7 and 9 featured slowed, chanting reading by syllables. In the non-linguistic domains, spatial constructional praxis was the only function that was consistently impaired in this cohort of patients. Visual spatial gnosis was compromised in seven of the ten patients. Somatospatial praxis was found to be impaired in five of them. Seven patients were impaired in calculation: even if they were able to perform simple arithmetic operations, comparison of numbers and extended math tasks were problematic.

As an individual example, Patient 1 demonstrated a typical profile of semantic aphasia, with difficulty of a spatial nature expressed in multiple cognitive domains. While being able to correctly comprehend irreversible sentences (e.g., *The boy is lying on the carpet*), he could not match any reversible sentence to the relevant picture, nor interpret any comparative, inverted or temporal sentence. He produced the drawing presented in Fig. 5 to the instruction *Draw a circle in the square*. Thus, logical-grammatical constructions were severely compromised in this patient. Most of the metaphors and proverbs tested were not properly interpreted.

In addition, Patient 1 made errors in the blind clock probe (see Fig. 6a) and in the mirror reflection probe (Fig. 6b), thus showing deficits in spatial constructional praxis. Visual spatial gnosis was also impaired as shown in the clock probe (Fig. 6c).

Only simple arithmetic operations using the numbers 1–10 were available to him. Writing was severely impaired: the patient could not integrate letters into holistic words.

In contrast to Patient 1, other patients were not as consistently impaired in all the tested domains. For example, Patients 2, 4 and 7 showed no signature of deficient visual spatial gnosis; Patients 2, 6 and 8 had no writing impairments, while Patients 2, 6, 9 had spared calculation abilities. Patients 3, 4, 5 and 9 experienced no difficulty in interpreting non-literal linguistic expressions. However, every patient in this group, in addition to the obligatory impairment of logical-grammatical constructions comprehension and spatial constructional praxis, showed deficits in at least several other relevant domains. Critically, the quality of the errors confirmed that the underlying reason for these deficits was of spatial nature. For example, Patients 6 and 10 demonstrated visual spatial discoordination in the blind clock probe (Fig. 7a); Patients 2 and 8 experienced confusion between left and right hands in the Head probe for somatospatial praxis; Patient 3 made errors in matching Roman and Arabic numerals due to

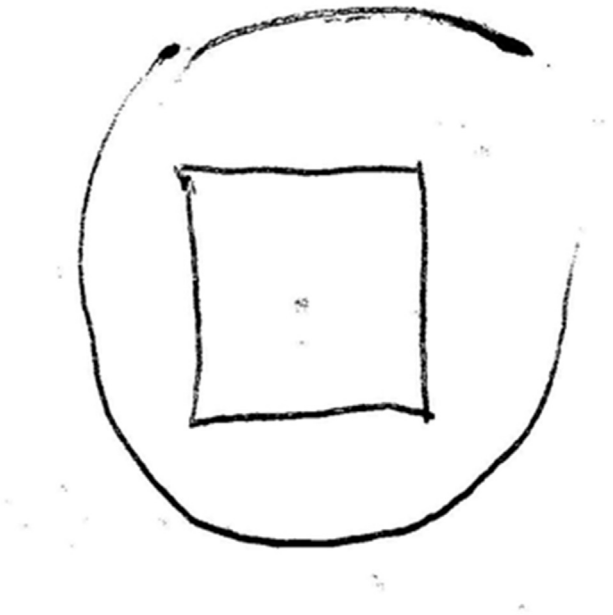

Fig. 5 – An error of Patient 1 in the probe "*Draw a circle in the square*".

Table 2 – Individual patients' performance on neuropsychological tests.

Functions tested	Patients									
	1	2	3	4	5	6	7	8	9	10
Logical-grammatical constructions	–	–	–	–	–	–	–	–	–	–
Metaphors	–	–	+	+	+	–	–	–	+	–
Writing	–	+	–	–	–	+	–	+	–	–
Reading	+	+	–	+	–	+	–	+	–	+
Spatial constructional praxis	–	–	–	–	–	–	–	–	–	–
Visual spatial gnosis	–	+	–	+	–	–	+	–	–	–
Somatospatial praxis	–	–	–	N.A.	+	N.A.	–	–	N.A.	+
Calculations	–	+	–	–	–	+	–	–	+	–

Note: – denotes an impaired function, + denotes a spared function, N.A. – the function was not assessed.

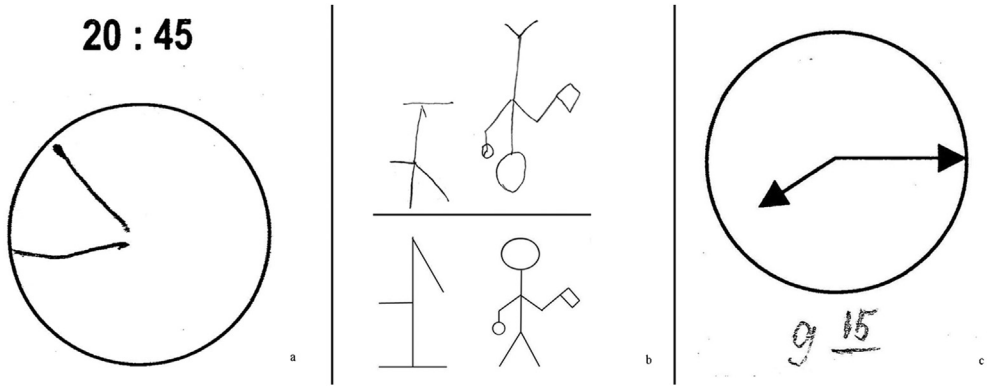

Fig. 6 – Errors of Patient 1 in setting the time on the blind clock (a), in the mirror reflection probe (patient's drawings on top, sample shapes to copy on the bottom; b), in telling the time from the set clock (c).

spatial transposition of elements (see Fig. 7b); restrictions on articulating words syllable by syllable and thus forcing the patient to rely on the whole word image reproduction rather than on the analytical strategy, boosted writing errors in Patients 4, 5 and 9; Patient 7 missed the holistic meaning of proverbs and tried to interpret them literally, e.g., *Don't count your chickens before they're hatched* as *Count if any of them died or not, survived or not.*

3.2. *Lesion analysis*

As a result of the lesion overlay of the ten patients' images (see Fig. 8), significant common areas of overlap were seen in no more than six patients. Mapping the lesion overlays to the AAL atlas resulted in identification of the affected cortical areas presented in Table 3. The cortical regions matching the Luria's list are highlighted in bold.

For our 10 current cases, a lesion overlay analysis using the overlay of at least four patient masks revealed a list of impaired left white matter pathways, which were anterior commissure; anterior thalamic projections; arcuate fasciculus, anterior, long and posterior segments; cingulum, including anterior and posterior segments; corpus callosum; corticospinal tract; face U-shaped tract; fornix; frontal aslant tract; frontal commissural tract; frontal inferior and superior longitudinal tracts; fronto-insular tracts 3 and 4; fronto-striatal projections; hand inferior, middle and superior U-shaped tracts; inferior fronto-occipital fasciculus; inferior longitudinal fasciculus; optic radiations, pons, and the three divisions of superior longitudinal fasciculus.

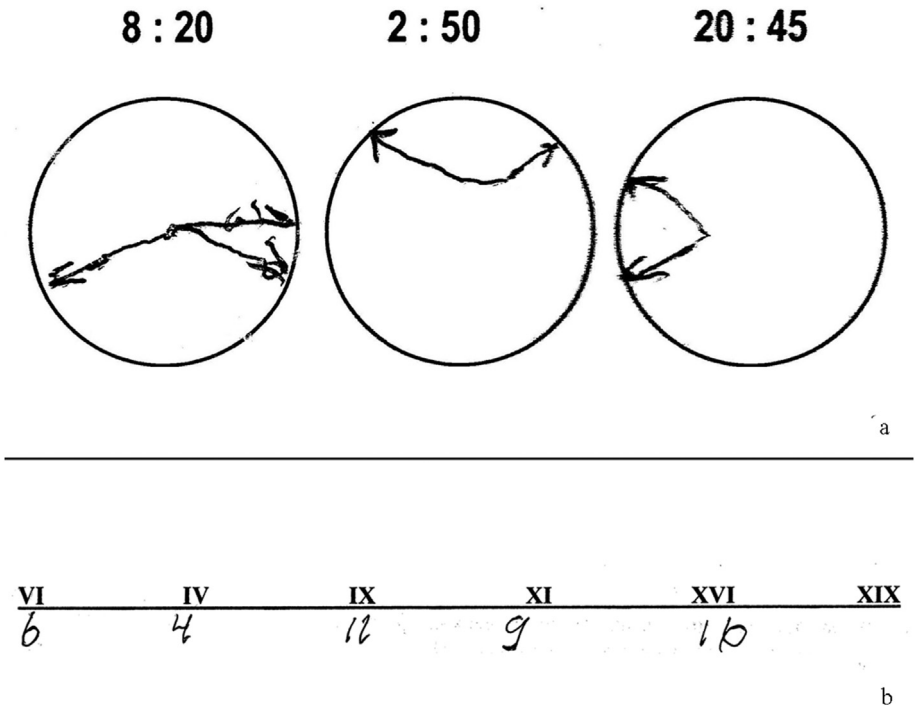

Fig. 7 – Discoordination errors of Patient 10 in the blind clock probe (a), errors of Patient 3 in matching Roman and Arabic numerals (IX, XI, XVI; b).

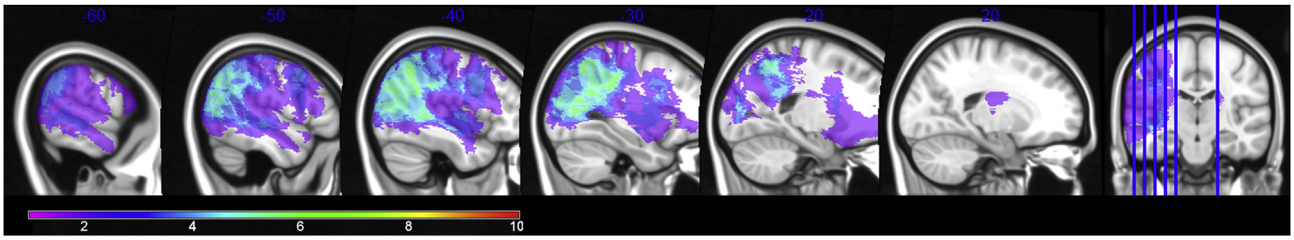

Fig. 8 – Lesion overlay of ten patients with semantic aphasia.

Table 3 – Percentage of left hemisphere regions from the AAL atlas involved in the lesion overlays of areas affected in six, five, and four patients, respectively.

AAL regions	6 Patients' overlay	5 Patients' overlay	4 Patients' overlay
Left angular gyrus	10.7	59.6	88.9
Left middle occipital gyrus	2.8	26.8	55.2
Left inferior parietal lobule	2.3	18.2	44.0
Left superior parietal lobule	1.6	12.0	24.0
Left middle temporal gyrus		3.6	11.4
Left supramarginal gyrus			7.2
Left postcentral gyrus		1.1	3.0
Left inferior occipital gyrus			.5

Note: The values represent the percentage of the voxels in each structure intersecting with the overlay. Only the structures for which the percentage of intersecting voxels equals or exceeds .5% are reported.

Table 4 summarizes the correspondence between the individual lesions and Luria's list. At the individual level, contrary to Luria's predictions, the lesions did not always involve the cortical structures outlined by Luria (1947/1970).

As far as the cortex is concerned, Patients 6, 7, 9 and 10 showed a pattern that was different from the other patients (see Fig. 8 for the images of 1 mm lesion masks over MNI152 T1 1 mm template). They had minor (Patient 7) to no (Patients 6, 9) involvement of the left angular gyrus and inferior parietal lobule, and the occipital lobe was spared in all four. Patient 10's lesion was in the right hemisphere, which made her case noteworthy to begin with; and none of the regions homologous to Luria's list were affected. The analysis of individual lesion mask intersections with the AAL atlas demonstrated damage to a variety of grey matter structures. In Patient 6 (see Fig. 9a), the left middle temporal gyrus was impaired, and the lesion also involved the left inferior and superior temporal gyri. The list of structures lesioned in Patient 7 was vast and included left putamen, inferior frontal gyrus – pars opercularis, insula, precentral gyrus, rolandic operculum, globus pallidus, caudate nucleus, superior temporal pole, and also parts of superior temporal, middle frontal, supramarginal, angular, transverse temporal, middle temporal, postcentral gyri; amygdala, hippocampus, inferior frontal gyrus – pars triangularis, and inferior parietal lobule (Fig. 9b). Patient 9 also had a lesion mainly involving the frontal parts of the brain (Fig. 9c), including left putamen, amygdala, superior frontal gyrus – orbital part, insula, caudate nucleus, olfactory cortex, medial orbitofrontal cortex, middle frontal gyrus – orbital part, inferior frontal gyrus – pars orbitalis, medial frontal gyrus; there was also some involvement of gyrus rectus, hippocampus, superior frontal gyrus, rolandic operculum, anterior cingulate gyrus, globus pallidus, superior temporal pole, parahippocampal gyrus, transverse temporal gyrus, inferior frontal gyrus – pars opercularis and triangularis, and middle temporal gyrus. The grey matter lesion of Patient 10 was restricted to the right hemisphere basal ganglia and encompassed the caudate nucleus, putamen and thalamus (Fig. 9d). Note that only the structures for which the percentage of voxels intersecting with AAL structures equaled or exceeded .5% are mentioned.

The discrepancy between these patients' clear semantic aphasia symptoms and the lack of cortical damage in the areas of Luria's list warranted a further investigation of the white matter tracts damaged in this cohort of patients. Table 5 presents the white matter tracts that were affected in at least four patients (according to the overlay analysis) and their damage in individual patients. In order to determine the tracts with the highest probability of disconnection, a *k*-means cluster analysis was performed using Dell Statistica 13.0 software. Three clusters were defined as having a high, medium, or low probability (see Table 6). The mean probability of the tracts disruption was .76 for Cluster 1, .42 for Cluster 2 and .92 for Cluster 3.

4. Discussion

Luria (1947/1970) explicitly linked a specific language deficit to a broader impairment of spatial analysis and synthesis, suggesting a comprehensive explanation of linguistic, non-linguistic symbolic (calculation), gnostic, and praxic problems that he observed in some of his patients. At the linguistic level, the deficit primarily manifested as difficulty in interpreting so-called logical-grammatical constructions (prepositional, instrumental, comparative, genitive, passive, inverted, temporal, double negation, and embedded clauses) – all of which required decoding semantically-reversible relations between referents or events from grammatical markers and integrating them into a holistic mental schema. Co-occurring problems in appreciating the sense of figurative language, as well as specific reading and writing errors were also suggested by Luria as reflecting difficulties with building integrated

Table 4 – Cortical regions from Luria's list involved in patients' lesions.

Luria' list	Patients									
	1	2	3	4	5	6	7	8	9	10
Angular gyrus	99.0	73.9	99.3	100	15.2		4.2	66.6		
Calcarine sulcus		7.8	.7							
Cuneus	.9	21.7	.7							
Fusiform gyrus		3.2								
Lingual gyrus		3.1								
Inferior occipital gyrus	7.5	20.8	15.8		.5			24.5		
Middle occipital gyrus	57.4	66.9	74.5	49.9	43.5			38.5		
Superior occipital gyrus	2.0	48.8	9.0	3.5	25.1					
Inferior parietal lobule	92.8	38.3	88.6	63.4	19.6		.8	18.3		
Inferior temporal gyrus	7.1	5.6	1.0			2.6		.9		
Middle temporal gyrus	66.2	22.1	18.6	14.3	1.2	32.6	3.5	5.4	.5	

Note: The values represent the percentage of the voxels in each structure intersecting with the lesion mask. Only the structures for which the percentage of intersecting voxels equals or exceeds .5% are reported. For Patients 1–9 the labels in the first column refer to the left hemisphere structures. The corresponding right hemisphere structures of Patient 10 were all intact.

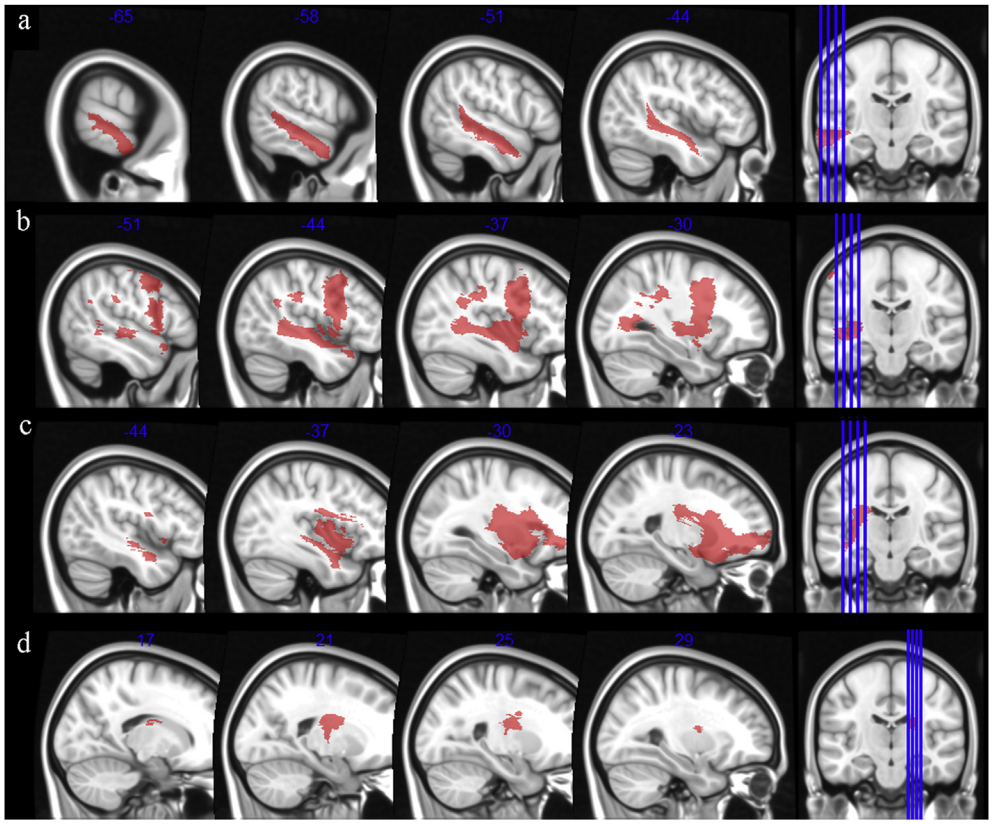

Fig. 9 – Lesion reconstructions of Patients 6 (a), 7 (b), 9 (c), and 10 (d).

representations. With respect to other cognitive functions, the syndrome included dyscalculia, constructional apraxia, body schema disorder, spatial agnosia, again attributed to disturbances of a spatial nature. Thus, Luria suggested a single spatial factor underlying operations both in real physical space, relevant to gnosis and praxis, and in mental quasi-space, critical for comprehension of logical-grammatical constructions, figurative language and calculations, and thus merged the linguistic disorder of semantic aphasia with other disturbances across multiple cognitive domains (Luria, 1947/1970, 1962/1966).

The neuropsychological profiles of 10 modern patients corresponded closely with the cases reported by Luria and matched Luria's interpretation of the syndrome. The tests used to diagnose semantic aphasia included probing both linguistic (logical-grammatical constructions and figurative linguistic expressions, reading and writing) and non-linguistic (spatial constructional praxis, somatospatial praxis, visual spatial gnosis, calculation) domains (Luria, 1962/1966). The critical sign of semantic aphasia – impaired comprehension of logical-grammatical constructions – was featured in all 10 patients. Since similar linguistic impairments may also be due

Table 5 – Probability of white matter pathway disconnection for each patient in tracts that were affected in at least four patients.

Tracts	Patients									
	1	2	3	4	5	6	7	8	9	10
Anterior commissure	.70	.55	.52	.46	.34	.54	.90	.45	.95	
Anterior thalamic projections	.44	.86	.88	.86	1.00		1.00	1.00	1.00	.98
Arcuate fasciculus, anterior segment	1.00	.86	1.00	.98	.90	.36	.96	.70	.94	.76
Arcuate fasciculus, long segment	1.00	1.00	1.00	1.00	1.00	.94	1.00	.94	1.00	.64
Arcuate fasciculus, posterior segment	1.00	1.00	1.00	1.00	.92	1.00	1.00	.98	.46	
Cingulum	1.00	1.00	1.00	1.00	.94		.94	.80	1.00	
Cingulum, anterior segment	1.00	1.00	.98	1.00	.96		.93	.71	.99	
Cingulum, posterior segment	.94	1.00	.91	.77	.29			.44	.24	
Corpus callosum	1.00	1.00	1.00	1.00	1.00	.98	1.00	1.00	1.00	.96
Corticospinal tract	.82	.20	.94	.70	.94		1.00	1.00	1.00	1.00
Face U-shaped tract	.78		.37	.31	.27		.47	.20	.22	
Fornix	.89	.21	.64	.29		.82	.92	.20	.86	
Frontal aslant tract	.98		.82	.24	1.00		1.00	1.00	1.00	.96
Frontal commissural tract	.68	.98	.92	.98	.94		1.00	.96	1.00	.54
Frontal inferior longitudinal tract	.61		.55		1.00		.98	.80	.88	.52
Frontal superior longitudinal tract	.22		.88	.32	1.00		1.00	1.00		
Fronto-insular tract 3	.68				.68		.72	.36	.68	.84
Fronto-insular tract 4	.98		.50		.60		.98		.98	.94
Fronto-striatal projections	.98	.50	.94	.92	1.00		1.00	1.00	1.00	1.00
Hand inferior U-shaped tract	.96	.55	.96	.94	.92		.86	.94	.29	
Hand middle U-shaped tract	.35		.35	.31	.33		.29	.35		
Hand superior U-shaped tract	.96	.84	1.00	.96	.96		.24	1.00		
Inferior fronto-occipital fasciculus	1.00	1.00	1.00	1.00	.94	1.00	1.00	.98	1.00	
Inferior longitudinal fasciculus	1.00	1.00	1.00	1.00	.96	1.00	1.00	1.00	1.00	
Optic radiations	1.00	1.00	1.00	1.00	.99	.97	1.00	1.00	.90	
Pons	.78	.84	1.00	.98	.98		1.00	1.00	1.00	1.00
Superior longitudinal fasciculus, I	1.00	1.00	1.00	1.00	1.00		1.00	.99	.80	
Superior longitudinal fasciculus, II	1.00	1.00	1.00	1.00	1.00	.80	1.00	1.00	.94	.54
Superior longitudinal fasciculus, III	1.00	1.00	1.00	1.00	1.00	.98	1.00	.96	1.00	.91

Note: The column names correspond to the individual patients. For Patients 1–9 the labels in the first column refer to the left hemisphere structures, and for the Patient 10 – to the right hemisphere structures.

to primary agrammatism or a sensory disorder and thus may belong to other aphasic syndromes, it was important to confirm that these patients experienced problems in spatial processing. Indeed, spatial constructional praxis was consistently impaired in all 10 patients. The impairment of other functions varied within this clinical cohort, with the majority of patients having compromised writing, metaphor appreciation, visual spatial gnosis, and calculation, and a few patients showing problems in somatospatial praxis and characteristic analytical reading strategies. Thus, the consistency of the deficits in the assessed domains varied from 7 tests (Patients 1, 3, 7) to 4 (Patients 2, 4, 6), see Table 2 for detailed assessment results. At the individual level, this resulted in clinical profiles including consistent and specific language comprehension problems, along with different combinations of other space-related impairments. Most importantly for the logic of Luria's qualitative neuropsychological assessment, the errors made by patients suggested the spatial nature of the underlying disorder, e.g., spatial discoordination and transpositions, left-right confusion, and an inability to rely on holistic reading and writing strategies.

These data show that semantic aphasia as a linguistic impairment is obligatorily accompanied by disorders in other cognitive domain, but not necessarily by all of them. The most consistent accompanying impairment is the one of spatial constructional praxis, the most optional being the impairment of somatospatial praxis. This could be related to a number of factors. For example, individual differences in lesion topography may cause variations in neuropsychological profiles. The limited sample size used in our study, however, does not allow generalizations about the correspondence of symptoms listed in Table 2 and individual lesion maps. Another speculation is related to the content of the tests. The test probing spatial constructional praxis included several tasks (copying a cube and a table, setting time-blind clocks, and mirror reflection of complex shapes), all relying on both high-order visual processing of artificial objects and shapes, and constructional drawing. These might be more challenging than the perception and copying of a body part (hand) configuration, as required in the somatospatial test. In addition, each test in Luria's battery only includes a few probes, which might prevent the identification of a deficit in mild cases. A more quantitative and normed version of Luria's battery is in high demand in Russian clinical settings. An attempt was made with the Assessment of Speech in Aphasia by Tsvetkova et al. (1981) and resulted in a useful tool, but it is focused on the evaluation of language and cannot replace a comprehensive neuropsychological assessment. All in all, our data suggest an intrinsic variation of non-linguistic symptoms accompanying semantic aphasia as they

Table 6 – Clusters of white matter pathways revealed by the cluster analysis.

Tract	Distance from the respective cluster center
Cluster 1	
Anterior thalamic projections	.22
Arcuate fasciculus, anterior segment	.17
Cingulum	.21
Cingulum, anterior segment	.21
Corticospinal tract	.24
Frontal aslant tract	.35
Frontal commissural tract	.13
Fronto-striatal projections	.18
Hand inferior U-shaped tract	.25
Hand superior U-shaped tract	.38
Pons	.18
Superior longitudinal fasciculus, I	.20
Cluster 2	
Anterior commissure	.25
Cingulum, posterior segment	.43
Face U-shaped tract	.20
Fornix	.32
Frontal inferior longitudinal tract	.28
Frontal superior longitudinal tract	.38
Fronto-insular tract 3	.28
Fronto-insular tract 4	.34
Hand middle U-shaped tract	.27
Cluster 3	
Arcuate fasciculus, long segment	.09
Arcuate fasciculus, posterior segment	.19
Corpus callosum	.19
Inferior fronto-occipital fasciculus	.13
Inferior longitudinal fasciculus	.12
Optic radiations	.12
Superior longitudinal fasciculus, II	.07
Superior longitudinal fasciculus, III	.17

are identified in the modern clinical settings using Luria's neuropsychological battery, the nature of this variation being open to further research.

The lesion profiles of the modern cases were, for the most part, in line with Luria's model of semantic aphasia functional anatomy. The correspondence between the left TPO region proposed by Luria and virtual lesions of the patients was established by studying the degree of intersection of Luria's list of structures involved in semantic aphasia with, first, our patients' lesion overlays (Table 3), and second, with individual lesion masks (Table 4). The cortical brain regions comprising lesion overlays for the most part corresponded to Luria's list: these were the left angular gyrus, middle and inferior occipital gyri, inferior parietal lobule, and middle temporal gyrus. Other structures (left superior parietal lobule, supramarginal gyrus and postcentral gyrus), which also appeared in the overlays, were not part of Luria's list. However, Luria (1947/1970) claimed that damage to BA 7 and 40, which correspond to the superior parietal lobule and the supramarginal gyrus, did not cause deficits characteristic of semantic aphasia unless a lesion is more extensive or comprises damage to the parietal cortex bordering the temporal-occipital areas. For that reason, we did not include BA 7 and 40 in Luria's list; at the same time, their emergence in the overlay maps was not unexpected and does not conflict with Luria's predictions. The role of the postcentral gyrus in semantic aphasia was not discussed in the original work of Luria (1947/1970), but it can be hypothesized that the incidence of postcentral gyrus lesions is likely related to the patients' etiology rather than to its intrinsic role in the syndrome. In this respect, a distinction between the focal gunshot trauma in Luria's patients and the larger stroke lesions in our clinical cohort might be critical and could be responsible for the broader involvement of neural tissue in the overlay maps. On the other hand, other areas included in Luria's list (calcarine sulcus, cuneus, fusiform, and lingual gyri) might not be identified in our overlay analysis due to less frequent occurrence in the sample; yet, they were involved in some individual lesions (see Table 4 and discussion below). Thus, at the cortical level, the overlay analysis demonstrates a very high degree of correspondence between the regions reported by Luria and the data acquired with modern neuroimaging techniques.

Individually, most of the patients (1, 2, 3, 4, 5, and 8) had lesions located around the left TPO region that encompassed Luria's predicted areas: there was damage to the inferior parietal lobule and the angular gyrus with additional involvement of the occipital lobe (inferior and/or middle and/or superior occipital gyri) and the middle temporal gyrus (see Table 4). Some of them also had damage to the inferior temporal gyrus (Patients 1, 2, 3, 6, and 8) and to the cuneus (Patients 1, 2, and 3). In addition, the lesion of Patients 2 and 3 involved portions of the calcarine sulcus; and fusiform, and lingual gyri were damaged in Patient 2. Despite the fact that the real lesions of these patients extended beyond Luria's list, it can be claimed that at least partly they matched the classical semantic aphasia brain topography and could account for its clinical manifestations.

However, an intriguing finding of the present study was related to the fact that four patients (6, 7, 9, and 10), who also had clear manifestations of semantic aphasia, lacked the expected lesion pattern. Minor to no damage to the left parietal regions (inferior parietal lobule and angular gyrus) was discovered in these patients, with the bulk of the lesion in other sites: left temporal (Patient 6), temporo-frontal (Patient 7), frontal (Patient 9) regions, or the right hemisphere basal ganglia (Patient 10). This is in contradiction to Luria's thinking about the neural underpinnings of semantic aphasia, but in line with some modern neuroimaging findings about the involvement of extra-TPO regions in specific aspects of linguistic and non-linguistic processing, which are relevant to semantic aphasia. For instance, there is evidence of association between verbal spatial processing (Amorapanth et al., 2012), as well as thematic role assignment (Wu et al., 2007), and temporal regions (damaged in Patient 6 and 7). Similarly,

prepositional constructions (Tranel & Kemmerer, 2004) and passive sentence (Yokoyama et al., 2007) processing was found related to the left frontal operculum (damaged in Patients 7 and 9). The impaired performance on spatial constructional praxis tasks was also not exclusively attributed to parietal damage, since it was found in patients with frontal lesions (Gross & Grossman, 2008), as well as with lesions to the right basal ganglia (as in Patient 10) or the left inferior frontal-parietal opercular cortices, including the inferior frontal gyrus, the lower segment of the precentral and postcentral gyri, the anterior part of the supramarginal gyrus, the insula, and the underlying basal ganglia (Tranel, Rudrauf, Vianna, & Damasio, 2008). Thus, we could hypothesize that in non-prototypical cases of Patients 6, 7, 9, and 10, we are not dealing with a complex syndrome of semantic aphasia but rather with a set of similar symptoms of a different neuro-anatomical nature. However, our data as well as other available neuroimaging findings do not allow us to fully accept this explanation; more comprehensive research is needed to establish the relation between cortical involvement beyond Luria's list of areas and deficits characteristic to semantic aphasia. Evidence conflicting with this suggestion is also related to the presence of space-related impairments in other cognitive domains in our 10 patients. Spatial constructional praxis was affected in all, and visual spatial gnosis and calculations in three of them. It seems unlikely that several distinct brain substrates are responsible for such very similar complex clinical profiles.

Alternatively, it can be suggested that not only damage to specific cortical areas might be responsible for semantic aphasia symptoms, but that their connectivity is also an important factor. Recent studies that highlighted the involvement of white matter underlying the supramarginal gyrus in preposition processing (Amorapanth et al., 2012; Tranel & Kemmerer, 2004) encourage this line of thinking. This is also consistent with Luria's idea that it is the integration of different kinds of information retrieved from various cortices that is critically affected in semantic aphasia, although Luria explicitly narrowed the neuroanatomy of semantic aphasia to the cortex (Luria, 1947/1970, 1962/1966). For our 10 current cases, a lesion overlay analysis revealed a number of affected white matter pathways, and the probability of their disconnection was estimated in each patient (see Table 5). Further cluster analysis demonstrated that Cluster 3, which had the highest mean probability of disconnection, contained the arcuate fasciculus, long and posterior segments; corpus callosum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, optic radiations and superior longitudinal fasciculus, II and III. All these white matter pathways were lesioned either in all patients (arcuate fasciculus, long segment; corpus callosum, and superior longitudinal fasciculus, II and III) or in all patients except for the RH Patient 10 (arcuate fasciculus, posterior segment; inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and optic radiations).

The arcuate fasciculus, corpus callosum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus are white matter fibers with purported terminations in the parietal areas (Catani, Jones, & ffytche, 2005; Duffau, Herbet, & Moritz-Gasser, 2013; Makris et al., 2005; Park et al., 2008; Rushworth, Behrens, & Johansen-Berg, 2006; Seghier, 2012; Uddin et al., 2010). The contemporary notions of the connectivity of the arcuate fasciculus may be conflicting (Dick et al., 2014; Dick & Tremblay, 2012), but in our analysis we used the three-segment model proposed by Catani et al. (2005), with the long segment corresponding to the classical arcuate pathway that include connections between Broca's and Wernicke's areas, whereas two additional indirect pathways connecting inferior parietal cortex with Broca's territory (anterior segment) and Wernicke's territory (posterior segment). The dorsal areas of the splenium and isthmus of the corpus callosum contain fibers that project to the parietal lobes (Park et al., 2008). The inferior fronto-occipital fasciculus connects the frontal lobe with the occipital and parietal lobes, and with the postero-temporal cortex (Duffau et al., 2013). The inferior longitudinal fasciculus has been traditionally described as connecting the temporal pole, hippocampal formation, and inferior temporal gyrus to the occipital lobe, and it's parietal connectivity remains unclear (Bajada, Lambon Ralph, & Cloutman, 2015); although there is evidence that it is a part of the angular gyrus connectivity system (Seghier, 2012) which connects it to the para-hippocampal gyrus (Rushworth et al., 2006) and to the hippocampus (Uddin et al., 2010). The superior longitudinal fasciculus is an association tract that connects parieto–temporal association areas and the frontal lobe, and consists of four subdivisions. Specifically, the second branch of the superior longitudinal fasciculus connects TPO and parietal regions (BA 19, 39 and 40), postcentral gyrus (BA 3, 1 and 2), precentral gyrus (BA 4), and middle frontal gyrus (BA 6 and 46); whereas the third branch courses between parietal BA 40, ventral part of pericentral BA 43, 2, 4 and 6, and frontal premotor area BA 44 (Makris et al., 2005).

The arcuate fasciculus, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, and superior longitudinal fasciculus that were affected in our cohort were shown to be involved in language processing and other functions that can be disrupted in semantic aphasia. Thus, Catani et al. (2005) suggested that the long segment of the arcuate fasciculus pertains to phonologically-based functions (for instance, automatic repetition), the anterior segment is involved in vocalizing semantic content, and the posterior segment is related to auditory semantic comprehension. Also, the damage to the temporal-parietal projections of the arcuate fasciculus was shown to correlate with repetition deficits (Kümmerer et al., 2013), although in this study the dorsal arcuate fasciculus is analyzed alongside with the dorsal superior longitudinal fasciculus. The suggested functions of both segments of the arcuate fasciculus are relevant to semantic aphasia. On the one hand, phonological deficits (sub-articulatory component) were proposed as the primary source of difficulties in processing reversible sentences (Richardson et al., 2010). On the other hand, Turken and Dronkers (2011) exploring the connectivity of the left middle temporal gyrus suggested that the fibers of the arcuate fasciculus (both direct and indirect segments) connecting to left middle temporal gyrus could relate to the integration of lexical semantics with other linguistic and cognitive mechanisms at the level of comprehension. In addition, Glasser and Rilling (2008) who elaborated another, two-segmented, model of the arcuate

fasciculus proposed that one of its segments, which terminates in the middle temporal gyrus, overlapped with lexical-semantic activations, as shown in functional neuroimaging studies. The involvement of the long and the posterior segments of the arcuate fasciculus in phonologically-based processes and the integration of semantic information during language comprehension suggests the importance of these pathways for semantic aphasia deficits.

The inferior fronto-occipital fasciculus is involved in language processing, as it was demonstrated in stimulation studies in awake neurosurgery. Direct electrical stimulation of the inferior fronto-occipital fasciculus elicits semantic paraphasias during picture naming (e.g., Duffau et al., 2013; Gil-Robles et al., 2013) and non-verbal comprehension disturbances (Duffau et al., 2013). Besides, this pathway was also suggested among the tracts crucial for supporting the language comprehension network (Turken & Dronkers, 2011).

As the inferior longitudinal fasciculus connects to the anterior temporal pole, which is associated with transmodal semantic representations, Bajada et al. (2015) suggest it might be critical for the interaction between the storage of these representation and processes supported by occipital and parietal regions. In a study by Turken and Dronkers (2011), the inferior longitudinal fasciculus was found to be among a number of critical pathways involved in language comprehension deficits. The degree of segregation of this tract from the inferior fronto-occipital fasciculus is unclear (Dick et al., 2014; Dick & Tremblay, 2012; Forkel et al., 2014), but both are thought to be involved in object recognition, face processing, and visual semantic memory (Dick & Tremblay, 2012), and also in visuospatial processing (e.g., Chechlacz et al., 2010, 2013). A number of visual pathologies are associated with damage to the inferior longitudinal fasciculus, including associative visual agnosia, prosopagnosia, and visual amnesia (Benson, Segarra, & Albert, 1974; Fernández-Miranda et al., 2008; Jankowiak & Albert, 1994; Meadows, 1974; Ross, 1980). Thus, given the assumed role of the inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus in semantic and visual processing, their damage can potentially contribute to linguistic and non-linguistic deficits observed in patients with semantic aphasia.

The superior longitudinal fasciculus could also be involved in both language and other cognitive domains. As for the involvement of the particular branches, Makris et al. (2005) hypothesized that the second branch of the superior longitudinal fasciculus could be involved in the perception of visual space, by maintaining the bidirectional connection between the prefrontal cortex and the parietal lobe or by supporting spatial working memory by means of connecting with the prefrontal area 46. The third branch connecting BA 44 with the BA 40 may play a role in the articulatory component of language (Makris et al., 2005). As the role of the superior longitudinal fasciculus in language remains uncertain and the anatomical and functional segregation of this tract and the arcuate fasciculus may remain a matter of contention (Dick et al., 2014; Dick & Tremblay, 2012), it has a more prominent role in visuospatial attention processing – a function that can be indirectly related to semantic aphasia. Thus, many recent studies demonstrated that the superior longitudinal fasciculus is one of the most important tracts in visuospatial attention network (e.g., Chechlacz et al., 2010, 2013; Umarova et al., 2010). Although the right hemisphere is usually treated as dominant for visuospatial processing (e.g., Umarova et al., 2010), the supporting evidence for this is stronger in cases of neglect than of extinction (Chechlacz et al., 2013). For example, Chechlacz et al. (2013) observed the same ratio of cases with extinction in patients with bilateral and left or right unilateral damage and revealed left-lateralized substrates for right extinction deficits, which implies the possibility of a critical left hemisphere role in visuospatial processing. Although standardized tasks for extinction or neglect are not usually used in the neuropsychological assessment of aphasic patients within the Lurian tradition, we might expect extinction to occur in patients with semantic aphasia, given the shared cortical and subcortical substrate.

Regarding the involvement of the optic radiations in our patients, its functional role in semantic aphasia is unclear. The optic radiations project from the lateral geniculate nucleus to the primary visual cortex in the occipital lobe (Yamamoto, Yamada, Nishimura, & Kinoshita, 2005). Although directly related to visual perception (when lesioned it causes quadrantanopsia affecting a part of the visual field), the optic radiations are unlikely to be implicated in the high-order spatial processing affected in semantic aphasia. Rather, their frequent involvement in the lesions of our patients may be an artifact of their proximity to the inferior longitudinal fasciculus. Although the two tracts can be separated with modern tractography techniques (Catani, Jones, Donato, & ffytche, 2003), their bundles run adjacent, so that earlier authors were not able to distinguish them (Tusa & Ungerleider, 1985).

Finally, the involvement of the corpus callosum in the list of the tracts that may contribute to semantic aphasia is an interesting finding, though it is hard to interpret at this stage. Certainly, a substantial amount of coordination and sharing of information between the cerebral hemispheres takes place across this tract, and there is evidence of its importance in the recovery of symptoms from stroke (e.g., Wang et al., 2012). Patients whose lesions include disconnection of the corpus callosum tend to recover more poorly than those without, ostensibly because the potential contributions of the intact hemisphere have been disengaged. In our cases, aphasic symptoms were still present in all cases at the time of testing, though it remains to be seen if the patients who were tested earlier post stroke will continue to show deficits over time.

As for the general subcortical involvement in semantic aphasia, each white matter tract should not be considered to be a sole contributor to the deficit. Luria stressed the integrative role of the TPO associative cortex lying at the intersection of these lobes (Luria, 1947/1970, 1962/1966). Our suggestions about the involvement of the white matter pathways underlying the TPO region are in agreement with the same principle of integration, although the long distance associations (e.g., to prefrontal areas) were not directly discussed by Luria. At this stage, we are not able to determine whether damage to a single tract or a combination of tracts result in the syndrome of semantic aphasia. A disconnection in any of these tracts could affect normal processing in the core TPO region and result in the symptoms of semantic aphasia and accompanying non-linguistic spatial disorders,

much as lesions directly in TPO area would affect these same functions.

In conclusion, semantic aphasia, described in detail and interpreted as a part of the neuropsychological syndrome of impaired spatial analysis and synthesis by Alexander Luria 70 years ago, still remains an interesting research topic for contemporary neuroscience. Luria's clinical descriptions represent the most comprehensive conceptualization of the involved behavioral deficits and their neuroanatomical underpinnings, which however deserve further examination with available modern methodologies. In this study, we made such a first attempt and analyzed neuropsychological and lesion profiles of 10 modern patients with semantic aphasia, thus contrasting Luria's predictions about the neuroanatomy of the syndrome and modern neuroimaging data. A large number of patients had left TPO lesions and thus followed Luria's predictions. However, the additional analysis of the lesioned white matter tracts, especially in non-prototypical cases of semantic aphasia (in which the left TPO area was relatively intact), suggested that white matter damage might play an important role in the syndrome. Indeed, the tracts that connect to the parietal areas – the arcuate fasciculus (long and posterior segments), the inferior fronto-occipital fasciculus, the inferior longitudinal fasciculus, the superior longitudinal fasciculus II and III, and the corpus callosum – were implicated in the linguistic and non-linguistic deficits of patients with semantic aphasia. Our findings are limited in a number of aspects: a larger sample size is desirable, the study could benefit from a more comprehensive behavioral examination of patients, and VLSM or tractography approaches would result in a more robust lesion analysis. However, even the use of standard neuropsychological protocols and routinely-available clinical MRI images of patients with this rare syndrome allowed us to confirm Luria's basic ideas concerning the functional neuroanatomy of semantic aphasia, while also suggesting some new directions of research.

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