Psychophysiological Analysis of the Influence of Vasopressin on Speech in Patients with Post-Stroke Aphasias

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Speech is an attribute of the human species. Central speech disorders following stroke are unique models for the investigation of the organization of speech. Achievements in neurobiology suggest that there are possible neuroendocrine mechanisms involved in the organization of speech. It is known that the neuropeptide vasotocin, analogous of vasopressin in mammals, modulates various components of vocalization in animals. Furthermore, the positive influence of vasopressin on memory, which plays an important role in the formation of speech, has been described. In this study, speech organization processes and their recovery with the administration of vasopressin (1-desamino-8-D-arginin-vasopressin) to 26 patients with chronic aphasias after stroke were investigated. Results showed that sub-endocrine doses of the neuropeptide with intranasal administration had positive influence primarily on simple forms of speech and secondarily on composite forms. There were no statistically significant differences between the sensory and integrative components of the organization of speech processes with vasopressin. In all cases, the positive effect of the neuropeptide was demonstrated. As a result of the effects, speech regulated by both brain hemispheres improved. It is suggested that the neuropeptide optimizes the activity both in the left and right hemispheres, with primary influence on the right hemisphere. The persistence of the acquired effects is explained by an induction of compensatory processes resulting in the reorganization of the intra-central connections by vasopressin.
Keywords: speech, functional asymmetry, aphasia, vasopressin

El habla es un atributo de la especie humana. Los trastornos centrales del habla después de una trombosis cerebral son modelos únicos para la investigación de la organización del habla. Los logros en la neurobiología sugieren que posiblemente haya mecanismos neuroendocrinos implicados en la organización del habla. Se sabe que el neuropéptido vasotocina, análogo de la vasopresina en los mamíferos, modula varios componentes de la vocalización en los animales. Además, se ha descrito la influencia positiva de la vasopresina en la memoria, que juega un papel importante en la formación del habla. En este estudio, se investigaron los procesos de la organización del habla y su recuperación con la administración de la vasopresina (1-desamino-8-D-arginin-vasopressin) a 26 pacientes con afasias crónicas después de una trombosis cerebral. Los resultados mostraron que las dosis sub-endocrinas del neuropéptido con administración intranasal tuvo influencia positiva primariamente en las formas simples del habla y, de manera secundaria, en las formas compuestas. No hubo diferencias estadísticamente significativas entre los componentes sensoriales e integrativos de la organización de los procesos del habla con vasopresina. En todos los casos, se demostró el efecto positivo del neuropéptido. Como resultado de los efectos, mejoró el habla regulado por ambos hemisferios. Se sugiere que el neuropéptido optimiza la actividad tanto en el hemisferio izquierdo como en el derecho, con influencia primaria sobre el hemisferio derecho. La persistencia de los efectos adquiridos se explica por la inducción de procesos compensatorios como resultado de la reorganización de las conexiones intra-centrales por la vasopresina.
Palabras clave: habla, asimetría funcional, afasia, vasopresina

Speech is a higher cortical function that is a complex and finely differentiated act with multilevel organization. Until recently, the understanding of the biochemical and neurophysiological basis for speech has remained limited. Despite much research, the problem of language competence of the brain hemispheres is still relevant. Specific language functions of the hemispheres have been studied at various levels: in volunteers, in patients following commissurotomy, in patients with organic brain damage, and in psychiatric diseases in conditions of transient hemisphere inactivation. (Balonov & Deglin, 1976; Buckner, Corbetta, Schatz, Raichle, & Petersen, 1996; Chertkow, Bub, Deaudon, & Whitehead, 1997; Gazzaniga, 1995; Loddenkemper et al., 2004; Luria, 1970; Luria & Hutton, 1977; Murphy et al., 1997; Nikolaenko & Egorov, 1998; Njiokikjien, Sonneville, & Vaal, 1994; Semmens, 1968; Sperry, Gazzaniga, & Bogen, 1969; Weiller et al., 1995; Wise, 2003).

The role of the dominant hemisphere (usually the left hemisphere in right-handed subjects) in the organization of speech and language has been relatively fully researched. It has been demonstrated that the principal speech zones, which function as a whole due to inter-cortical and cortico-subcortical connections, are within the left hemisphere (Buckner et al., 1996; Radanovic & Scaff, 2003). Usually the left hemisphere recognizes more rapidly infrequent (rare), morphologically complex, abstract words, adjectives, and verbs (Efron, 1990; Eviatar, Zaidel, & Menn, 1990; Goodal, 1984; Sperry et al., 1969; Zaidel, 1978, 1989). It is also is involved in the formation of speech motor programs, and the last structure of declared speech (Luria, 1970; Luria & Hutton, 1977). Included in the functions of this hemisphere is the ability to produce speech. It is also responsible for highly specialized linguistic mechanisms of phonetic decoding and analysis (Sharp, Scott, & Wise, 2004; Sperry et al., 1969; Zaidel, 1978). Also included in the functions of the left hemisphere are phonetic hearing or audio-verbal gnosis, writing, and reading (Dronkers, Wilkins, van Valin, Redfern, & Jaeger, 2004; Hagoort, 1993; Larsen, Skinhoj, & Lassen, 1979; Saygin, Wilson, Dronkers, & Bates, 2004). In left-sided injury to the superior temporal and angular gyrus, comprehension of speech is impaired (Dronkers et al.; Josse & Tzourio-Mazoyer, 2004). The structures of the left hemisphere form the morphological substrate for logical thought.

The right hemisphere recognizes simple single-syllable common (frequent) concrete nouns and sentences consisting of simple words (Goodal, 1984; Nikolaenko & Egorov, 1998). It is considered to participate partially in the comprehension of spoken and written speech, and it accepts, analyzes, and stores holistic components of speech or indivisible code units (Sperry et al., 1969; Zaidel, 1978). It has been determined that the right hemisphere perceives words according to their acoustic but not phonetic features. The activity of this hemisphere has been associated with the perception and reproduction of the acoustic contour of words, silent reading of simple words, and the analysis of non-verbal prosodic elements of speech (Ghacibeh & Heilman, 2003, Heilman, Leon, & Rosenbek, 2004; Sperry et al., 1969). It dominates in the establishment of common links between various aspects of information leading to the formation of the prerequisites for simplified context identification and the creation of a holistic impression. Included in the functions of the right hemisphere is the imprinting of words in orthographic form— type, letter, color, etc.—(Sperry et al.; Zaidel). It is essential in associative–empirical thought, although it is considered to lack the ability to form the movements required for the production of speech. Thus, research over the past decades provides evidence for the fact that the intact brain acts as a whole by means of the interaction of the hemispheres, and yet, each hemisphere is functionally specific for the performance of various aspects of speech (Zaidel; Nikolaenko & Egorov).

The most severe and widespread speech disturbance is post-stroke aphasia. Aphasia is central damage to previously fully formed speech in subjects with intact articulation and hearing, with partial or complete loss of the ability to use words for the expression of thought and the comprehension of directed speech (Nikiforov, 1997; Saygin et al., 2004). Aphasia is present in up to 38-54 % of patients following stroke (Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995). Such speech disturbances result from focal injury to cortical and subcortical structures of the hemisphere specific for speech (usually in the left hemisphere in right-handed subjects). These disturbances are of systemic nature, with disruption of expressive and impressive speech (Clark, 1994; Druks & Marshall, 1995; Chertkow et al., 1997).

On the basis of neuropsychological research by Luria (Luria, 1970; Luria & Hutton, 1977), various forms of aphasia are explained by defects in various components (factors) of the function of speech (efferent, afferent, etc.). There are several forms of aphasia depending on the localization of brain damage. Amnestic or acoustico-amnestic aphasia occurs in left-sided (in right-handed subjects) occlusion of distal sections of the median cerebral artery. In these cases, ischemia occurs within the medial gyrus of the temporal lobe—Brodman areas 37 and 40—(Karbe et al., 1995; Luria, 1970; Luria & Hutton 1977). In acoustico-amnestic aphasia, disturbance in retention and reproduction of verbal material is associated with increased retro- and proactive verbal trace inhibition. Here, spontaneous speech is characterized by searches for required words and frequent verbal paraphasias. Central in such speech disturbance is the disturbance of audio-verbal memory, which manifests in defects of object naming and related actions, and impairment of aural retention of auditory and verbal series. Patients are able to reproduce no more that two or three elements of the series, whereas normally, the volume of short-term auditory verbal memory consists on average of 7 ± 2 units. Secondly, as a result of a decrease in verbal information processing, there is impairment of directed speech comprehension.

Acoustico-agnostic aphasia occurs in stenosis or occlusion of distal portions of the left (in right-handed subjects) median cerebral artery, with the formation of the brain lesion within the superior temporal gyrus in Wernicke's area—Brodman areas 21 and 22—(Abo et al., 2004; Luria, 1970). Acoustico-agnostic aphasia or fluent aphasia is essentially equivalent to Wernicke's sensory aphasia. The primary defect in such forms of central speech impairment is the disturbance of phonetic hearing or audio-verbal gnosis (Sharp, Scott, & Wise, 2004). In acoustico-agnostic aphasia differentiation of sounds and words, differing in some trait (sonority, hardness), is impaired. In this case, the primary defects of impressive speech manifest in the impairment of comprehension of oral and written speech (Hagoort, 1993). Expressive speech is impaired secondarily as a result of the deficiency of aural control of the patient's own speech (Druks & Marshall, 1995). In severe disorders, the patient's speech becomes incomprehensible as a result of a multitude of literal and verbal paraphasias—substitutions and omissions of sounds and words—(Vasserman, Dorofeeva, & Meerson, 1997). Also present is speech disinhibition (logorrhea). It has been shown that in such forms of aphasia, there is impairment of short-term acoustic and long-term semantic memory (Beeson, Bayles, Rubens, & Kaszniak, 1993; Graham, Hodges, & Patterson, 1994; Ronnberg et al., 1996).

Different forms of aphasia following focal brain injury present a valuable model for the study of speech organization in its entirety, and in its components related to perception, comprehension, and production. Using the analysis of spontaneous and induced recovery of speech, it is possible to identify the specific input of the brain hemispheres in communication and to study the neurochemical and neurohumoral components of speech regulation.

A stroke is an acute disruption of brain blood circulation manifesting with deficit brain function lasting no less than 24 hours (Vilenski, 1995; Whisnant, Basford, & Bernstein, 1990). Ischemic strokes are more frequent than brain hemorrhages. During the process of infarct formation, there is necrosis in the central part of the ischemic zone and formation of an area of relative ischemia (ischemic penumbra), which is a region of unstable brain tissue metabolism. The velocity of brain blood-flow within the ischemic penumbra is greater than the level at which brain cell death occurs, and therefore, neurons are able to maintain a state of unstable metabolism (Kassel & Torner, 1984). On the contrary, within the infarct, blood flow is insufficient for the maintenance of normal electrophysiological neuronal activity and leads to cell death—apoptosis—(Kerr, Wyllie, & Currie, 1972; Nitatori, 1995). Thus, the rate and extent of speech and other function recovery depends on the level of collateral circulation and the activation of functionally inactive reserve connections of the regions surrounding the necrotic area (Kassel & Torner).

Despite extensive experience in the development of speech rehabilitation in aphasias (Fernandez et al., 2004; Perani et al., 2003; Weiller et al., 1995; Xu et al., 2004; Zahn et al., 2004), the neurochemical mechanisms of speech compensation in speech impairment and the role of the hemispheres in this process are still poorly understood.

Over the past years, data has been compiled proving the existence of a neuro-endocrine component of speech regulation. A high density of vasopressin receptors has been revealed in a number of mammal brain areas involved in vocalization (Boyd, 1997; Brudzynski, Eckersdorf, & Golebiewski, 1995; Voorhuis, Kloet, & Wied, 1988). On the other hand, in experiments with injury to central motor analyzer regions, the neuropeptide vasopressin induces the reorganization of intra-central connections leading to the recovery of motor function (Vartanian & Klementiev, 1991). It is known that vasopressin possesses anti-amnestic properties (Vawter, Wied, & van Ree, 1997; Wied, Diamant, & Fodor, 1993). In turn, aphasia is accompanied by impairment of verbal memory (Beeson, Bayles, Rubens, & Kaszniak, 1993; Radanovic & Scaff, 2003; Martin & He, 2004; Ullman, 2004; Ween, Verfaellie, & Alexander, 1996). See in Table 1 some examples of the influence of vasopressin on speech in various forms of aphasia.

The aim of this study was to evaluate the state of speech functions in patients with acoustico-agnostic and acoustico-amnestic aphasia of vascular origin under the influence of the neuropeptide arginin-vasopressin.

Method

Participants

The study included 26 patients with aphasia following stroke: 17 male subjects (65%) and 9 female subjects (35%) with mean age 61.4±3 years and mean duration of post-stroke period of 1.4±0.1 years. Thus, the patients selected for the study were in the residual stage of stroke. All participants were right-handed. In a majority of the patients, the etiology of stroke factors was the combination of atherosclerosis and arterial hypertension (76%); in the remaining patients, the etiology of stroke was cerebral vessel atherosclerosis, rheumatic heart disease with thromboembolism, cerebral vessel aneurism, and thrombosis of unknown origin (24%).

Assessment

In all cases, aphasia was the consequence of ischemic stroke in the territory of the left middle cerebral artery. In each patient, diagnosis was confirmed by the results of computerized and/or magnetic resonance tomography. In cases of stroke with a predominance of damage to the superior temporal gyrus, there was acoustico-agnostic aphasia; with damage predominantly to the medial temporal gyrus, there was acoustico-amnestic aphasia.

Diagnosis was made according to the classification of Luria (Luria, 1970; Luria & Hutton, 1977). Acoustico-agnostic aphasia was diagnosed in 16 patients, and acoustico-amnestic aphasia in 10. Neuropsychological testing included the assessment of expressive and impressive speech of the patients (Vasserman et al., 1997)**.** The patients own speech was characterized by spontaneous, dialogue, and automatic speech (serial counting from 1 to 10, naming of week days and months), and narrative speech (formation of sentences and stories according to illustrations, retelling of simple texts). Repetition speech was assessed by the repetition of simple words, word series, vowels and consonants, complex and simple foreign (English) words, series of sounds and syllables, complex sentences, oppositional series of syllables and words. Nominative function was defined as the patient's ability to name objects and actions (according to illustrations of objects and actions).

Speech comprehension was assessed during conversations with the patients. The comprehension of everyday speech, simple instructions, separate words, and complex grammatical constructions was assessed. The presence of word sense alienation of objects and face parts was evaluated. Acoustic-verbal memory was assessed by the retention of speech series (series of vowels and consonants, syllables, words, and simple sentences). Phonetic analysis included word analysis with one or two phonemes, letter choice at the beginning or end of words, the definition of the phonetic components of words presented by the investigator and visually presented on images. The reading of syllables, simple words, and automatic ideograms, letters, written instructions, complex words, sentences, and text out loud, matching picture to text, and silent reading and comprehension was assessed. Writing was assessed by copying of simple phrases, writing by dictation, automatic engrams (speech stereotypes), letters, syllables, words, phrases, independent written object-naming, formation of words from letters.

All indices were rated using a 4-point system in which 0 corresponded to correct execution of task (*no impairment*); 1 point to *mild impairment*; 2 points to *moderate impairment*; 3 points to *severe impairment*.

Materials and Procedure

1-desamino-8-D-arginine-vasopressin (desmopressin), a selective vasopressin V2-receptor agonist, was administered intranasally fractionally for the duration of 1.5-2 months with a single dose of 0.1μg and total dosage of 4μg. Assessment of the effect of the medication was carried out using a scale in which improvement in no less than three aspects of speech indicated a good effect; in two components, a satisfactory effect; and in one component, a minimal effect.

The control group consisted of the same 26 patients who, prior to the intranasal administration of vasopressin were administered an intranasal sterile physiological saline solution (placebo) for 2 weeks in the same regimen as the consecutive vasopressin administration. The study was carried out under double blind controlled conditions. Follow-up investigation and repeated administration of arginine-vasopressin were carried out in these same 26 patients with aphasia 1-2 years after completion of the first course.

For the interpretation of the effect of vasopressin, speech was examined as a functional system, the afferent, central and efferent components of which correspond to the processes of perception, comprehension, and production of speech, (i.e., the sensory, integrative, and motor components). In order to assess these components, specific neuropsychological tests were used to rate the separate components of speech.

The sensory component of speech was characterized by indices such as: speech comprehension, writing by dictation, phonetic analysis, silent reading, and its comprehension. The integrative component, reflecting the state of acoustico-verbal memory, was evaluated by the retention of auditory verbal series (repetition of a series of vowels and consonants, words and sentences), object naming, and matching picture with text. Changes in the separate components of speech were assessed by comparing the total arithmetic mean values prior to the administration of the neuropeptide arginine-vasopressin, after placebo and subsequent to the course of treatment after 1_-2 months. During the period of investigation, the patients continued to take medication previously prescribed, such as antiaggregant and/or hypotensive drugs.

To identify speech components that changed significantly under the influence of vasopressin, we used paired-samples Student's *t*-test.

Results

Speech improvement was noted in 23 patients (88% of cases) following the administration of vasopressin. Selectivity of the effects of the neuropeptide was revealed. One hundred percent of the cases with acoustico-amnestic aphasia and 90% with acoustico-agnostic aphasia showed improvement following treatment (see Table 1).

In the cases with acoustico-amnestic aphasia, recovery was noted in the fields of both the expressive and impressive components of speech (see Table 2). Within this group, there was improvement of independent speech ($p < .05$), including spontaneous speech ($p < .05$). Patients showed an increase in active vocabulary: They were able to remember simple words with greater ease. In speech production, there were less frequent pauses, verbal, and literal paraphasias ($p < .05$). Text retelling in a majority of patients became more detailed as a result of an increase in the amount of words per sentence ($p < .05$). There was a significant improvement in naming ($p < .05$), including the naming of separate items

($p < .05$). As a result of optimization of acoustico-verbal memory in patients with acoustico-amnestic aphasia, there was a secondary improvement in phonetic analysis ($p < .05$). Following treatment with arginine-vasopressin, patients more often correctly analyzed the phonetic composition of recalled simple words ($p < .05$). It is a well known fact that the primary component of speech impairment in cases of acoustico-amnestic aphasia is a defect in either audio-verbal memory (Luria, 1970) or in the integrative component of speech. Vasopressin induced the recovery of the integrative component of speech in these patients ($p < .01$), as shown in Figure 1. There was no placebo-effect in this group.

Thus, the present study demonstrated the efficacy of vasopressin in the correction of systemic speech impairment in acoustico-amnestic aphasia. A more defined positive effect in these disturbances was noted in the expressive component of speech. The therapeutic effect of vasopressin in patients with acoustico-amnestic aphasia was characterized by recovery of the integrative component of speech. First, arginine-vasopressin restored relatively simple speech forms (automatic speech, object naming), and then complex forms.

Case 1 illustrates the influence of vasopressin on speech in cases of acoustico-amnestic aphasia. Patient no. 4 (see
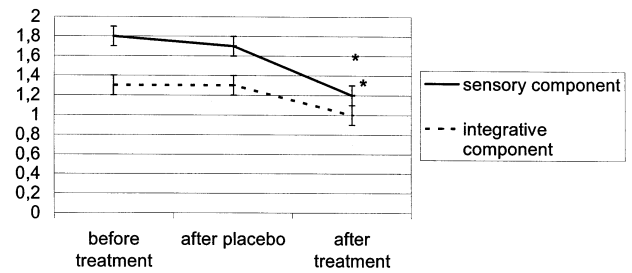

Figure 1. The effect of DDAVP (1-desamino-8-D-arginine-vasopressin).on the sensory and integrative components of speech in patients with acoustico-agnostic and acoustico-amnestic aphasia. Y-axis = severity of speech impairment in points.
* $p < .01$ significance of variance.

Table 3), 56 years, with higher education (by profession an economist), right-handed with arterial hypertension and cerebral atherosclerosis, suffered an ischemic stroke in the territory of the left middle cerebral artery. Following the stroke, the patient developed acoustico-amnestic aphasia and mild right-sided hemiparesis. He was admitted into a municipal hospital. On admission, he complained of difficulty

Table 1

The Influence of DDAVP on Speech in Various Forms of Aphasia

Forms of aphasia	Number of subjects	Effect of the administration of DDAVP in aphasia									
		Good		Satisfactory		Insignificant		Absent		Good positive effect	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Acoustico-amnestic	16	7	(44)	5	(31)	4	(25)	0	(0)	14	(100)
Acoustico-agnostic	10	6	(60)	0	(0)	3	(30)	1	(10)	9	(90)
Total number (%)	26	13	(50)	5	(19)	7	(27)	1	(4)	23	(88)

Note. DDAVP = 1-desamino-8-D-arginine-vasopressin.

Table 2

The Effect of Vasopressin on Speech in Acoustico-Amnestic Aphasia (M ± m, rate)

N	Indices of speech activities	Prior to treatment	Following treatment
1.0	Independent speech	1.0 ± 0.1	0.7 ± 0.1*
1.1	Spontaneous speech	1.2 ± 0.2	0.8 ± 0.1*
1.2	Dialogue	0.8 ± 0.2	0.4 ± 0.2*
1.3	Automatic: listing of months	0.7 ± 0.2	0.2 ± 0.2*
1.4	Narrative speech (text re-telling)	1.9 ± 0.2	1.4 ± 0.2*
2.0	Paraphasias	0.9 ± 0.1	0.6 ± 0.1*
3.0	Naming	1.6 ± 0.1	1.3 ± 0.1*
3.1	Item naming	2.0 ± 0.2	1.4 ± 0.2*
4.0	Phonetic analysis	1.0 ± 0.1	0.5 ± 0.1*
4.1	Analysis of recollected words	1.3 ± 0.2	0.4 ± 0.2*

Note. N = 1.0, 2.0, 3.0, 4.0 = several parts of speech function.
1.1, 1.2, 1.3, 1.4; 3.1; 4.1 = sample components of relative speech function.
* = significant changes in indices after treatment course with DDAVP ($p < .05$ in all variances).

speaking and weakness in the right extremities. During the acute period post-stroke period, he received conventional medication and speech therapy. He was then discharged for out-patient treatment. Five months after the stroke, the patient's speech consisted only of simple words, that is, speech remained significantly impaired, leading to difficulty in communication. One and a half years after the stroke, the patient was admitted to the neurological rehabilitation department of the V.M. Bekhterev Saint Petersburg Psychoneurological Research Institute. Prior to the course of treatment with vasopressin, the patient was examined using neurological and neuropsychological methods. Moderate acoustico-amnestic aphasia and mild right-sided hemiparesis were diagnosed. The patient's expressive speech was unintelligible due to a large amount of verbal substitutions (see Table 3). Repetition was impaired non-uniformly: impairment was present only in relation to the repetition of sound and speech series. Pronunciation was normal. Distinct difficulties occurred in attempts to name objects and related actions. Comprehension of daily activity speech was intact with impairment only in relation to complex grammatical constructions. Written speech had more significant impairment: The patient was only able to write separate words and copy simple sentences. Phonetic analysis and reading were significantly damaged. The patient's speech was impregnated with paraphasias. There was no placebo effect. The patient was administered a course of treatment with arginine-vasopressin: intranasal single administration of 0.1μg of the neuropeptide daily for 2 months with a total dosage of 4μg.

After treatment, there was an improvement in expressive speech, including spontaneous, dialogue, and automatic speech (see Table 3). Changes in repetition were less pronounced, with an improvement in retention and repetition of a series of vowels and "pseudo-words." There was significant improvement in object naming. When naming objects and in related actions, paraphasias occurred less frequently than before. The patient experienced less difficulty in the comprehension of grammatical constructions. There was less alienation of word sense for face parts. On the whole, there was no change in writing, although there was a decrease in the amount of paragraphias. There was significant regression of impairments of phonetic analysis and reading. Thus, there was a positive effect of arginine-vasopressin on speech in a patient with moderate acoustico-amnestic aphasia in the remote period following stroke. In this patient, improvement in speech following one course of treatment was persistent, as the improvement continued to be present at follow-up (1/2 year after completion of the first course). There were no adverse effects in the above-described administration of the neuropeptide arginine-vasopressin.

In cases of acoustico-agnostic aphasia, the administration of vasopressin also led to a regression of systemic speech impairment: primary impairment of the impressive component, typical for these forms of aphasia, and secondary impairment of expressive speech. In patients with acoustico-agnostic aphasia, there was significant improvement of writing ($p < .01$). In written object naming, paragraphias were less frequent ($p < .05$). In the majority of patients, reading improved ($p < .05$).

Table 3
The Effect of DDAVP on Speech in Patients with Acoustico-Amnestic Aphasia

Subject no.	Time following stroke (years)	Severity of speech impairment	Separate components of speech								Treatment results
			IS	Rep.	N	Com	W	PA	Read	Para	
1	1.1	Severe	2/2	2/2	3/3	2/2	3/3	2/1	3/3	2/2	Insignificant
2	1.0	Moderate	1/1	1/1	2/1	1/1	2/2	2/1	2/2	1/1	Satisfactory
3	1.0	Moderate	2/2	2/2	3/2	1/1	2/2	2/0	2/2	1/1	Satisfactory
4	1.5	Moderate	2/1	1/1	2/1	2/1	2/2	2/1	3/2	1/0	Good
5	1.0	Mild	1/0	0	1/0	1/0	1/0	1/1	1/0	1/0	Good
6	1.4	Mild	1/0	0	1/0	1/0	1/0	1/1	1/1	1/0	Good
7	1.0	Mild	1/0	0	1/0	1/0	1/0	1/0	1/0	1/0	Good
8	1.0	Mild	1/1	1/1	2/1	1/1	1/1	2/2	0	1/0	Satisfactory
9	1.1	Mild	1/1	1/0	1/0	1/1	0	0	0	1/1	Satisfactory
10	1.4	Mild	1/0	0	1/0	1/0	1/0	0	1/0	1/0	Good
11	1.1	Mild	1/0	0	1/0	1/0	1/0	1/0	1/0	1/0	Good
12	1.5	Mild	1/0	0	1/0	1/0	1/0	0	1/0	1/0	Good.
13	1.1	Mild	1/1	1/0	1/0	1/1	0	0	0	1/1	Satisfactory
14	1.0	Mild	1/1	0	2/2	0	2/2	2/1	0	1/1	Insignificant
15	1.0	Mild	1/0	1/1	2/2	0	0	0	0	0	Insignificant
16	1.5	Mild	0	0	1/0	0	0	0	0	0	Insignificant

Note. DDAVP = 1-desamino-8-D-arginine-vasopressin. Separate components of speech: IS = independent speech, Rep = repetition, N = naming, Com = comprehension, W = writing, PA = phonetic analysis, Read = reading, Para = paraphasias. The numbers in the cells represent the results of investigation prior to treatment course / after 1 course of treatment with DDAVP (in points).

More often, they were able to read silently correctly and to match picture to text. In some patients, there was improvement of comprehension of situational language, simple instructions and complex logical grammatical constructions. In 50% of the patients, there was less difficulty in the phonetic analysis of words. With treatment with vasopressin, this group of patients showed a regression of secondary defects of expressive speech. There was significant improvement of independent speech ($p < .05$). Spontaneous speech and dialogue in patients with acoustico-agnostic aphasia became more detailed, with varied vocabulary, in combination with a decrease of vocal disinhibition. On the whole, within the group, there was a decrease in the frequency of literal paraphasias and sensory agrammatism. In a majority of cases, there was recovery of automatic speech, including listing of months of the year ($p < .05$). In this group, there was improvement of repetition ($p < .05$). In the repetition of complex and foreign words, sound and speech series, and simple sentences, paraphasia occurred less frequently. The positive changes in independent speech in this group correlated with the improvement in object and action naming ($p < .05$). In cases of acoustico-agnostic aphasia, the leading factor of impairment was the sensory component of speech or audio-verbal gnosis (recognition) (Luria, 1970; Luria & Hutton, 1977). In this group of subjects, vasopressin led to significant recovery of the sensory component of speech ($p < .01$) (see Figure 1). In 17% of the cases with acoustico-agnostic aphasia, there was a placebo-effect; however, comparison of speech after administration of vasopressin showed significant improvement as compared to the placebo.

The following is case 2, illustrating the effect of the neuropeptide vasopressin of the state of speech in acoustico-agnostic aphasia. Patient no. 8 (see Table 4), 36 years old, had higher education (by profession, an engineer), and was right-handed. The patient was admitted for treatment by the Neurological Rehabilitation Department of the V.M. Bekhterev Saint Petersburg Psychoneurological Research Institute. Diagnosis on admittance: sequela of stroke in the watershed area of the left median cerebral artery, mild acoustico-agnostic aphasia, mild right-sided hemiparesis, mild right-sided hemi-anesthesia. On admission, the patient complained of difficulty speaking and clumsiness in the right extremities. Neuropsychological testing revealed that the patient's speech consisted of phrases, without noticeable agrammatism, but predicative: In the production of speech there was a predominance of verbs (see Table 4). There was a tendency towards vocal disinhibition. In more complex forms of oral speech (e.g., story-telling), there were agrammatic turns of speech. Paraphasias occurred in the repetition of complex, foreign, and pseudo words, and complex sound and speech series. In the repetition of sentences, there were incorrect grammatical agreements of the separate parts of speech. There was no impairment of pronunciation. Naming was insignificantly impaired. In object naming, difficulty occurred only in complicated conditions: during spontaneous speech and simultaneous naming of several objects. Directed speech was well understood, although difficulties occurred when there was an unexpected address in conversation with several persons in the ward; there was poor apprehension of television and radio programs. The patient's speech worsened in the presence of sound interference. Impairment of comprehension of complex grammatical constructions typical of the Russian language was revealed. Retention of speech series was limited to 3-4 words. There was slight impairment in writing. Infrequently paragraphias occurred in the writing of syllables, words, dictated sentences, and independent writing. Phonetic analysis and reading showed mild impairment. Reading out loud and silently and text comprehension were intact. There was slight dyslexia noted only when reading complex words and pseudo words.

After the administration of arginine-vasopressin in the above-described standard regimen, expressive speech was recovered (see Table 4). Spontaneous speech became detailed without vocal disinhibition. After the course of treatment with the neuropeptide, sound interference did not affect the perception of directed speech. In dialogue, there were no longer agrammatic turns of speech. There was improvement of complex forms of oral language. In the compilation of

Table 4

The Effect of DDAVP on Speech in patients with Acoustico-Agnostic Aphasia (M ± m, rate)

N	Indices of speech activities	Prior to treatment	Following treatment
1.0	Independent speech	1.5 ± 0.1	0.9 ± 0.1*
1.1	Automatic (listing of months)	1.6 ± 0.5	0.5 ± 0.5*
2.0	Repetition	1.8 ± 0.1	1.4 ± 0.1*
3.0	Naming	1.9 ± 0.3	1.2 ± 0.3*
4.0	Writing	2 ± 0.1	1.4 ± 0.1*
4.1	Written naming of items	2.5 ± 0.4	1.6 ± 0.4*
5.0	Reading	1.4 ± 0.2	0.9 ± 0.2*

Note. DDAVP = 1-desamino-8-D-arginine-vasopressin.

N = 1.0, 2.0, 3.0, 4.0, 5.0 =– several parts of speech function,

1.1, 4.1 = sample components of relative speech function.

* = significant changes in indices after treatment course with DDAVP ($p < .05$ in all variances)

Table 5
The Effect of DDAVP on Speech in Patients with Acoustico-Agnostic Aphasia

Subject no.	Time following stroke (years)	Severity of speech impairment	Separate components of speech								Treatment results
			IS	Rep.	N	Com	W	PA	Read	Para	
1	1.1	Severe	3/2	3/3	3/2	3/2	3/2	3/3	3/2	2/1	Good
2	2	Severe	3/3	2/2	3/3	3/3	3/3	3/3	3/3	3/3	Absent
3	1.2	Moderate	2/1	2/2	3/2	2/2	3/2	3/2	2/1	2/1	Good
4	1.5	Moderate	2/1	2/1	3/2	2/2	3/2	3/2	2/1	2/1	Good
5	1.3	Moderate	2/1	2/2	2/2	1/1	2/1	1/0	1/0	2/1	Good
6	1.5	Mild	1/0	2/1	1/1	1/1	1/1	1/1	1/1	0	Insignificant
7	1.2	Mild	1/0	1/0	1/0	1/0	1/0	1/0	0	1/0	Good
8	1.1	Mild	1/0	1/0	1/1	1/1	1/1	1/1	0	0	Insignificant
9	1.5	Mild	1/0	2/2	1/1	1/1	2/2	1/1	1/1	0	Insignificant
10	1.0	Mild	1/0	1/0	1/0	1/0	1/0	1/0	0	1/0	Good

Note. DDAVP = 1-desamino-8-D-arginine-vasopressin. Separate components of speech: IS = independent speech, Rep = repetition, N = naming, Com = comprehension, W = writing, PA = phonetic analysis, Read = reading, Para = paraphasias. The numbers in the cells represent the results of investigation prior to treatment course / after 1 course of treatment with DDAVP (in points).

sentences and narratives to illustrations, there were less frequent verbal substitutions. There was a regression of impairment of repetition. There was recovery of the repetition of complex, foreign and pseudo words, and sentences. In object naming, no paraphasia was noted. There was improvement in the comprehension of directed speech. Paragraphias occurred less frequently than previously during dictated and independent writing. The patient carried out phonetic analysis with ease. On the whole, there was a decrease in paraphasia. Thus, with treatment with arginine-vasopressin in a patient with mild acoustico-agnostic aphasia, there was marked improvement in speech. There was no placebo-effect.

Twelve patients with acoustico-amnestic and acoustico-agnostic aphasia received a second course of treatment with the neuropeptide (see Table 5). Improvement in speech was noted in 65% of the patients. On the whole, there was further improvement in independent speech ($p < .01$), repetition speech ($p < .01$), object naming ($p < .01$), reading ($p < .01$), phonetic analysis ($p < .01$) and speech comprehension ($p < .01$). There was further optimization of expressive and impressive speech. The effect of the first treatment course persisted and the second course of treatment with the neuropeptide induced further improvement in speech.

Discussion

Under the condition of double blind control, it was observed that 1-desamino-8-D-arginine-vasopressin, a selective vasopressin V2-type receptor agonist, induces the recovery of speech with sensory aphasic disturbances by positively influencing the expressive and impressive components of speech. The therapeutic effect of arginine-vasopressin is typified by regression of primary speech impairment: optimization of the afferent component of speech in acoustico-

agnostic and of the integrative component or audio-verbal memory in acoustico-amnestic aphasias, and it was comparable in efficacy relative to the integrative and sensory components of speech. The observed effect was persistent and did not regress after cessation of treatment during the entire follow-up period. Repetitive courses of treatment induced further improvement in the speech of these patients.

The positive effect of the neuropeptide arginine-vasopressin on speech in acoustico-amnestic aphasia is most probably due to its mnemotropic properties, as the specificity of this form of aphasia lies in the selective central impairment of audio-verbal memory (Luria 1970; Luria & Hutton, 1977), and vasopressin possesses anti-amnestic properties (Wied et al., 1993; Vawter et al., 1997). It is considered that optimization of memory by arginine-vasopressin occurs by means of its modulation of catecholaminergic, serotoninergic, and other neurotransmitter systems (Kovacs, Bohus, & Versteed, 1980; Lanca, Liu, Man, & Kalant, 1995; Winnicka & Wisniewski, 1998). Probably, this process comprises one of the components of the compensation of speech impairment.

The current study has shown that after administration of arginine-vasopressin to patients with acoustico-amnestic aphasia, during independent speech, there is faster reproduction of simple words. The speech of such patients shows less verbal and literal paraphasias, and improvement in naming objects with simple nouns. Phonetic analysis of recalled simple words (by illustrations) recovered. It is known that stimuli expressed with high-frequency, single-syllable, words are more quickly and more correctly perceived by the right hemisphere (Goodal, 1984; Nikolaenko & Egorov, 1998), and phonetic analysis is specific for the left hemisphere (in right-handed subjects) (Sperry et al., 1969; Zaidel, 1978). The results obtained and literature review allow one to conclude that the recovery of expressive and impressive speech with the administration

of vasopressin in patients with acoustico-amnestic aphasia is likely to be due to the organization of audio-verbal memory. Furthermore, there was primary activation of neuronal connection of the intact right hemisphere and secondary activation within the damaged left hemisphere.

In patients with acoustico-agnostic aphasia, treatment with vasopressin led to regression in impairment of language gnosis (recognition), the principal factor leading to speech impairment in this form of aphasia (Luria, 1970; Luria & Hutton, 1977). There was a decrease in the severity of primary impairment of impressive speech and in secondary impairment of expressive speech. In this group of patients, there was improvement in writing, including the writing of object names, silent reading and matching of text to picture. According to the review of the literature, normally inherent speech, and silent reading in particular, is accompanied by bilateral neuronal activation within the sensorimotor cortex, thalami, cerebellum, and supplementary motor regions (Murphy et al., 1997). This suggests that the recovery of impressive speech in patients with acoustico-agnostic aphasia results from the activation of intact structures of the right hemisphere and secondary activation of surviving target-neurons in the left hemisphere by vasopressin. In patients with acoustico-agnostic aphasia in expressive speech (independent, automatic and repetition speech, object and action naming), there was a decrease in vocal disinhibition. With treatment, patients showed a decrease in amount of paraphasias in tests of repetition of complex and foreign words, and in the reproduction of series of sounds and words, and simple sentences. The administration of vasopressin in this group of patients led to regression of impairment of the sensory component of speech. The optimization of the afferent component of speech by the neuropeptide in acoustico-agnostic aphasia was most likely due to its participation in the process of regulation of the sensory component of speech both in impairment and in intact speech. Such an assumption may be justified, as it is considered that vasotocin in birds—an analogue of mammal vasopressin—participates in the regulation of the acoustic component of vocalization (Voorhuis et al., 1988), and the cerebral control of vocalization in animals and humans is supposed to share similarities (Bieser & Muller-Preuss, 1996; Gemba, Miki, & Sasaki, 1997).

To account for the data obtained, it is necessary to bear in mind that in experiments on damaged central motor systems in the left hemisphere, vasopressin in a similar dose range induces the reorganization of intra-central connections leading to the involvement of the neurons of the intact right hemisphere in the compensation process (Vartanian, Klementiev Neuimina, & Novikova, 1994). As the dominant hemisphere in relation to speech and motor activity coincides in most cases, it is possible that recovery of speech in cases of central motor speech impairment was also due to primary activation by vasopressin of the reserve connection of the intact right hemisphere and secondary activation of the surviving cells of the left hemisphere.

According to the data of functional magnetic resonance tomography, during the recovery period after stroke, there is primary activation of right-sided speech (language) homotopic regions, whereas the area of the brain tissue surrounding the infarct is activated much later (Cappa, et al., 1997; Fernandez et al., 2004; Heiss, Thiel, Kessler, & Herholz, 2003; Xu et al., 2004). Thus, there is spatial-temporal reorganization of the brain following focal brain injury, typified by involvement of both hemispheres in the compensation-recovery process, with primary activation of the right hemisphere in left-sided damage.

The present study has demonstrated that vasopressin is equally effective in the correction of speech impairment in acoustico-amnestic and acoustico-agnostic aphasias. Considering literature reviews and the results of the present study, speech recovery in these cases is due to several factors. Firstly, there is functional compensation and reorganization of speech, manifesting in the increased activation of normally deactivated homologous regions of the right hemisphere. Secondly, recovery is associated with a simultaneous with treatment increase of the neuronal activity of the partial deafferentation of the nerve cells of language zones of the left hemisphere within the ischemic penumbra. Thirdly, recovery is associated with the involvement of alternative pathways of the ipsilateral (left) hemisphere as a result of the direct action of the neuropeptide. Thus, the therapeutic effect of vasopressin is a result of the optimization of structural and functional systems in the formation of speech. During the study, it was observed that repeated treatment courses with the neuropeptide induce further improvement in speech, reflecting the presence of supplementary reserve ability.

According to literature reviews, arginine-vasopressin possesses neurotrophic properties. In hippocampus cell cultures, infiltration of the neuropeptide results in an increase in the amount of dendrites and the length of nerve fibers (Chen et al., 2000; Wu, Lanca, Liu, Man, & Kalant, 1995). This suggests that the persistence of the effects of vasopressin in the correction of speech impairment in aphasia may be due to similar cytoarchitechtural reorganization.

It is known that in early ontogenesis, even with widespread brain injury, it is possible to achieve practically complete compensation of speech (Bryden, 1982). In turn, vasopressin optimizes the maturation of nerve cells during this period (Brinton & Gruener, 1987), and possesses neurotrophic properties (Chen et al., 2000; Wu et al., 1995). In this consideration, it is probable that speech recovery in aphasia of varying severity is due to activation by vasopressin of reparative processes, similar to those mechanisms that occur in the developing nervous system.

Thus, it has been shown that arginine-vasopressin improves speech in acoustico-amnestic and acoustic-agnostic aphasia by means of activation of the V2-receptors of the central nervous system and the consecutive reformation of intra-central connections. The results obtained provide the basis of the suggestion that the endogenous neuropeptide arginine-vasopressin participates in the regulation of several components of speech, both in pathology and, most likely, normally.

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