



Phonological agraphia following a focal anterior insulo-opercular infarction

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Abstract

Following a unique infarction, restricted to the left anterior insula and the adjacent part of the intrasylvian frontal opercular cortex, an 83-year-old right-handed patient acutely developed a severe speech disorder that evolved into mere mutism within a few hours. After rapid recovery from mutism, oral language was characterized by severe apraxia of speech. In-depth language investigations further disclosed an isolated, highly selective disturbance of the spelling system (phonological agraphia) which resolved rapidly. One year after onset of neurological symptoms, the apraxia of speech had almost completely receded. The anatomoclinical findings in this first representative of pure and nearly isolated phonological agraphia complement previous neuroanatomical and neurolinguistic accounts of phonological agraphia. The data not only seem to enrich current insights in the anatomical locus for phonological agraphia, they also seem to contribute to a further delineation of the insular role in phonologically mediated aphasic manifestations. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

In contrast to 'lexical agraphia' [8], the concept of 'phonological agraphia' [58,63] refers to the neurolinguistic condition in which the ability to spell pronounceable nonwords as well as unfamiliar or novel real words is deficient, while the spelling of both orthographically regular and irregular familiar words is retained. The disorder is said to reflect a selective functional disruption within the phoneme-to-grapheme conversion system, where the translation of sound sequences into letter sequences takes place. Notwithstanding the anatomical and clinical variability between cases, the anatomical substrate of phonological agraphia, determined on the basis of superimposed computerized tomography scans of the brain, is

classically related to damage to the anterior–inferior supramarginal gyrus of the language dominant hemisphere and the adjacent insular structures medial to it [56,58,63]. As reflected by the small number of cases reported in the literature, this aphasic phenomenon is only exceptionally found in isolation and mostly occurs in a context of additional dysfunctions of the written language system. Reviewing the literature from the initial description of the concept by Shallice in 1981 [63], Alexander et al. [3] only retained 11 linguistically and neuroanatomically sufficiently documented cases of phonological agraphia. Only four of these cases [10,11,23,63] had normal or almost normal real word spelling and were identified as representatives of isolated phonological agraphia. In all cases reported so far, however, the agraphic symptoms not only extended beyond the restrictive boundaries of pure phonological processing mechanisms, but also occurred in association with other aphasic disturbances.

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In contrast to the referred to documented cases, we had the unique opportunity to study a patient with a pure and nearly isolated phonological agraphia. The patient displayed no concomitant aphasic symptoms, but a selective disorder of articulate speech (apraxia of speech). In further discordance with the reported cases of phonological agraphia, neuroradiological findings in our patient did not disclose involvement of the expected anatomical loci, but a surprisingly small and circumscribed lesion in the anterior insular cortex and the adjacent frontal opercular cortex. In light of our anatomical findings, we propose to enrich the underlying neuroanatomical substrate for phonological agraphia with the notion of anterior insular damage. Our findings further seem to illustrate an unexpected dimension of the role of the insula in phonological language disturbances.

2. Case report: history

Following a 2-day period of intermittent complaints of vertigo and headache, the here presented independently-living 83-year-old right-handed woman acutely developed severe speech disturbances. Within a few hours, the expressive language symptoms evolved from mere articulatory distortions to near mutism, in which any attempt to speak resulted in undifferentiated, incomprehensible grunting. Notwithstanding the fact that speech had already reappeared when she was admitted to hospital a few hours later, she was only able to utter fragments of articulatory severely distorted speech. Marked articulatory deviances, such as phonemic errors, altered production of vowels and consonants, a marked tendency to protract speech sounds, intersyllabic interruptions resulting in scanned speech fragments and abnormal speech rate characterized the patient's oral-verbal output. Consciousness was not clouded and the patient was fully cooperative. There was no bucco-labio-lingual or facial apraxia and limb praxis was bilaterally intact. Auditory-verbal comprehension was functional on the complexity level of daily conversation and she could easily follow three-step written commands. She wrote with her right hand and produced orthographically well-formed letters. Dictation writing of a short sentence was normal.

The patient's medical history consisted of intermittent arterial atrial fibrillation, arterial hypertension, hypothyroidism and recurrent urinary tract infections. The general physical examination on admission was unremarkable. Pulse rate was regular, 72 per minute and blood pressure was 140/80 mmHg. Except for the severe speech disturbances, the elemental neurologic examination was normal. Muscle tone and strength, coordination and sensation were intact. Tendon reflexes were symmetrical and the plantar responses were flexor.

Cranial nerve examination was normal. Laboratory results showed an increased serum cholesterol value (259 mg/dl), increased TSH levels (52 μ U/ml), decreased fT3 (2.6 pmol/l) and fT4 (6.5 pmol/l) levels. Vitamin B₁₂ and folic acid levels were normal. Serologic tests for syphilis were negative. A chest radiograph was normal. An electrocardiogram (ECG) revealed a normal sinus rhythm, a first degree atrioventricular (AV) block and signs of a mild left ventricular hypertrophy. Transesophageal echocardiography disclosed no abnormalities. Echo Doppler-duplex-examination of the carotid arteries showed diffuse atheromatosis at both bifurcations with a maximal stenosis of 40% on the right side. An oto-rhino-laryngeologic exam, including an audiogram, was within normal limits. A standard electroencephalogram (EEG) showed bilateral slow wave activity (θ range) more pronounced over the left hemisphere. A computerized tomography (CT) scan of the brain 4 days after onset of neurological symptoms disclosed localized hypodensities demonstrating left insulo-opercular softening.

A Tc-99m-ECD single photon emission tomography (SPECT) scan of the brain on day nine of admission revealed a left hypoperfusion involving the gyrus frontalis inferior and gyrus precentralis. A crossed cerebellar diaschisis was demonstrated as well (Fig. 1a,b).

Brain magnetic resonance imaging (MRI) performed 17 days after stroke demonstrated a focal anterior insulo-opercular lesion. T1-weighted coronal and horizontal images demonstrated lesions occupying the sulcus circularis insulae, the gyri breves insulae and the gyrus frontalis inferior (especially the pars opercularis) (Fig. 2a–d). There was a disturbance of the blood-brain barrier, as demonstrated by gadolinium positivity of part of the lesion. Involvement of the gyrus precentralis was shown as well. In addition, a mild degree of symmetrical status lacunaris of the basal ganglia and several small bilateral white matter lesions — presumably of vascular origin — were observed. The patient was discharged after 18 days hospitalization and returned home again. Regular neurological follow-up and intensive speech therapy were started. On a repeat MRI study of the brain, performed 3 months after onset of neurological symptoms, the lesions became gadolinium-negative. Lesions were still visible at the rostral part of the gyri breves, the pars opercularis of the gyrus frontalis inferior, the sulcus precentralis and the gyrus precentralis. In this stage, the lesions were hypointense and cystic.

3. Neurocognitive assessments

Language and other cognitive functions were examined longitudinally in agreement with a three epoch

time-frame for models of aphasia, developed by Maz-zocchi and Vignolo [38]. In order to avoid remote functional lesion effects, generally accounting for the instability of the aphasic profile during the acute phase, extensive examinations were not undertaken within the fortnight following the onset of neurological symptoms. During the acute phase (from days one to 14 approximately), language functions were evaluated on mere clinical grounds by means of short, bed-side screening instruments and close neurobehavioral observations. During the subsequent lesion phase, which might last up to 4 months and which is considered to offer the most pure and robust anatomo-clinical correlations [2,40], a formal neuro-linguistic work-up was done. Language functions were reevaluated again in the 'late phase', 1 year post onset of neurological symptoms. The neurolinguistic

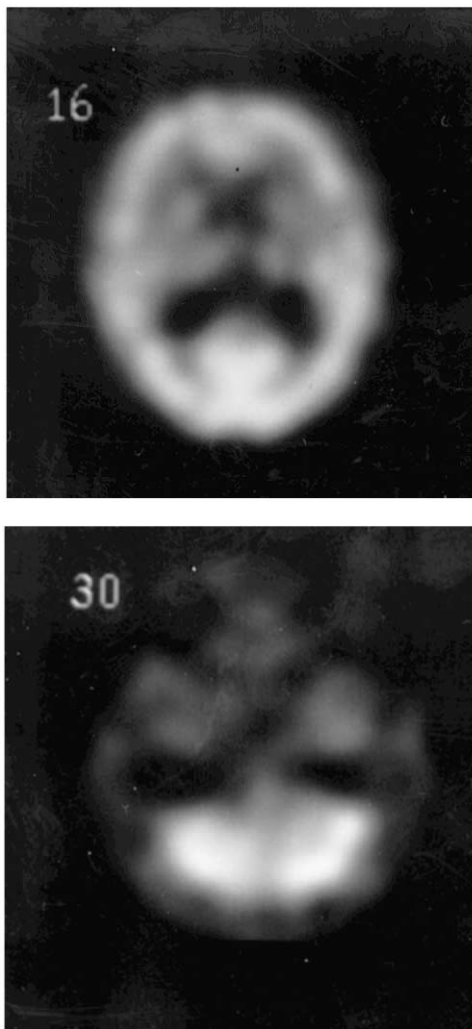


Fig. 1. Tc-99m-ECD SPECT scan of the brain performed 9 days after stroke demonstrating (a) hypoperfusion in the left gyrus frontalis inferior and left gyrus precentralis and (b) crossed cerebellar diaschisis.

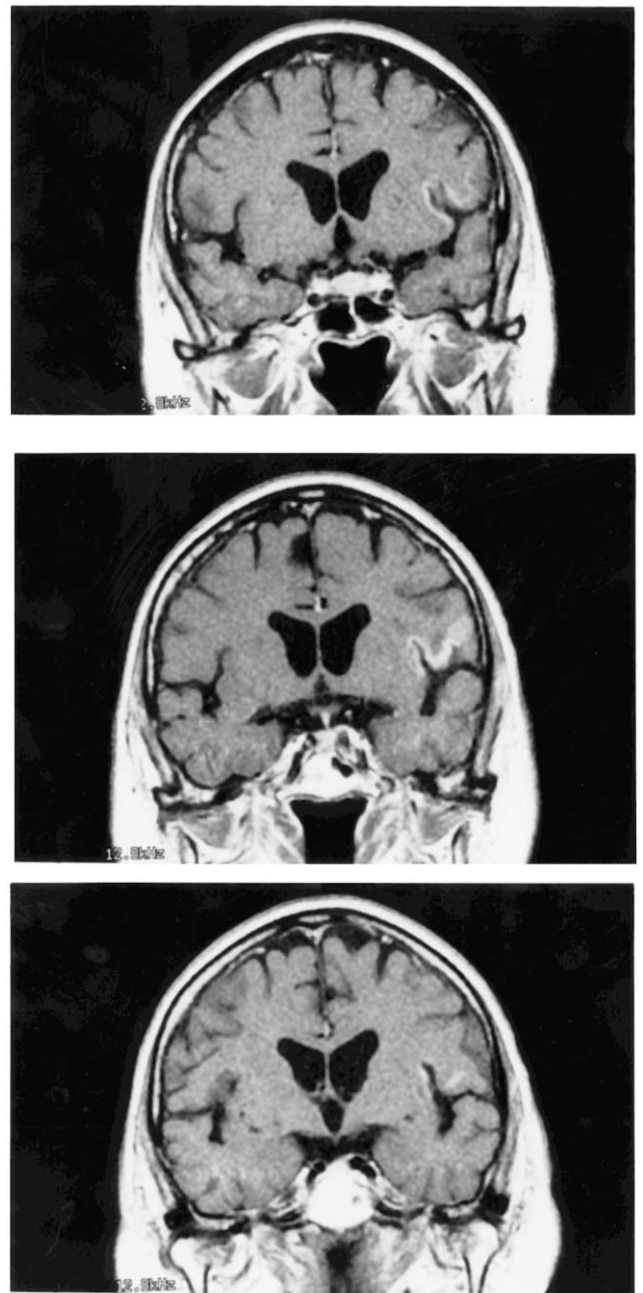


Fig. 2. Brain MRI (a–c: from rostral to caudal) coronal and (d) axial T₁-weighted slices disclose in the left hemisphere a focal anterior insulo-opercular lesion occupying the sulcus circularis insulae, the gyri breves insulae, the gyrus frontalis inferior and the gyrus precentralis. Gadolinium positivity of part of the lesion demonstrates a disturbance of the blood brain barrier. Several small bilateral white matter lesions of presumed vascular origin are also shown.

test battery mainly consisted of the Dutch version of the Aachener Aphasia Test (AAT) [26], subtests of the Boston Diagnostic Aphasia Examination (BDAE) [24], the Boston Naming Test (BNT) [27], the Token Test [17] and a selection of subtests from the Dutch version of the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) [6].

Neurocognitive investigations were performed in the lesion phase at day 27 and 2.5 months post-stroke by means of the following standardized tests: the Mini Mental State Examination [22], the Alzheimer's Disease Assessment Scale [59], the Raven Coloured Progressive Matrices [52] and the Hierarchic Dementia Scale [13]. Handedness was formally assessed with the Edinburgh Inventory [47].

3.1. Acute phase findings: neurolinguistic observations

The day after admission, apraxia of speech most markedly characterized the patient's oral-verbal output. Speech was slowly and hesitantly articulated in a slightly hypophonic way. In addition, effortful articulatory struggles, which particularly affected consonant clusters, vowel and consonant lengthenings, decreased stress and a general flattening of voice volume severely disrupted prosody and melody. As a result, syllables tended to become isochronous and of equal prominence (scanning speech). Though the articulatory distortions affected speech rather inconsistently, errors predominantly consisted of phonemic substitutions. Articulatory groping and struggling, which induced sequential errors and mostly unsuccessful efforts to self-correction alternated at times with 'islands of error-free speech'. Errors increased with word length and were not task dependent. No improvement was found when the patient recited, repeated, cursed or read aloud. Aside from this selective impairment of speech movements, no accompanying aphasic or dysarthric disturbances were found. A concise screening of auditory-verbal and written comprehension, expressive and receptive syntax, word-finding and written confrontational naming and dictational writing disclosed no structural linguistic deficits. The next day, the apractic speech symptoms substantially improved. Articulation rate remained bradylic, but voice amplitude normalized. Vowel and consonant distortions still occurred and sporadically even blurred target words phonetically. Most of the time, however, these phonetic alterations of vowel and consonant production did not give the examiners the impression that a phoneme different from the target phoneme had been used. On the third day of admission, the significant reduction of oral-verbal output, the diminution of speech initiation and the often effortful and fragmented attempts to formulate ideas, resembled adynamia of self-generated speech. In contrast to marked problems in spontaneous speech, the patient obtained better results when speech was imposed or when the conversation was stringently guided by the interlocutor. Articulatory distortions, however, still intruded speech at all levels. At day six of admission, no overt problems in the dynamics of speech were found, but speech sound production remained distorted.

3.2. Lesion phase findings

3.2.1. Neurolinguistic findings: day 15

Table 1 displays the neurolinguistic results obtained 15 days post onset neurological symptoms.

Auditory-verbal comprehension was, as illustrated by the AAT auditory comprehension test results, entirely normal for words and sentences (-0.14 and -0.23 S.D., respectively). Auditory-verbal comprehension of daily, conversational language (e.g. BDAE commands 15/15) and comprehension of spatial prepositions embedded in reversed sentences [48] was also normal (100% correct). The patient frequently requested to repeat the instructions of parts III–V of the Token Test and obtained a deviant score of 38/50 (-3.53 S.D.). All 12 errors occurred in part IV and V for which she often indicated not having recalled the second part of the instructions. As a consequence, deficient Token Test performances most likely seemed to reflect working memory difficulties rather than a genuine auditory-verbal comprehension deficit.

Spontaneous and imposed oral language examinations, as displayed in Table 1, disclosed normal results. The AAT repetition and visual confrontation naming tests were normal. On the BNT, 49 of the 60 items were named correctly. In comparison with a gender, age and education adjusted mean of 43.3 and a S.D. of ± 5.45 , this score also represents a normal result [34]. Qualitative analysis of the naming errors according to a classic neurolinguistic taxonomy [15,24,29], revealed the error profile not being essentially different from the profile encountered in a reference group of 200 healthy elderly [34]. Most naming errors (6/11) consisted of adequate circumlocutions (e.g. 'an instrument used by a doctor to listen to your heart' for 'stethoscope'). Two errors were considered 'porte-manteau words' or semantic neologisms (e.g. 'ijsgrijper' ('icegrabber) for 'suikertang' (tongs)), another two were classified as foreign words (e.g. 'boulier compteur' for 'telraam' (abacus)) and the remaining error, which phonological structure overtly resembled the target word ('strot' (throat) for 'strop' (noose)), was a verbal morphological paraphasia. Verbal fluency for 1 min semantic categories (animals, transport, vegetables, and clothes) and 2 min phonological categories (phonemes [f], [a] and [s]) matched gender, age and education means (unpublished personal data). All utterances were of normal length and were (morpho)syntactically well-structured.

Though not reflected by the formal test results, apractic speech symptoms intruded oral verbal output. Inconsistent non-sequential substitutions of target phonemes and phonetic alterations, such as prolongations and reductions of speech sounds and diphthongizations, characterized spontaneous and imposed speech. Since these articulatory deviations are phonetic

distortions of apractogenic origin they were not classified and scored as aphasic errors.

Oral reading, contaminated by phonetic alterations, revealed no errors of aphasic origin. Normal AAT results were found at the grapheme, morpheme and textual level.

Reading comprehension for words, sentences and texts was within entirely normal limits. The patient was

also perfectly able to summarize the contents of a short newspaper article accurately.

Dictational writing scored irrespective of some obvious spelling errors within entirely normal limits on the AAT. The patient obtained a score of 24/30 on dictational writing which represents 1.08 S.D. below the mean of 28/30 (± 3.67 S.D.). Most of the misspelled words contained phonemic paraphrasias that

Table 1
Neurolinguistic test results 15 days post onset^a

Neurolinguistic tests	Results	Percentile	Maximum	Control	
				Mean	S.D.
<i>Aachener Aphasia Test</i>					
Comprehension	106	90	120	108.5	10.24
Auditory: words	26	83	30	26.49	3.30
Auditory: sentences	26	81	30	26.79	3.41
Total	52	85	60	53.28	6.08
Written: words	26	67	30	28.30	2.29
Written: sentences	28	95	30	26.91	3.39
Total	54	89	60	55.21	4.90
Token Test	12	83	0	2.28	2.75
<i>Spontaneous speech</i>					
Communicative behaviour	5		5	4.63	0.54
Articulation and prosody	4		5	4.63	0.67
Automatisms	5		5	4.59	0.65
Semantic structure	5		5	4.59	0.53
Fonematic structure	4		5	4.54	0.56
Syntactic structure	5		5	4.41	0.55
<i>Imposed speech</i>					
Total repetition	143	92	150	144.1	8.07
Phonemes	30	88	30	28.91	2.09
Monosyllabic words	28	68	30	29.22	1.32
Loan- and foreign words	30	95	30	28.94	2.31
Compounds	27	85	30	28.45	2.22
Sentences	28	93	30	28.55	1.90
Total naming	118	100	120	109.3	8.42
Simple nouns	30	97	30	27.92	2.90
Color names	28	86	30	27.69	1.99
Composed nouns	30	99	30	28.04	2.61
Sentences	30	100	30	25.69	3.72
Written language			90	85.52	7.63
Reading aloud	30	96	30	28.95	1.93
Composing	26		30	28.57	2.75
Dictational writing	24	76	30	28	3.67
BDAE auditory comprehension	15		15		
Spatial Comprehension Test	12		12		
Boston Naming Test (BNT)	49		60	43.3	5.45
Verbal fluency–semantics	41			43.4	11.67
Animals	12				
Transport	6				
Vegetables	10				
Clothing	13				
Number of perseverations	1				
Number of intrusions	0				

^a Performance was considered impaired if the score fell more than 2 S.D. below the mean achieved by controls.

Table 2
Test results PALPA dictational writing single syllable words (37) and nonwords (43) 1 month (score A) and 2.5 months (score B) post onset^a

	Words (PALPA 37)				Nonwords (PALPA 43)			
	Score A	Score B	Mean (S.D.)	Range	Score A	Score B	Mean (S.D.)	Range
3 Graphemes	6/6	6/6	6.00 (0.58)	5–6	3/6	6/6	5.92 (0.22)	5–6
4 Graphemes	6/6	6/6	5.88	–	4/6	6/6	5.83 (0.38)	5–6
5 Graphemes	4/6	6/6	5.90 (0.33)	5–6	4/6	6/6	5.85 (0.36)	5–6
6 Graphemes	6/6	6/6	5.98 (0.30)	5–6	2/6	5/6	5.70 (0.46)	5–6
Total results	22/24	24/24	23.75 (0.15)	21–24	13/24	23/24	23.33 (0.96)	21–24
Percent	92	100			54	96		

^a Means (S.D.) and range obtained by the reference group consisting of 40 healthy volunteers.

induced errors of the verbal morphological type (e.g. 'werker' (worker) instead of 'werkster' (female worker)). Aside from letter omissions, substitutions (e.g. 'scheent' instead of 'schicht' (flash)) and transpositions (e.g. 'montega' instead of 'montage' (assembly)) of letters occurred. Orthography was unaffected. Tempo was normal and letters were well-formed.

3.2.2. Additional neurolinguistic investigations: 1 month post onset

In addition to the AAT data obtained at day 15, further specification and differentiation of the spelling problems was elicited during the lesion phase by means of an additional neurolinguistic work-up, consisting of a selection of tests extracted from the PALPA. The selection consisted of subtests exploring several dimensions of dictational writing and reading.

3.2.2.1. Neurolinguistic methods. Spelling tests consisted of dictational writing of:

- 24 concrete single syllable nouns varying in length from three to six graphemes (e.g. 'wit' (white), 'kist' (coffin), 'kunst' (art), 'kracht' (strength)) (PALPA test 37)
- 40 nouns, 20 orthographic regular (e.g. 'lucht' (air)) and 20 orthographic irregular ones (e.g. 'douche' (shower)), varying in imageability (high/low) (e.g. 'kachel' (stove)/'couplet' (stanza)) and frequency (high/low) (e.g. 'kam' (comb)/'routine' (routine)) (PALPA test 42)
- 24 orthographically pronounceable single syllable nonwords varying in length from three to six graphemes (e.g. jit, bist, munst, kricht) (PALPA test 43)
- sentences and entire paragraphs extracted from a magazine.

Reading tests consisted of:

- 30 nonwords varying in syllable length from one to three syllables (e.g. kruft, duter, inima) (PALPA test 8)
- 24 concrete nouns consisting of a single syllable and varying in length from three to six graphemes (e.g.

'dak' (roof), 'hand' (hand), 'broek' (trousers)) (PALPA test 37).

3.2.2.2. *Statistical methods.* Reference values of test scores were obtained in a sample of 40 healthy volunteers [6]. The 95% confidence interval for the mean test score was calculated as the confidence interval for the binomial probability $P: P \pm z_{\alpha/2} \sqrt{(pq/n)}$ with P , the reference score in proportion of correct responses on total responses; $q = 1 - P$; $z_{\alpha/2} = 1.96$, normal curve area for $\alpha = 5\%$; and n , the total number of responses. Significance of the difference between proportions of correct responses between tests was assessed with Fisher exact test.

3.2.2.3. Results

Dictational writing. Statistical analysis of the data revealed that the total result on PALPA test 37 (Table 2) fell below the lower limits of the 95% confidence interval (CI) for the reference score obtained in 40 healthy volunteers. The 95% CI for the reference score is between 22.8 and 24/24. Dictational writing of single syllable words (22/24) scored below the lower limit of the reference 95% CI. Dictational writing of nonwords (PALPA test 43) was considerably worse than dictational writing of words. Indeed, dictational writing of nonwords (13/24) (Table 2) scored well below the 95% CI for the reference score (21.8–24/24), and the proportion of correct responses for nonword writing (54%) was significantly lower than the proportion for words (92%; $P = 0.008$, Fisher exact test).

The 95% CI for the reference score of dictational writing of regular words (Test 42) is between 18.7 and 20/20 and for irregular words between 15.5 and 20/20 (Table 3). The patient obtained a score of 14/20 for dictational writing of regular words, which represents a result well below the 95% CI for the mean reference score, whereas the score for irregular words (18/20) fell within the reference 95% CI. However, the difference in the proportion of correct responses between regular and irregular words did not reach statistical significance ($P = 0.14$, Fisher exact test).

Table 3
Test results PALPA 42 dictational writing regular and irregular nouns varying for regularity, frequency and imageability 1 month (score A) and 2.5 months (score B) post onset^a

	Regular words				Irregular words			
	Score A	Score B	Mean (S.D.)	Range	Score A	Score B	Mean (S.D.)	Range
LI	6/10	9/10	9.88 (0.40)	8–10	10/10	10/10	9.28 (1.34)	5–10
HI	8/10	9/10	9.78 (0.61)	7–10	8/10	9/10	8.88 (1.71)	2–10
LF	7/14	12/14	13.88 (1.23)	8–14	15/17	14/17	15.1 (2.64)	5–17
HF	6/6	6/6	5.68 (0.91)	3–6	3/3	3/3	2.85 (0.36)	2–3
Total results	14/20	18/20	19.73 (0.87)	15–20	18/20	18/20	18.10 (2.93)	7–20
Percent	70	90			90	90		

^a Means (S.D.) and range obtained by the reference group consisting of 40 healthy volunteers. LI, low-imageability; HI, high-imageability; LF, low-frequency; HF, high-frequency.

Reading. In further contrast to nonword spelling, the patient scored significantly better on nonword reading tasks (e.g. PALPA 43 = 24/24). No aphasic reading errors (i.e. paralexias) were encountered, but as the result of speech apraxia inconsistent phonetic alterations of the target sounds intruded oral. The proportion of correct responses for nonword writing (54%) proved to be significantly lower than the proportion of correct responses for nonword reading (100%; $P < 0.001$, Fisher exact test). No effect of regularity, length, frequency, imageability or morphologic category (functors, verbs, nouns, adjectives, nonwords) was found.

3.2.3. Neurolinguistic findings: 2.5 months and 1 year post onset

Following a 2.5 month period of intensive language therapy, reevaluation of language functions disclosed a further improvement of apraxia of speech and a complete remission of phonological agraphia. Apractic speech symptoms were mainly inconsistent articulatory deviations and phonetic alterations that induced non-sequential substitutions of target phonemes. Aside from these distortions, some stress aberrations occurred. In marked contrast to prior findings, the patient obtained entirely normal results for all variables of dictational writing (Tables 2 and 3). Complete remission of dysfunctional nonword writing is reflected by a normal score of 23/24 (95.8%) on PALPA test 43. Readministration of PALPA test 37 (dictational writing of single syllable words) and 42 (dictational writing of nouns), the AAT, the Token Test, the BNT and the verbal fluency task was also normal.

One year post onset of neurological symptoms, the apraxia of speech had improved to such an extent that hardly any articulatory distortions were perceived. A concise reevaluation of language revealed normal results.

3.2.4. Neurocognitive findings: day 27 and 2.5 months post onset

Formal neuropsychological investigations were performed on day 27 after onset of neurological symptoms.

For ten out of ten unimanual tasks, the patient indicated a strong and consistent right hand preference. This manual dominance was later confirmed by means of the Edinburgh Inventory yielding a laterality quotient of +100. Orientation, gnosis, praxis, problem solving, calculation, concentration and intelligence were normal. The Mini Mental State Examination scored 26/30, matching normal levels [16] for age and 11 years of education. Percentile 90 was reached on the Raven Coloured Progressive Matrices and the subtests 'word recall task', 'commands', 'naming fingers and objects', 'constructional praxis', 'ideational praxis', 'orientation' and 'word recognition task' of the cognitive part of the Alzheimer's Disease Assessment Scale all scored normal [68,69]. No evidence was found for a dressing, visuo-constructive, ideomotor apraxia or for visuo-spatial defects. Visual, tactile and auditory gnosis was normal. On the Hierarchic Dementia Scale the memory subtests 'registration', 'recent memory' and 'remote memory' scored normal. Drawing praxis, written calculation and visual concentration was normal. Psychometric retesting at 2.5 months post stroke did not disclose any substantial changes in the neurocognitive profile.

4. Discussion

Following an acute stroke involving the left anterior insula and a small part of the adjacent intrasylvian frontal opercular cortex, our patient acutely developed a rapidly progressive speech disturbance resulting from disruptions at the articulatory level. The anatomical and functional description of the lesion was based on MRI and SPECT observations that indicated the acute nature, localisation and distant functional repercussions of the lesion. Within a few hours, the apraxia of speech evolved into mere mutism, while auditory-verbal comprehension as well as reading and writing remained functional. Speech reappeared within the early acute phase and was characterized by apractic and adynamic features. In its further course, a rapid and complete

recovery of the adynamia occurred. No dysarthric or aphasic symptoms were observed in the acute phase. In addition to apraxia of speech, in-depth neurolinguistic investigations, performed in the lesion phase, disclosed a modality-specific language impairment consisting of a remarkably pure and nearly isolated phonological agraphia. Apart from this spelling disturbance, no other aphasic manifestations were encountered in either written or oral language. Three months later, no further word-class or familiarity effects were found in dictatorial writing. One year post onset of neurological symptoms, the apraxia of speech had almost completely receded. Regarding the progression of symptoms in the presence of a lesion of the frontal operculum, the rapid recovery from initially severe oral–verbal language disturbances adds further evidence to the growing collection of observations that show rapid subsidence of initial mutism and subsequent language deficits after restricted damage to so-called Broca's area [41–43,66].

During the last two decades several cognitive processing models for written language have been advanced [14,19,30,32,49,51,54,55]. These algorithmic classification schemes basically discern two distinct types of parallel processing strategies for spelling and writing: a phonological processing system and a lexical processing system. A third major component, consisting of the semantic or 'cognitive' system has later been added [49]. Letter-to-sound conversion mechanisms are considered operational in the phonological reading system for nonwords or unfamiliar words. The whole word retrieval strategy from lexical memory has been identified for accessing the phonology of regular and irregular words. In line with this view, phonological alexia results from disruption of the former system, while disruption of the latter system causes lexical alexia or surface dyslexia. In critical difference with phonological alexia, patients with deep alexia [37] produce additional reading errors of the semantic type (semantic paralexias). Similar parallel processing systems have been proposed for written spelling. Disruption of the phoneme-to-grapheme coding system produces 'phonological agraphia'. Damage to the lexical writing route, which relies on a whole word retrieval process from internally stored orthographic images, causes 'lexical agraphia'. Destruction of the semantic system or disconnection of semantics from spelling results in so-called semantic agraphia [57], a condition in which the ability to spell and write with meaning is lost. As already implicated in the classical Wernicke–Lichtheim model, two distinct routes — phonological and lexical-semantic — have also been distinguished at the level of repetition [25,39,45].

Following the observation that the bulk of patients reported with phonological agraphia had spelling impairments that extend beyond the pure phonological level, Alexander et al. [3] concluded that the neural

basis for phonological writing is nested in the neural system for lexical writing. Among the many hypotheses regarding the relationship between phonological reading and spelling, Nolan and Caramazza [46] suggested that both phonological agraphia and phonological alexia result from a failure to an identical phonological processing system subserving both reading and writing. Beauvois and Dérouesné [8] alternatively claimed that defects within independent phonological systems underlie both these conditions. In a similar way, at least two distinct explanations for the relationship between the lexical systems of reading and spelling have been advanced: a common versus a separate lexical system for both reading and spelling. A number of published cases with dissociated written language profiles seem to indicate that phonological and lexical agraphia and phonological and lexical alexia represent pathophysiological distinct phenomena mediated by different operational processing systems. Since the initial description almost two decades ago, phonological agraphia has been reported in combination with phonological alexia [63], lexical alexia [62] and the absence of alexia [56]. Combinations of lexical agraphia with phonological alexia [7], with lexical alexia [53] and with the absence of alexia [60] have been documented as well. The dissociations in the written language profile of our patient (disturbed nonword writing versus normal nonword reading) corroborate the view that distinct phonological processing systems subserve written phonology in a modular way.

Based on the CT findings in four patients with phonological agraphia, Roeltgen et al. [58] postulated that the anterior–inferior portion of the supramarginal gyrus is the most likely anatomical substrate for phoneme-to-grapheme conversion. Reviewing the literature on phonological agraphia, Alexander et al. [3] firmly contested this claim. Out of 11 cases reported with phonological agraphia, they retained only a minority of four patients [10,11,23,63] with normal or almost normal real word spelling. Of these four cases with nearly isolated phonological agraphia, three had an extreme anomalous lesion-behavior profile. Notwithstanding extensive perisylvian left hemisphere damage that even encompassed Wernicke's language area, the patient reported by Shallice [63] showed only mild conduction aphasia. Bolla-Wilson et al. [10] reported a sinistral patient with large frontal and anterior parietal right hemisphere destruction causing transcortical sensory aphasia that rapidly evolved to mere anomia. Fournet et al. [23] documented phonological agraphia in a crossed aphasic dextral with conduction aphasia following a right perisylvian, perirolandic and frontal infarction. Only the patient of Bub and Kertesz [11] had a lesion-behaviour profile within the classical expectations of standard aphasic syndromes. On the basis of these atypical configurations, Alexander et al. [3] concluded that a dissociation of the neural basis for

phonological writing and lexical writing only occurs easily when the overall neural organization for language is strikingly anomalous. Our observations do not corroborate this view. At onset, our patient developed, in the absence of oral apraxia [65], a persistent apraxia of speech that was typically characterized by inconsistent misarticulations, articulatory groping, prosodic abnormalities, scanning speech and 'islands of fluent speech' [28]. Berthier et al. [9] reported a similar speech disorder following vascular destruction of the insula and the adjacent white matter. The patient reported was considered a representative of crossed aphemia, since the aphemia occurred in a dextral after an ipsilateral right insular lesion. Recently, Dronkers [18] localized the crucial anatomical seat of this articulatory planning and coordination disorder in the precentral gyrus of the language dominant insula, directly anterior to the central insular sulcus. Exactly the same insular locus, which is only exceptionally injured in isolation [36], was found in our patient. Consequently, the association of speech apractic symptoms following damage to the dominant anterior insula does not represent an anomalous anatomoclinical finding. In discordance with the classical anatomoclinical view on phonological agraphia [56,58,63], repeated neuroimaging studies in our patient ruled out involvement of the expected brain structures. Functional involvement of the supramarginal gyrus was excluded by SPECT that demonstrated a hypoperfusion involving the gyrus frontalis inferior and gyrus precentralis of the left hemisphere. A recent SPECT and MRI study of Abe et al. [1] added evidence to the view that (1) these anatomic sites are crucial in the production of classical Broca's aphasia [44,67]; and (2) that these sites are anatomically and functionally closely connected to the cerebellum. Our SPECT study similarly discloses the phenomenon of crossed cerebellar diaschisis — reflecting a distant metabolic impact of the cerebral lesion on the contralateral cerebellum following a disrupted excitatory input and provides results in support of the increasing amount of evidence from previous clinical (e.g. Refs. [20,33,35]), experimental and neuroimaging (e.g. Ref. [21]) studies that evidence that the cerebellum contributes to a variety of linguistic processes. As a consequence, our data, for the first time obtained in an exceptionally plain case of pure and nearly isolated phonological agraphia, seem to illustrate that the anterior–inferior supramarginal gyrus of the language dominant hemisphere and the adjacent insular structures medial to it do not constitute the sole anatomical substrate of phonological agraphia. Our findings corroborate the conclusions of Alexander et al. [3] that phonological agraphia can follow damage over a range of perisylvian cortical regions that participate in central phonological processing. Recent evidence derived from brain activation studies [12,31,50,61] indeed confirm that the processing of phonological mate-

rial implies a variety of perceptual and mnemonic processes that differentially engage various brain regions within a large scale language network.

During the past decades a variety of experimental and clinical observations has led to a better understanding of the functional role of the insular cortex as multifaceted area. Augustine [5] extensively reviewed circuitry and functional aspects of the insular lobe in primates including humans and demonstrated in a wide range of neurobehavioral phenomena insular involvement. He concluded that the insula has its designation as: (1) a visceral sensory and visceral motor (autonomic) area; (2) a motor association area; (3) a vestibular area; (4) a somatosensory area; (5) a multifaceted sensory area involved in feeding and neglect; (6) a limbic integration area; (7) a language area; (8) a functional subpart of the verbal component of working memory (articulatory loop); (9) a selective visual attention area; and (9) an area crucially involved in Alzheimer's disease. Analogous to the anterior–posterior distribution of the classical aphasic syndromes, Ardila et al. [4] discerned in their overview of the insular role in language and communication distinct aphasic syndromes depending on the insular topography. Anterior insular damage was often found present in cases of moderate to severe Broca's aphasia, conduction-like repetition seemed frequently associated with damage to the middle part of the insula and verbal–auditory agnostic symptoms, as in severe Wernicke's aphasia, correlated with posterior insular damage. On the basis of strong anatomical interconnections of the anterior insula with the hypothalamic–limbic structures and the greater transverse of pathways from anterior to posterior insular structures, it was conjectured that the insula modulates language at basic affective, emotional and motivational levels. In our patient, the temporary inhibition of self-generated speech during the acute phase may add evidence to the view that the anterior insula also acts as a so-called cortical modulating device of certain limbic informations to subserve linguistic behaviour at basic, motivational levels. In the same way, the adynamic speech characteristics of the patient with focal damage to the anterior insula reported by Shuren [64] may be explained.

Though isolated injury to the Island of Reil occurs only exceptionally, similar observations are needed to further explore, in addition to its apractogenic power, the exact role of the anterior insula in phonologically mediated language processes. Future evidence may further clear the issue whether the aphasiogenic locus encountered in our patient either constitutes an intrinsic phonological language area (that enriches at least the functional anatomy of phonological agraphia) or less likely merely reflects in an exceptional individual the expression of a selectively anomalous intrahemispheric language organization.

5. Conclusions

Summarizing our data we conclude that:

- The constellation of neurolinguistic symptoms in our patient reflects a pure phonologically induced central processing disorder that affected oral and written language in a highly selective way, resulting in persistent speech apraxia and transient phonological agraphia.
- Because of absence of coexisting aphasic manifestations our patient constitutes within the strongly limited group of patients with isolated phonological agraphia the first representative of phonological agraphia in a pure and isolated form. In addition, the symptomatological purity is subserved by a unique lesion configuration encompassing selective damage to the anterior insular cortex and the adjacent part of the frontal opercular cortex.
- In contrast to the classical conviction that the causative lesion of phonological agraphia involves the anterior–inferior supramarginal gyrus of the language dominant hemisphere and the adjacent insular structures our observations corroborate the view of Alexander et al. [3] which posits that phonological agraphia can follow damage over a range of perisylvian cortical regions that participate in central phonological processing.

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