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Investigation of Apraxia of Speech and Linguistic Dysprosody following Acute Ischaemic Hemispheral Stroke

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The Faculty of Medicine

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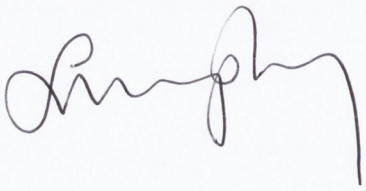

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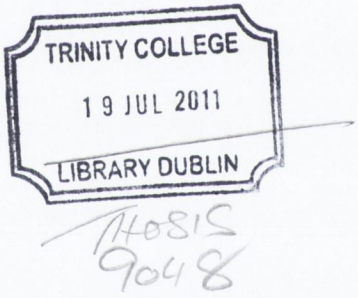

Summary

Apraxia of speech (AOS) is a disorder of motor speech programming. Affected patients typically have hesitant, groping speech with impaired prosody. Automatic speech is relatively well preserved compared to propositional speech. There is little data on frequency of AOS following stroke. There are suggestions, however, that when it occurs following stroke, AOS may show rapid improvement. Linguistic prosody encompasses the use of pitch, loudness and length to produce emphasis and signal and interpret linguistic information. Traditionally prosody was thought to be mediated by the right hemisphere; however, the occurrence of dysprosody in patients with AOS (which is almost invariably caused by left hemisphere lesions) suggests a role for the left hemisphere in prosody.

My main hypothesis was that AOS occurred more frequently following acute ischaemic hemispheral stroke than previously thought and that, as an apraxia, it occurs due to disrupted functional anatomic connections and is, thus, amenable to rapid recovery.

The specific aims of the study were to determine the frequency and natural history of AOS following acute ischaemic hemispheral stroke and its association with orofacial apraxia (OFA); the anatomical substrate of AOS; whether the Psycholinguistic Assessment of Language (PAL) word/non-word repetition test was useful in the assessment of patients with AOS; the frequency and natural history of receptive linguistic dysprosody following stroke as well as its association with AOS; and the neuroanatomic substrate for linguistic dysprosody of identification and discrimination.

In order to test this hypothesis, I performed an observational longitudinal study of 50 patients with acute ischaemic hemispheral stroke. A speech and language battery was performed to document the presence or absence of AOS and comprehension of linguistic dysprosody. Stroke severity was assessed using the National Institute of Health Stroke Scale (NIHSS) and MRI

was performed to localise the acute lesion. The test battery was performed as soon as possible after the stroke, at a three to five day interval and at six months. Final stroke outcome was assessed using the Barthel Index and modified Rankin Score.

Throughout the course of the study, 18 patients of 45 (40%) who could be tested had evidence of AOS. Eleven patients with AOS also had OFA, while none of the patients without AOS had OFA. All 11 patients with OFA also showed evidence of AOS indicating a significant association between the two conditions. Although the severity of AOS lessened with time, I did not observe the rapid recovery which has been suggested by some authors. All patients with AOS had left hemisphere stroke. The regions of greatest overlap in patients with AOS included the left insula, claustrum and putamen. However, there was no single brain region that was always involved in AOS. There was an association between AOS severity and lesion volume, as well as with clinical stroke severity. The PAL word/non-word repetition test did not discriminate between patients with or without AOS. In addition, 26 patients of 45 (58%) who could be tested had evidence of linguistic dysprosody following stroke. Patients with linguistic dysprosody for identification all had left hemisphere lesions while those with linguistic dysprosody for discrimination had either left or right hemisphere lesions.

In conclusion, AOS occurred frequently following acute ischaemic hemispheral stroke, as did impaired comprehension of linguistic prosody. There was a significant association between AOS and OFA. Severity of AOS improved over time, but rapid recovery did not occur. There was no single brain region implicated in either AOS or linguistic dysprosody. However, linguistic dysprosody for identification and discrimination occurred independently. These results suggest that a dynamic interaction must occur between the two hemispheres for the correct processing of linguistic prosody in spoken language.

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And finally, I would like to thank the Irish Heart Foundation for awarding me a grant to fund the project and all the patients who agreed to participate in this study despite having recently suffered a stroke.

Stroke

A poem by Arthur H Ginsberg MD [1] (Used with permission)

comes down, white as an avalanche,
erasing the playground of speech,
piles up in a drift at the tip
of Veida's tongue. She cannot repeat,
no ifs, ands, or buts, calls a comb,
bone, pen, *cow*. Frustration bleeds
through her brokenness, shudders in
chaotic clutching of spindly fingers,
as if, the right word could be plucked
from air. *Veida, Veida, listen to me.*
Follow my hand with your eyes. Eyes
brimming, she nods and follows, pendulum
on command. Stroke pitches camp,

lays rebar, pours cement. She grows to
know me and I, her, without ancestral
gift; small patch of brain, ordered as
the stars. From bedside, touch speaks,
vision flows in syllables, unfettered as
a child skipping rope. Fingertips vibrate
loquaciously as lips, extolling all the hope
of eighty-five years; married to darling Jack,
librarian, re-building spines of orphaned books.

Stroke binds her in the vault of our audacious
builder, pitiless as, buried alive. I visit Veida
each day, stunned by peals of laughter at
her own infirmity, that come from cosmic space,
roiling up through ghostly cracks to pry open,
the lock. Waylaid by walls, eyes fade, no word
to frame, *good-bye*. Undoing speaks to
the marvel of design, more eloquent
than speech, the vespers of silence.

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Abbreviations

AOS	Apraxia of speech
ABA II	Apraxia Battery for Adults second edition
CE	Coefficient of error
CLP	Central language processor
CT	Computed tomography
CVC	Consonant-vowel-consonant
CCVCC	Consonant-consonant-vowel-consonant-consonant
DICOM	Digital Imaging and Communications in Medicine
DTI	Diffusion tensor imaging
FDG-PET	Fluorodeoxyglucose-positron emission tomography
fMRI	Functional MRI
FWHM	Full width half maximum
fo	Fundamental frequency
GCS	Glasgow Coma Scale
ICC	Intraclass correlation
LHD	Left hemisphere damage
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSE	Motor speech examination
MSP	Motor speech programmer
NIHSS	National Institute of Health Stroke Scale
OFA	Orofacial apraxia
PAL	Psycholinguistic Assessment of Language

PD	Parkinson's disease
PET	Positron emission tomography
RHD	Right hemisphere damage
rCBF	Regional cerebral blood flow
RIP	Patient deceased
ROI	Region of interest
SD	Standard deviation
SPECT	Single photon emission computed tomography
SPGI	Superior prefrontal gyrus of the insula
SPM5	Statistical Parametric Mapping version 5

Chapter 1: Introduction to apraxia of speech (AOS) and linguistic dysprosody

1.1 Background

Human language is a unique code, which allows man to communicate. Although the individual functions of language, such as reading, writing, speaking and auditory comprehension are often described in isolation, in fact, all processes must run in parallel. Importantly, these processes operate unconsciously. Most individuals can have a conversation without paying any attention to the details such as the sound of words or structure of sentences. In addition, these processes operate rapidly and very accurately. To produce a spoken word one must search though the mental lexicon (containing about 30,000 items [2]), as well as programming, processing and articulation. However, normal speakers easily produce 150 words per minute (or more if under pressure) with a miniscule error rate of only one mis-selected word and one mis-pronounced word per million [3]. Figure 1.1 is a diagrammatic representation of single word processing.

1.2 Definition of AOS

AOS is a disorder in "programming the speech musculature to produce the correct sounds of words in the proper sequence with the appropriate timing" [4]. AOS has previously been classified as a dysarthric disorder [5] as well as an aphasic disorder, but it is now recognised as being a distinct disorder of motor planning or programming [6-9].

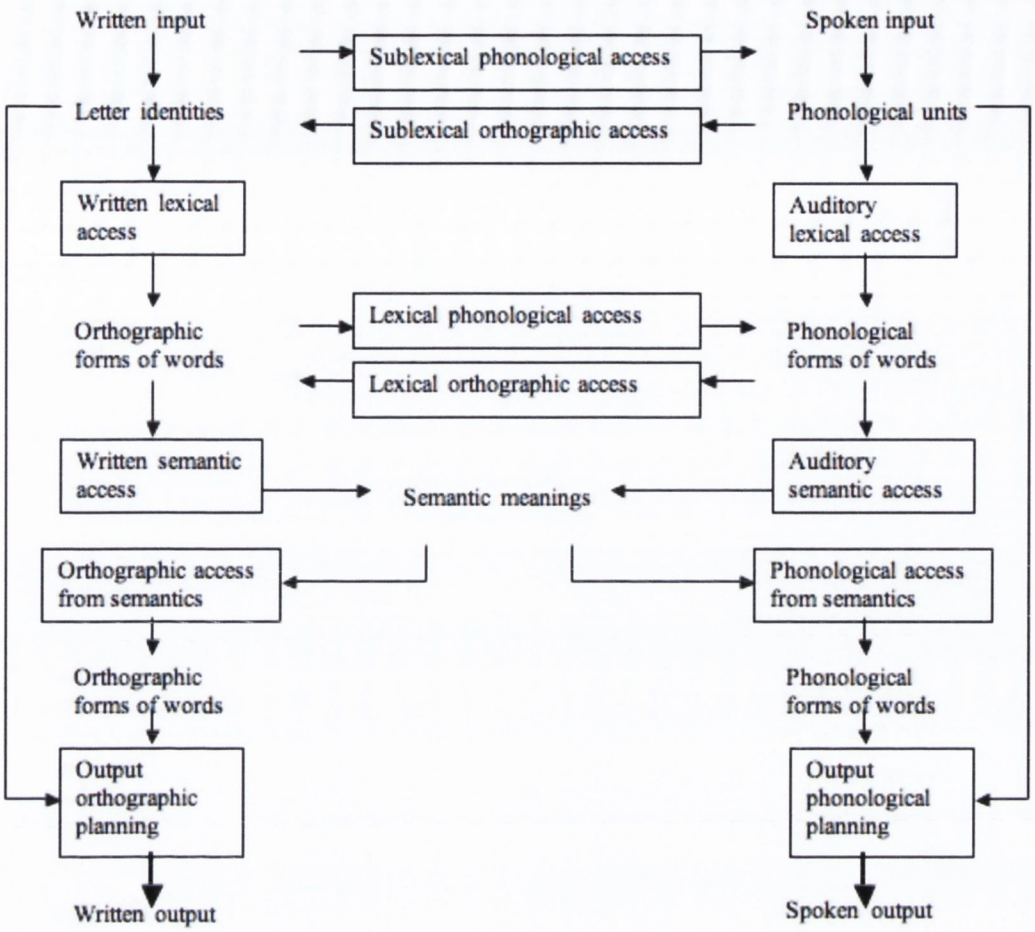


Figure 1.1: Diagrammatic representation of the sequence of activation of the components of the processing system for single words

Processing components are in boxes, arrows represent the flow of information. Adapted from [10].

1.3 Nomenclature

The word apraxia is derived from the Greek, *a* meaning "without", *praxia* meaning "skilled movement". A patient with AOS is therefore literally without the skilled movement required for speech. Use of the word apraxia in the term distinguishes AOS from the dysarthrias, which can be caused by neuromuscular problems, and from the aphasias, which are higher order linguistic problems [11].

The term AOS itself has been the subject of much heated debate. Perhaps the first description of a patient with AOS was Broca's famous patient Leborgne, also known as Tan, as this was the only sound he could utter. Broca termed Leborgne's disability *aphemia*. He wrote " The general faculty of language persists in these patients … the oratory apparatus is intact … they have all their intelligence … the patients understand completely articulate and written language … those who can write … bring their ideas well on paper. What is lost, therefore, is not the faculty of language, is not the memory of the words nor the action of the nerves and of muscles of phonation and articulation. It is … the faculty to coordinate the movements that belong to the articulate language, or, simpler, it is the faculty of articulate language; for without it, no articulation is possible."[12]. Rather confusingly, what is now known as Broca's aphasia is not the symptom complex which Broca originally described. As the term aphasia suggests, such patients have a linguistic problem which includes difficulty with grammar and naming as well as a similar difficulty with writing, features which Broca's aphemic patients did not have.

At least 24 other terms have been used to describe AOS, including afferent motor aphasia, anarthria, aphemia, apraxic dysarthria, articulatory dyspraxia, ataxic aphasia, Broca's aphasia, Little Broca's aphasia, cortical dysarthria, efferent motor aphasia, expressive

aphasia, oral verbal apraxia, speech apraxia, peripheral motor aphasia, phonematic aphasia, phonetic disintegration, primary verbal apraxia, pure motor aphasia, secondary verbal apraxia, sensorimotor impairment, speech sound muteness, subcortical motor aphasia, word muteness and verbal aphasia [11, 13].

Although Liepmann was one of the first to develop the concept of apraxia [13], the term AOS was really coined by Darley in 1968 in a paper entitled "Apraxia of Speech: 107 years of Terminological Confusion" [13]. Some 40 years earlier, however, Kinnier-Wilson had remarked upon the apraxic nature of the disorder, although at that time it was known as motor aphasia. He wrote "When a patient cannot express himself in speech, though by other methods he indicates that he understands, it is natural to describe his defect as a motor defect; it is a form of paralysis … since he can utilise the same muscles for other physiological functions we are again led to the idea of the apraxic nature of this motor disorder". He went on to state: "Since the articulatory muscles are not paralysed in motor aphasia, that symptom may be legitimately called an apraxia of the speech musculature … he is unable to reproduce the combinations of their movements requisite for the act of speaking."[14].

1.4 Historical background / Theories regarding AOS

The basis of AOS remains hypothetical. Several models have been proposed, some of which are discussed here. In order to understand differences between proposed models, it is necessary to give a brief outline of the two major and opposing theories in neurology.

Carl Wernicke (1848-1905) was really the founder of the disconnectionist theory, although Geschwind revived it in a modern form in the 20th century. Franz Joseph Gall (1758-1828), a famous neuroanatomist, was the first to recognise the division between grey and white matter. He used external cranial features to imply underlying cortical size and this later evolved into phrenology. Theodore Meynert (1833-92), a neuroanatomist as well as professor of psychiatry, classified the white matter fibres into projection fibres (ascending and descending pathways arising and terminating in the cortex), commissural fibres (connecting cortex across both hemispheres) and association fibres (connecting cortical regions within a hemisphere) [15]. Wernicke proposed that the brain was an arrangement of areas containing memory images located in primary sensory and motor areas. However, he felt that higher functions were the result of associations between motor and sensory memory image areas rather than localised in specific brain regions. Thus disorders of higher functions resulted from a breakdown in connections or *disconnection*. Wernicke described the classical disconnection syndromes, including conduction aphasia and visual agnosia. Hugo Liepmann (1863-1925) joined Wernicke as an assistant and later proposed a disconnectionist theory of the apraxias. He suggested that the left hemisphere was dominant for complex movement control and any lesion disconnecting this from other brain regions would lead to an apraxia.

Localisationism had a brief resurrection in the 20th century, with accounts of brain regions specialised for higher functions; however an anti-associationist, anti-localisationist, 'holist' movement led by Henry Head (1861-1940) then dominated until Geschwind's associationism revival in the 1950s [16]. The holist model proposes that a brain region acts as a whole to support all functions associated within it.

Kinnier-Wilson suggested that "the paralysis is not of projection but of association-systems … As the arousing of latent visual and kinaesthetic 'engrams' is essential for the execution of limb movements, so the motor or executive part of the speech function depends on ability to awaken auditory and kinaesthetic 'engrams'."[14].The term engram was used to refer to the physical change in the nervous system that occurred as a result of experience. It was thought that there was a particular location in the brain where memories for actions were stored. Thus, Kinnier-Wilson ascribed to the dissociation theory when he postulated that if this area of the brain was disconnected, this would produce the deficit we now know as AOS.

In more recent years, Levelt described a phonological output buffer, a short-term store for sequences of phonemes to be articulated. He proposed that most syllables are overlearned and these overlearned articulatory motor patterns are stored in the premotor cortex [17]. Not unlike Kinnier-Wilson's engram!

Neurolinguistic models for the most part agree that the sound of a word is produced in several steps, although the details vary. Firstly, a phonological representation of a word is accessed, then that representation is translated into a form that is suitable for programming the articulatory muscles [18].

Darley proposed a three-stage model of speech production that involves a central language processor (CLP), a motor speech programmer (MSP) and a motor speech cortex [19]. The CLP selects phonemes and sequences of phonemes for speech and translates them into a neural code that drives the MSP. The MSP projects directly to the motor cortex and activates the appropriate musculature to produce the speech sounds in the correct order. In this model, AOS represents a disorder of motor speech programming. That is, the linguistic plans are intact but there is a problem in the programming of the speech musculature.

Van der Merwe described a four-stage model by subdividing Darley's MSP into motor planning and motor programming stages [20]. In this model, phonemes are selected and are converted into motor code during the motor planning (second) phase. These motor plans are then fed into a motor programming (third) phase which produces muscle-specific motor programs. In the fourth stage the plans and programs are transformed into muscle movements. Van der Merwe then described AOS as a motor planning disorder.

A more contemporary description is that AOS is a phonetic-motoric disorder caused by inefficiencies translating a phonological framework into kinematic parameters for carrying out an intended movement [21].

1.5 Clinical features of AOS

Although terminology has been fraught, the description of the articulatory output in AOS is fairly uniformly agreed upon. A patient with AOS typically has groping, hesitant speech. They make attempts at self-correction; however, there are articulatory inconsistencies on repeated attempts of the same utterance. Initiation of the sound or word is usually the most troublesome. Patients often speak slowly, perhaps because they anticipate difficulty, and prosody may be impaired. Articultory errors include substitutions, distortions, omissions and repetition. Errors tend to increase with increasing word length and complexity, and patients find repetition of nonsense words particularly difficult [6-8, 22]. A unique feature in AOS is the marked contrast between automatic and propositional speech [19]. A patient with AOS may have fluent islands of automatic speech, for example, counting, reciting prayers or everyday overlearned expressions of greeting. Propositional speech, however, is characterised by hesitant, groping, poorly articulated attempts.

1.6 Inventory of characteristics of AOS

Dabul developed an inventory or listing of the characteristics of AOS that is helpful in clinical bedside assessment (Table 1. 1)

Table 1.1 Inventory of characteristics of AOS [22]

Speech behaviour
1. Exhibits phonemic anticipatory errors (gleen glass for green glass)
2. Exhibits phonemic perseverative errors (pep for pet)
3. Exhibits phonemic transposition errors (Arifca for Africa)
4. Exhibits phonemic voicing errors (ben for pen)
5. Exhibits phonemic vowel errors (moan for man)
6. Exhibits visible/audible searching
7. Exhibits numerous and varied off-target attempts at the word
8. Errors are highly inconsistent
9. Errors increase as phonemic sequence increases
10. Exhibits fewer errors in automatic speech than in volitional speech
11. Exhibits marked difficulty initiating speech
12. Intrudes a schwa sound /e/ between syllables or in consonant clusters
13. Exhibits abnormal prosodic features
14. Exhibits awareness of errors and inability to correct them
15. Exhibits a receptive-expressive gap

AOS often co-exists with aphasia or dysarthria, which may make differentiation of individual speech deficits difficult. However, there are distinct differences between these three speech disorders.

1.7 Distinguishing AOS versus dysarthria

Dysarthria is a motor speech disorder that is due to a disturbance of basic motor processes involved in articulation. However, this definition does not distinguish it well from AOS. Dysarthria may occur as a result of weakness, abnormal tone, incoordination, abnormal force or range of movement.

1.7.1 Anatomy

AOS is a supratentorial disorder, almost always due to left hemisphere lesions. In contrast, dysarthria may result from lesions anywhere along the neuro-axis, including supratentorial, posterior fossa, brainstem or peripheral nerve.

1.7.2 Aetiology

AOS is most often caused by vascular lesions; although more recently it has also been recognised as occurring in a number of neurodegenerative disorders [6, 23]. In contrast, dysarthria may result from myriad causes: toxic and metabolic, structural, demyelinating, neurodegenerative, neuromuscular and, of course, vascular.

1.7.3 Oral mechanism findings

Although upper motor neuron facial weakness (usually right-sided) may occur in patients with AOS (due to the left hemisphere lesion), this alone cannot explain the difficulty encountered in speaking. Often there may be no abnormality of oral mechanism in a patient with AOS. The only oral mechanism abnormality which is regularly associated

with AOS is orofacial apraxia (OFA) (also known as non-verbal oral apraxia) [24]. In contrast, many oral mechanism abnormalities are associated with dysarthria, including hypotonia, atrophy, fasciculations, nasal regurgitation and palatal weakness in flaccid dysarthria; dysphagia, drooling and pseudobulbar signs in spastic dysarthria; hypomimia and jaw/lip tremor in hypokinetic dysarthria; involuntary movements of jaw/palate/respiration, head deviation, sensory tricks and myoclonus in hyperkinetic dysarthria [25]. In addition, patients with AOS can often perform near normally on rapid alternating articulatory tasks, while those with dysarthria usually show reduced range, speed and strength [24].

1.7.4 Speech characteristics

Dysarthria and AOS do share some characteristics and discrimination of the two depends on recognising deviant speech characteristics which are present in AOS and not in dysarthria. An important distinguishing characteristic of dysarthria from AOS is that dysarthria should affect both speech and similar non-speech movements in the same way [21]. Thus, dysarthria affects not only articulation and prosody, but also phonation, respiration and resonance [19, 26-28]. The abnormal speech characteristics in dysarthria are fairly consistent across utterances and not influenced by the type of utterance (e.g., automatic versus propositional) or stimulus modality (e.g., spontaneous speech, reading, repetition). On the other hand, in AOS there are often fluent islands of relatively normal speech, automatic speech is usually better than propositional speech, and errors are influenced by word length and complexity.

Although dysarthria and aphasia may occur together, they are not functionally associated; while AOS frequently occurs in association with aphasia [24]. Errors in dysarthria are usually related to sound level distortions whereas in AOS repetitions, substitutions and

additions may also occur. Patients with AOS frequently attempt to correct themselves while this does not typically occur in those with dysarthria. The errors in dysarthria are usually consistent and predictable, which is not the case in AOS.

Table 1.2: Traditional differentiating characteristics of AOS and dysarthria

adapted from [21]

FEATURE	AOS	DYSARTHRIA
Lesion location	Unilateral / anterior supratentorial	Bilateral if cortical, more often subcortical
Psychophysiological level / mechanism	Motor programming	Movement execution
Observed deviant speech behaviour	Speech initiation, selection and sequencing; phoneme substitution; abnormal prosody; infrequent metathetic errors	Sound level distortions
Speech processes involved	Essentially normal: resonance, respiration, phonation	Frequent disturbance of: resonance, respiration, phonation
Physiological manifestations	Free from paralysis, paresis, ataxia, involuntary movements	Presence of paralysis, paresis, ataxia, involuntary movements
Influence of nonphonologic (phonetic) factors	Affected by word length; error inconsistency	Less affected by word length; errors are more consistent
Oral nonverbal apraxia	Frequently present	Absent

1.8 Distinguishing AOS versus aphasia

It may be more difficult to distinguish AOS from aphasia for a number of reasons. Firstly, the underlying lesion location and aetiology are very similar. Secondly, although aphasia often occurs without AOS, AOS is commonly accompanied by aphasia in stroke patients. Thirdly, although the speech errors occur due to differing underlying mechanisms (a linguistic problem in aphasia and a motor programming problem in AOS) the sound errors may sound very similar.

Aphasia is a higher order linguistic problem, with impairments in comprehension, grammar, word meaning and word finding [19]. Patients usually have a similar difficulty in reading and writing as they do with speaking, whereas these processes are unimpaired in patients with pure AOS. This was well expressed by Broca in his original report [12]. Although AOS often occurs in association with aphasia, either can occur independently. The errors produced in aphasic disorders occur due to deficits in phoneme selection, while patients with AOS select phonemes correctly but have difficulty with motor execution [6].

Although it may be impossible to determine whether a patient with severe aphasia also has AOS because of their inability to provide a sufficient speech sample, it is usually quite easy to determine if a patient with AOS also has aphasia as other language modalities are affected.

Patients with AOS usually make many attempts at self-correction, while aphasic patients may not recognise their errors. The articulatory complexity of a target word affects apraxic errors much more than aphasic errors [25].

1.9 Diagnosis and assessment of AOS

Although the characteristics of AOS are widely agreed upon and there is a standardised battery available which is based on these characteristics, the method used to diagnose AOS differs greatly between studies.

1.9.1 Apraxia Battery for Adults (ABA)

The ABA was originally published in 1979 and a second edition became available in 2000 [22]. It was developed by Dabul and subsequently administered to a group of patients with either aphasia, aphasia and AOS or dysarthria. On the basis of these patients' performance the battery was revised to include six subtests. In 1980 the battery was administered again to a group of patients with and without AOS, and the results guided the revised version of the battery. The second edition of the test has a number of more complex items included to raise the ceiling of subtests. Internal consistency reliability coefficients and validity studies are also available within the manual [29].

The ABA-2 verifies the presence of AOS and estimates the severity of the disorder. It comprises six subtests:

Subtest 1: Diadochokinetic rate

The patient repeats one, two and three syllable combinations as quickly as possible within a time limit. This measures volitional control over the articulators.

Subtest 2: Increasing word length

The patient repeats words that increase in number of syllables, e.g., love, loving, lovingly. This measures the ability to sequence the proper number of syllables in the correct order.

Subtest 3A: Limb apraxia

The patient is given 10 oral commands which require use of the hands or arms, e.g., wave goodbye

Subtest 3B: Oral apraxia

The patient is given 10 oral commands which require manipulation of the oral apparatus, e.g., kiss a baby

These subtests measure the ability to produce an accurate movement to an oral command.

Subtest 4: Latency time and Utterance time for polysyllabic words

The patient is presented with 10 pictures which he must name. The time taken to initiate the word and the total time it takes to produce the word are measured.

Subtest 5: Repeated trials

The patient is asked to repeat 10 polysyllabic words three times each, e.g., telephone. This measures the change in word production over successive attempts.

Subtest 6: Inventory of articulation characteristics of apraxia

Standardised spontaneous speech (describing a picture), reading and automatic speech (counting) are assessed. The number of apraxic speech behaviours are recorded.

The ABA II can be completed in approximately 20 minutes and the results grade the degree of AOS as none, mild, moderate or severe. The results of the test can also be used to guide treatment plans. The ABA II has been shown to be a reliable and valid test with reliability coefficients >0.80 for all subtests [22].

1.9.2 Other methods of diagnosing AOS

The ABA II is readily available and frequently used by speech and language therapists in practice. Published studies and case reports have used it as their method of determining the presence and severity of AOS, as it is the only normed and standardised test for AOS [6, 30]. However, many of the published studies examining patients with AOS did not use this

battery [31-33]. Hillis used a battery comprising verbal picture description, repetition, oral reading and spoken picture and object naming. AOS was defined as >10% total errors in each oral task, variable off-target attempts at articulation, distorted groping articulation and impaired prosody [33]. Hillis did not use the ABA II as it was felt to take too long as a bedside evaluation.

Other methods of diagnosing AOS have been to use the motor speech evaluation (MSE) and to document the salient signs [32]; however, the ABA II may be more specific [6]. Some authors feel that there remains a lack of consensus on AOS and prefer to view it as a syndrome comprising a collection of symptoms and features: thus it is more accurate to describe in detail the specific features a patient has rather than labelling them with the diagnosis of AOS [8].

A battery suggested by Wertz, LaPointe and Rosenbeck for patients with suspected AOS comprises an extensive list of tests, including the Porch Index of Communicative Ability (PICA) [34], Boston Diagnostic Aphasia Examination (BDAE) [35], Communicative Abilities in Daily Living [36], Motor Speech Evaluation, sound by position tests, A Deep Test of Articulation [37], Templin-Darley Tests of Articulation [38], oral peripheral examination, tests of isolated oral movement, tests of oral motor sequencing, Coloured Progressive Matrices [39], Token Test [40] and the Reading Comprehension Battery for Aphasia [24, 41]. It would take many hours to perform this extensive battery and this is not practical on most patients with acute stroke.

1.10 Causes of AOS

AOS may be developmental or acquired. In developmental cases, the disorder is present from birth and there is no evidence of any structural brain lesion in such patients; however, there is often a family history of similar language problems, suggesting a genetic component and some cases have been reported with specific mutations [42, 43]. In contrast, acquired AOS is caused by an insult to the brain. The most commonly reported cause is stroke or intracerebral haemorrhage [4, 9, 44-46]. However, acquired AOS has also been reported in structural brain lesions and neurodegenerative conditions [23, 47].

1.11 Clinical course of AOS

There is very little epidemiological data on the frequency of AOS. One study of patients referred to a speech pathology centre found that only 6% of referred patients had either AOS or dysarthria, [48]. Similarly, AOS accounted for 9% of the motor speech disorders seen at the Mayo Clinic [11]. These figures imply that AOS is much less common than other speech disorders, but these figures reflect only those patients who were referred for therapy. As there is little evidence on best therapy for AOS [49, 50], such patients may be referred less often than those with other language disorders. Another explanation for the low proportion of patients with AOS being referred for speech and language therapy is that it is often considered a secondary diagnosis in patients with some other speech impairment [11]. My study will document the frequency of AOS following acute hemispheral stroke, thus providing useful epidemiological data.

To date there are no natural history studies on patients with AOS, and therefore a lack of information regarding prognosis. A number of case reports and one case series of four patients suggested that occasionally patients with AOS may show an unexpectedly rapid recovery of their speech and language deficit despite established infarction [9, 45, 51]. The mechanism of this remains unclear. By assessing patients longitudinally over a six-month period following acute hemispheral stroke, my study will determine whether rapid recovery of AOS occurs following stroke, and if so, how frequently.

Wertz, LaPointe and Rosenbeck suggest that a patient may have temporary AOS, which may recover rapidly, within hours to days. However, "Apraxia of speech that persists for more than a week is apraxia of speech that will persist. Like alcoholism and drug

addiction, there are, in our experience, no ex-apraxic patients." However, they go on to state that AOS may improve to some extent with treatment [24].

In aphasia, there is evidence that one can predict change and eventual language ability using four predictors: age and three language related measures (gestural, verbal and graphic behaviour) [52]. This aids a clinician to select appropriate treatment candidates and plan realistic goals for individual patients. However, in AOS, there is no such evidence.

1.12 Treatment of AOS

In clinical practice, many different methods are used for treatment of AOS. However, there are no randomised controlled trials of any speech and language therapy in AOS following stroke [50]. It is likely that the controversy over the definition of AOS and the difficulty recruiting patients with pure AOS have contributed to this deficit in the literature. Also because of the lack of data regarding prognosis, the efficacy of any treatment is difficult to determine. My study will provide data on the clinical course of AOS, which may be useful for future therapeutic trials.

1.13 Localisation of lesions causing AOS

There are many theories as to what is the actual deficit which causes AOS. The difficulty is that speaking is a highly complex overlearned skill, and language is still not fully understood. Overlearning is the continued practice of a skill even after the skill has been mastered, resulting in the skill becoming automatic. The overlearning process results in a transition from controlled to automatic processing. This transition is accompanied by a decrease in prefrontal cortical activation suggesting reduced demand on cognitive control processes [53, 54]. As decreased activation in specialised brain regions occurs during learning, there is an increase in effective functional connectivity between distinct cortical areas [55]. There is relative agreement about which brain regions are involved in speech, but dispute over their precise function and pathways. Simply because AOS occurs when a particular brain region is damaged does not mean that that particular area is the centre for speech praxis, it may simply have resulted due to interruption of a neural network.

Darley and van der Merwe both suggest that motor speech planning/programming is mediated by cortical association areas, including the premotor cortex, supplementary motor area, prefrontal areas and posterior parietal areas. Their theories also imply that damage to lower segmental structures including the basal ganglia should not cause AOS, but rather cause a dysarthria. However, others have shown that AOS may result from damage to basal ganglia and subcortical strucures [46].

The original patient with AOS, Leborgne or "Tan" as Broca called him, had a lesion in the third left frontal convolution [12]; however, it was not until some years later that it was realised that it was the left hemisphere in particular which was important for speech [12]. At the time this was very controversial as the "law of symmetry" implied identical

functions to each hemisphere. The publishing of the report itself caused significant controversy as, after its publication, Gustave Dax submitted a statement to the Academy of Medicine indicating that his father, Marc Dax, had previously reported this finding, although this paper had not been published. In fact, Broca did not dissect the brains of his aphasic patients and thus, when the brains were later re-examined and imaged, it became clear that the lesions were more extensive than Broca had realised. In Leborgne's case the lesion involved the left inferior frontal gyrus, deep inferior parietal lobe, anterior temporal lobe, insula and extensive subcortical areas including the claustrum, putamen, globus pallidus, caudate, internal and external capsules and fronto-parietal white matter. Lelong's lesion (Broca's less well-known second patient with aphasia) involved the posterior inferior frontal gyrus as well as temporal white matter fibres. Importantly, the insula was not involved [56].

An often cited paper studied 25 patients with chronic stable AOS and performed lesion overlap studies to show that all 25 had lesions involving the left precentral gyrus of the insula [4]. However, these 25 patients were assessed many years following stroke and had fixed neurological deficits. They had also presumably undergone variable amounts of rehabilitation. Most were diagnosed using CT which is insensitive for small areas of infarction.

More recently, Hillis investigated 80 patients, 40 with and 40 without AOS, but all with left middle cerebral artery (MCA) infarction [33]. The presence or absence of AOS was determined clinically; however, standardised tests of AOS were not used as these were felt to be too time consuming for bedside use. This study found that there was no association between the presence of AOS and left insular damage; however, there was an association between AOS and hypoperfusion or infarction of Broca's area. Interestingly, there was a group of five patients with AOS who did not have involvement of either Broca's area or

the insula. To account for this finding, the authors suggested that this may result from anatomic variability of Broca's area or individual cortical representation of language. Four patients in the same study with marked involvement of Broca's area did not have any evidence of AOS. To account for this, the authors suggested that Broca's area may have functionally distinct subregions, only some of which are responsible for motor speech planning and programming.

A study of patients with stroke confined to the insula, a rare occurrance, reported two patients with aphasic syndromes and dysarthria. One patient had a fluent aphasia with comprehension difficulty, the other a non-fluent aphasia with paraphrasias and anomia but preserved repetition. More detailed description was not provided, thus the presence or absence of AOS in these two cases is unknown [57].

There has been one case report of a patient with AOS caused by an infarct in the right frontal lobe, involving the head of the caudate and putamen [30]; this occurred in a right-handed patient. The authors suggested that this case supported the inclusion of the right hemisphere as a critical neural location for the MSP in right-handed adults. However, this is the only report of AOS occurring due to a right hemisphere lesion, although there are many reports of ideomotor apraxia occurring following right hemisphere lesions [58, 59]. Some reports have suggested evidence of a dissociation between praxis and language [58]. Although there is much evidence that praxis, even more so than language, is strongly related to handedness, case reports of exceptions to the rule suggest individual variability.

A functional MRI study of speech movements in normal people found activation of the left inferior frontal gyrus and bilateral middle frontal gyri, thalami and lateral temporal cortices. The insula was not significantly activated [60].

Differences in results of localisation studies may in part be due to differences in defining AOS, variable time after onset of symptoms and differing imaging techniques. One difficulty is that most of the regions implicated in AOS are supplied by the left middle cerebral artery. Stroke in its territory may cause infarction in one area and only temporary hypoperfusion in another. Static imaging may therefore not be sensitive to all these changes.

My study will investigate localisation of lesions in patients with AOS following acute hemispheral stroke and provide further evidence for the brain regions involved in speech praxis.

1.14 Lesion volume and AOS

Clinical stroke severity has been shown in some studies to correlate significantly with infarct size on MRI [61]. Other studies have found relatively poor correlation between MRI lesion volume and National Institute for Health Stroke Scale (NIHSS) score [62]. However, in animal models of acute stroke, diaschisis has been shown to occur, where a small cortical stroke produces a large area of hypometabolism in brain areas which are distant from the area of ischaemia [63]. One theory is that diaschisis results from a lack of neuronal input from the ischaemic brain region and may be part of a process of structural or functional reorganisation post stroke. However, diaschisis is not due to hypoperfusion but hypometabolism, and is therefore not visible on static imaging such as MRI. This means that visible lesions on MRI may not be responsible for all the clinical deficits which occur following stroke. This is one potential confounding factor when correlating clinical deficits with lesions on imaging.

Only one study has investigated the association between AOS severity and lesion volume [32]. The authors recruited 18 patients with AOS and eight patients without AOS. All patients had had left hemisphere infarction at least one year previously. Lesions were evaluated with either CT or MRI. A significant association was found between the severity of AOS and the lesion volume. My study will provide further evidence for the association between AOS severity and lesion volume.

1.15 Definition of prosody

Prosody refers to the suprasegmental properties of language, or the melody of speech. Both comprehension and production of spoken language require an inherent understanding of prosody. Processing of spoken language requires complex mental activity. The system must extract segmental information to identify phonemes, content words and syntactic elements as well as suprasegmental information (prosody) to identify separation of different constituents and stresses on particular words. Prosody encompasses the use of pitch (fundamental frequency), loudness (intensity), length (duration) and voice quality [19] to produce emphasis and add interest to speech, i.e., "It's not what you said, it's the way you said it."

1.15.1 Prosody subtypes

At least five different types of information can be identified within the functions of prosody: emotional or affective, attitudinal, pragmatic, linguistic and idiosyncratic [64-66]. Affective and linguistic dysprosody have been the subject of more investigation than the other subtypes.

1.16 Hypotheses regarding prosody

1.16.1 Functional-cognitive model

This hypothesis suggests that the function served by a stimulus determines laterality of processing rather than the stimulus itself [67]. This theory was supported by a study which demonstrated different evoked potentials over the left hemisphere during tasks requiring analysis of the same speech signal depending on whether linguistic or non-linguistic parameters were used [68].

1.16.2 Parallel processing hypothesis

This hypothesis suggests that both hemispheres simultaneously participate in processing various components of a stimulus for which each hemisphere is specialised [69]. This is similar to the Dynamic Dual Pathway model which suggests that the left hemisphere processes all segmental, lexical and syntactic information while the suprasegmental information (accentuation, boundary marking expressed by pitch variations) is processed by the right hemisphere. Processes of the right and left hemisphere interact dynamically in time during spoken language comprehension [70].

1.16.3 Attraction (or physical stimulus) hypothesis

This hypothesis states that complex behaviours, such as language, make use of differing components (e.g., temporal elements, pitch) which independently evoke differing laterality [71].

1.16.4 Brain-behaviour model

This more recently proposed hypothesis encompasses the associated neurological symptoms and signs together with the brain regions affected. Production or perception of any or all of the elements of prosody may be impaired by damage at various levels of the nervous system which can be due to dysfunction of either hemisphere [64].

1.17 Linguistic dysprosody

The example below indicates how linguistic prosody is used to convey meaning to the sentence. The comma indicates the intonational pause.

The boy, said the teacher, is not paying attention.

The boy said, the teacher is not paying attention.

Linguistic prosody thus influences syntactical processes and comprehension of sentences.

Investigations into linguistic prosody are relatively few, and results vary. Many studies have focused only on patients with right hemisphere lesions and such patients have been reported with impaired comprehension and production of linguistic prosody [72, 73].

1.17.1 Receptive linguistic dysprosody

A study of normal controls demonstrated a left ear advantage for the identification of both affective and linguistic prosody, suggesting a role for the right hemisphere in prosodic processing [71]. Nicholson described a patient who, following a right hemisphere stroke, was unable to use prosodic information to discriminate between statement-question pairs or to categorise a sentence as a statement or a question [72]. Weintraub examined receptive linguistic dysprosody in a group of patients with right hemisphere damage, using discrimination of stress in compound words (e.g., *green house* versus *green*-house) and discrimination of statement-question pairs, and found that patients scored significantly worse than controls [73]. These studies thus suggest a role of the right hemisphere in processing of linguistic prosody.

In contrast, a number of authors have suggested that linguistic prosody is a function of the left hemisphere. Pell found that left hemisphere damaged patients were significantly impaired compared to controls and right hemisphere damaged patients in perceiving emphatic stress [74]. Heilman found that patients with right hemisphere lesions had impaired comprehension and production of emotional prosody but intact linguistic prosody [75]. A Chinese study examining perception of prosody concluded that the right hemisphere was primarily involved in complex sound analysis but that the left hemisphere was recruited when language processing was required [76]. Hughes examined 12 Chinese speakers with right hemisphere strokes for dysprosody in the initial two months following stroke and found that although there was a trend for impairment of comprehension of linguistic prosody, it was not statistically significant when compared to controls [77]. Comprehension of semantic intonation was tested by showing the patient a card containing four pictures of objects or animals; the names of two of the four pictures sounded identical when spoken without appropriate intonation. The examiner said the name and the patient pointed to the appropriate picture. Thus, this test was assessing linguistic prosody for identification. The authors suggested that linguistic prosody was a function of propositional language and therefore likely to be primarily served by the left hemisphere. As a language, however, Chinese is quite different to English. Prosody, especially linguistic, is particularly important in Chinese (arguably more so than in English) as intonation changes the meaning of single words, and a single phoneme may have up to seven different meanings depending on the tone in which it is spoken.

Heilman found that patients with either right or left hemisphere lesions had reduced comprehension of propositional prosody compared to normal controls [78]. In another study, Pell found that both right and left hemisphere damaged patients performed slower but as accurately as controls in a discrimination task for both affective and linguistic prosody, while both groups performed significantly worse than controls in a linguistic

prosody identification task. The patients with left hemisphere lesions performed substantially worse than those with right hemisphere lesions, however the difference was not statistically significant [79]. In addition, a small number of fMRI studies in normal controls have shown bilateral activation during processing of linguistic prosody [80-82].

Thus, the lack of clear lateralisation has led some to suggest a role for both hemispheres in linguistic prosodic processing and lends support to hypotheses which invoke cooperation between the hemispheres.

1.17.3 Production of linguistic prosody

The group of patients described above with right hemisphere damage and impaired receptive linguistic prosody also had difficulty producing linguistic prosody when asked to repeat statement-question intonation contours and production of emphatic stress in sentences [73]. Blonder described the prosodic abnormalities in a patient following a right hemisphere stroke. This patient produced a significantly restricted range in beginning, peak and end fundamental frequency (*fo*). The rate of speech was faster with a more restricted variance in pause duration, leading to an abnormal rhythm contributing to the monotonous impression of her spoken language [83]. Hird also demonstrated that patients with right hemisphere damage produced sentences of shorter duration than controls. In this study, patients with Parkinson's disease (PD) and multiple sclerosis (MS) were also examined and these two groups, despite difficulty coordinating muscles of respiration, articulation and phonation, were able to make durational changes to signal lexical stress and pragmatic information compared to the right hemisphere damaged group [65].

Walker, on the other hand, found no evidence that patients with right hemisphere damage had significantly different accuracy producing linguistic prosody than controls in an

experiment where patients and controls were asked to produce lexical stress differences (e.g., *com*bine versus com*bine*); produce linguistic prosodic structures that determined the location of syntactic boundaries (e.g., The father said, listen to the choirboy. versus The father said, listen to the choir, boy.); or produce linguistic prosodic structures that conveyed a statement or a question (e.g., The airport was closed? versus The airport was closed.) [67]. Similarly, Behrens investigated right hemisphere damaged patients and found that they had preserved ability to convey linguistic stress [84].

From these studies then, lateralisation of production of linguistic prosody remains unclear.

The non-linguistic functions of prosody (e.g., emotional prosody) are language independent, explaining why we know whether someone is angry or happy when speaking in a foreign language, even if we do not understand the words [85]. However, the linguistic functions of prosody appear to differ between languages. Non-native speakers of English may use linguistic prosody incorrectly when speaking English, adversely affecting comprehension by native listeners; improvement in their prosody makes a larger difference to comprehensibility than correction of phonemic errors [86]. Little research has been performed on different English dialects/accents with regard to prosody. Spanish speakers from different regions (e.g., Ecuador, Cuba, Spain) have some differences in production of linguistic prosody (however, there are also differences other than prosody between these dialects) [87]. Speakers of Swiss-French and native French use different prosodic clues to map the acoustic signal of speech onto linguistic categories [88]. However, it is not clear that these accent- or dialect-related differences affect individuals' comprehension of linguistic prosody.

1.18 Dysprosody in AOS

Dysprosody is a characteristic feature of AOS [11, 89]. The prosodic abnormalities seen include a slow rate with prolongation of vowels and consonants. There are often pauses before initiation of an utterance as well as in between syllables or words, giving words and sentences a disjointed character. Stress may be equally placed across syllables and words and there may be difficulty varying the stress in propositional speech. Pitch and loudness are restricted. These prosodic abnormalities have given rise on occasion to a "foreign accent". One functional study of a patient with foreign accent syndrome due to an infarct in the left putamen found increased cortical activation in the central sulcus and ventricular angular gyrus. As the putamen is implicated in speech motor control, the authors postulated that this increased cortical activity reflected increased motor processing load caused by the damage to the putamen [90].

It is unclear whether dysprosody in AOS occurs as a compensatory mechanism, i.e., the rate slows and pauses occur because the patient anticipates the difficulty he is going to have with an utterance, or whether it is an intrinsic part of AOS caused by the problem with motor programming.

Traditionally prosody was thought to be mediated by the right hemisphere and hence the concept that dysprosody in AOS (caused by a left hemisphere lesion) must occur as a compensatory mechanism. Darley suggested that patients with AOS deliberately altered the prosody of their speech to compensate for the defect [19]. However, acoustic studies documenting prosodic abnormalities in AOS support the theory that in AOS there is simplification of the motor programming such that speech is programmed in a syllable-by-

syllable manner [91, 92], and therefore that dysprosody is an intrinsic part of AOS and is caused by left hemisphere lesions.

There have been few studies on prosody in AOS. Although the mechanism of the prosodic disturbance in AOS is not fully understood, it had traditionally been assumed that it was an "output" or production problem. One study asked patients with AOS to produce emotionally charged statements and found that they were unable to perform this task [89]. Odell examined groups of patients with dysarthria, AOS and aphasia and found significantly higher rates of prosodic production errors in the AOS group compared with the aphasic or dysarthric group [93]. These findings could be used to support the view that dysprosody is an integral part of AOS. Alternatively, the fact that aphasic patients with left hemisphere lesions did not have dysprosody could be used to support the argument that dysprosody occurs as a compensatory mechansim in AOS, as if dysprosody was due to a left hemisphere lesion one would expect the aphasic group to be similarly affected.

Studies of prosody in AOS have focused on the production of prosody. If linguistic dysprosody in AOS occurs as a result of compensatory mechanisms and is mediated by the right hemisphere, one would expect that receptive prosody should be unaffected in patients with AOS. However, a study on children with developmental AOS (although arguably a different condition than acquired AOS) found that affected children were impaired in a discrimination task suggesting that they had abnormal auditory processing. This study also found that the degree to which auditory processing was affected impacted on the frequency of articulatory substitutions, indicating interdependance of perception and production [94].

My study will investigate perception of linguistic prosody in patients with stroke and thus provide information on lateralisation of linguistic prosody and the association between linguistic dysprosody and AOS.

Chapter 2: Hypothesis and aims

2.1 Main hypothesis

In the natural history of language recovery following ischaemic hemispheral stroke, reports of rapid recovery of speech output over days suggest that apraxia of speech (AOS) may play a significant role in these cases. My hypothesis is that AOS is more common following stroke than previously thought; that as an apraxia it is largely due to disrupted functional anatomic connections and thus is amenable to rapid recovery; that such recovery is also common; and in part this may be the explanation for rapid recovery of speech in the early stages of stroke in some cases.

2.2 Specific aim 1

Aim

To determine the frequency and natural history of AOS following acute ischaemic hemispheral stroke, and its association with orofacial apraxia (OFA).

Rationale

As outlined in the previous chapter, there are little epidemiological data on AOS. To date, there are no studies investigating the frequency of AOS after acute ischaemic hemispheral stroke or its clinical course following stroke and thus a lack of information on prognosis. Most of the studies on AOS have been performed by speech and language pathologists or neuropsychologists in the chronic phase after stroke, when patients' deficits are stable and patients can participate in extended testing in a controlled environment. Thus, the literature does not reflect what practising neurologists experience when seeing patients in the acute period after stroke. Case reports and small case series have suggested that some patients who are initially mute after acute stroke, rapidly regain speech over a period of days; their deficits have been postulated to be due to AOS. The mechanism of the rapid recovery in these patients' speech and language deficit is unclear, as some sustained established brain infarction and do not have rapid recovery of their other neurological deficits.

AOS often co-exists with OFA, however, the association between AOS and OFA is not well understood as AOS has also been reported occurring without OFA. In addition, functional data from healthy individuals suggest that speech and non-speech movements

recruit different parts of the brain [60]. The fact that they can occur independently argues against the theory that AOS results from impaired orofacial control.

Validated tools are available for testing of AOS, these have not been used extensively in the acute stroke population. Indeed, reports of patients in the acute stroke period have mainly relied on descriptive accounts of the speech and language deficit as standardised batteries are often time consuming and inappropriate for bedside testing of patients with acute stroke.

Studies of patients with speech disorders referred for speech and language therapy suggest that AOS is much less frequent than other speech disorders such as aphasia or dysarthria. This may be because there is little evidence on best therapy for AOS and thus such patients may be referred less. In addition, many patients with AOS have other speech and language disorders, such as associated aphasia, and AOS may be considered a secondary diagnosis in these cases.

2.3 Specific aim 2

Aim

To determine the neuroanatomical substrate of AOS in patients following acute ischaemic hemispheral stroke, and thus how regional abnormalities may explain the concept of rapid recovery.

Rationale

Apraxias are often thought of as being due to a disconnection between functionally related areas, e.g., ideomotor apraxia is thought to be due to a disruption in the system between processing a command, accessing stored information about tools/gestures, and translating these into a motor output.

Lesion location in AOS is controversial. Several studies have sought to address this issue and found conflicting results. Early literature suggested that patients with AOS following stroke had lesions of the left prefrontal gyrus of the insula; however, subsequent studies have implicated many different regions, including Broca's area and multiple subcortical structures. The only unifying feature is that virtually all reports suggest a left hemisphere location. One of the difficulties in interpreting this literature is that patient assessment has occurred at different time points following stroke, often many years later, when recovery and functional brain reorganisation is likely to have occurred.

If AOS is due to a disconnection between functionally related areas, as in other forms of apraxia, then this would explain why the literature has found discordant results regarding

lesion location. A disconnection may also be more amenable to recovery/reorganisation than if the deficit was due to infarction of a vital region containing a "speech motor programming centre", thus this may explain the potential for rapid recovery of AOS following acute stroke.

One study to date has described an association between lesion volume and AOS severity. If this association can be confirmed, it may support the hypothesis that AOS is due to disconnection of functionally related areas. The larger the brain lesion, the more likely it may be that functional networks are disrupted and thus result in AOS. It may also be that larger lesions may result in more persistent speech deficits due to less potential for functional reorganisation within that region.

2.4 Specific aim 3

Aim

To determine whether the Psycholinguistic Assessment of Language (PAL) word/non-word repetition test is useful in the assessment of AOS in the acute post-stroke period.

Rationale

There is no universal agreement on how best to evaluate for AOS. Different authors have used different methods of assessment, from descriptive accounts to extensive time-consuming batteries. When assessing patients in the acute stage following stroke, it is necessary to use a battery which takes as little time as possible, while collecting all the required information. Because most of the published studies on AOS examined patients a long time after stroke, this was not a requirement of the batteries they used. However, the Apraxia Battery for Adults II (ABA II) is a validated test battery for assessment of AOS and can be performed within 20 minutes at the bedside.

Patients with AOS are worse at non-word repetition than word repetition; however, non-word repetition is not assessed by the ABA II which is a potential weakness of this particular battery. The PAL subtest 7 assesses word and non-word repetition, can be performed in a few minutes at the bedside and has been validated against controls. This may be a useful addition to the armamentarium in the assessment of patients with AOS following acute ischaemic hemispheral stroke.

2.5 Specific aim 4

Aim

To determine the frequency and natural history of receptive linguistic dysprosody following acute ischaemic hemispheral stroke, as well as its association with AOS.

Rationale

Most studies investigating prosody have performed testing at a single time point following brain damage (including stroke), thus it is not known how frequently linguistic dysprosody occurs following acute ischaemic hemispheral stroke and little is known regarding its natural history or prognosis.

Expressive dysprosody is a characteristic feature of AOS and was initially thought to occur as a compensatory mechanism, as prosody was thought to be mediated by the right hemisphere. However, later studies suggested that dysprosody was an intrinsic part of AOS, and thus the left hemisphere must be involved in prosodic processing. Whether patients with AOS also have impaired perception of prosody is unknown, although children with developmental AOS have impaired auditory processing of prosody. Perception of linguistic prosody has been shown to be normal in patients with right hemisphere lesions and other studies have demonstrated that patients with left hemisphere lesions are impaired at perceiving linguistic prosody. Thus, if the left hemisphere is involved in the perception of linguistic prosody and expressive dysprosody is an intrinsic part of AOS, it is likely that there is an association between perception of linguistic prosody and AOS.

2.6 Specific aim 5

Aim

To determine the neuroanatomic substrate for receptive linguistic dysprosody (for identification and discrimination) in patients following acute ischaemic hemispheral stroke.

Rationale

Many studies have suggested that perception of linguistic prosody is mediated by the right hemisphere. However, one study found that lesions in either hemisphere impaired perception of linguistic prosody. Study of normal control subjects has also demonstrated bilateral hemisphere activation during prosodic discrimination tests. There have been some suggestions that discrimination tasks may be mediated more by the right hemisphere, while identification tasks may be mediated more by the left hemisphere. However, the tasks used in these studies have varied; some using prosodic discrimination and others identification. Thus, the question of which hemisphere is involved in the perception of linguistic prosody remains unanswered. In addition, prior studies have not investigated whether a specific brain region is always involved in patients with receptive linguistic dysprosody.

2.7 Specific objectives

1. To perform prospective clinical and language evaluation of a sample of 50 patients admitted to a university teaching hospital with acute ischaemic hemispheral stroke.
2. To assess patients after admission to hospital, at a 3-5 day interval and at 6 months.
3. To use clinical tools including the NIH Stroke Scale, modified Rankin Scale and Barthel Index; and language tools including the ABA II, PAL word/non-word test and prosodic discrimination/identification tests.
4. To use MR imaging to document lesion location and measure lesion volume.

Chapter 3: Subjects and methods

3.1 Subjects

3.1.1 Patient sources

Patients with suspected stroke were identified in a number of ways. The admission list in the emergency department and the CT brain log book were reviewed each working day to identify any patients admitted acutely with stroke. The neurology on-call non-consultant hospital doctors were asked on each post-call working day about admissions or transfers of stroke patients from outside hospitals. During the study period a stroke consult service operated, whereby most patients with stroke within the hospital were referred to the stroke neurology service. The stroke referrals were accessed daily and all potentially suitable patients reviewed. Finally, all consultants within the hospital were contacted in writing prior to commencement of the study and asked to refer any suitable patients.

Stroke was diagnosed by WHO criteria as a clinical syndrome of rapid onset of focal, or sometimes global, cerebral deficit with a vascular cause, lasting more than 24 hours or leading to death [95].

All patients identified as having an acute stroke were reviewed. Those that fulfilled inclusion criteria were asked to participate. If the patient was unable to give informed consent, the next of kin was asked to provide assent.

Control subjects were English speaking individuals without any history of central nervous system disorder or hearing impairment.

3.1.2 Inclusion criteria

- Age >18 years
- First ever stroke
- Native English speaker

3.1.3 Exclusion criteria

- Prior clinical stroke or evidence of existing major arterial territory infarct on brain imaging
- Reduced level of consciousness
- Brainstem or cerebellar stroke
- Intracerebral or subarachnoid haemorrhage
- Co-existing central nervous system disorder, e.g., Parkinson's disease, multiple sclerosis, cognitive impairment, learning disability, partial epilepsy etc.
- History of pre-existing significant hearing or visual loss which would interfere with testing.

3.2 Clinical assessment

A full medical history was taken from each patient or family members if the patient was unable to provide a history. This included details of the acute stroke event such as time of onset and symptoms, as well as past medical history and vascular risk factors. A full neurological examination was performed, including assessment of clinical stroke severity using the NIHSS [96] (Appendix 6) . This was followed by the speech and language battery.

3.3 Speech and language battery

The speech and language battery comprised an initial test of comprehension adapted for an Irish population (Appendix 4)[97]. If the patient scored significantly better than chance (≥20/30) the remainder of the battery was performed: consisting of the Apraxia Battery for Adults II (ABA II), the Psycholinguistic Assessment of Language (PAL) word/non-word repetition test and prosodic tests (described below).

3.3.1 Auditory comprehension / Yes / No responses

The patient was asked 30 questions (Appendix 4). The patient had to answer either "yes" or "no" to each question. This is adapted from a battery suggested by LaPointe to elicit responses to personal, immediate environment and informational questions, in order to test auditory comprehension [98].

3.3.2 Apraxia Battery for Adults II (ABA II) (Appendix 9)[22]

Description

The ABA II [22] was designed to verify the presence of AOS and to estimate the severity if present. It comprises six subtests: 1) diadochokinetic rate; 2) increasing word length; 3) limb and oral apraxia; 4) latency time and utterance time for polysyllabic words; 5) repeated trials and 6) the inventory of articulation characteristics of apraxia. Each subtest is scored separately and, when completed, the battery gives a qualitative score ranging from none to severe AOS.

Subtest 1: Diadochokinetic Rate

The patient repeats one, two and three syllable combinations as quickly as possible within a given time period. This measures volitional control over the muscles of articulation.

Subtest 2: Increasing Word Length

The patient repeats similar words that increase in syllable number, e.g., "love", "loving", "lovingly". This measures the ability to sequence the correct number of syllables in the proper order.

Subtest 3a and b: Limb Apraxia and Oral Apraxia

The patient is given 10 oral directions requiring the use of hands and arms, e.g., "make a hitchhiking sign". The examiner then gives the patient 10 oral directions requiring manipulation of the oral structures, e.g., "lick your lips". This measures the ability to produce a movement to an oral command.

Subtest 4: Latency Time and Utterance Time for Polysyllabic Words

The patient is asked to name 10 items presented in picture format. A stopwatch is used to measure the amount of time it takes to begin initiation of a word and the amount of time it takes to produce a word once it is initiated.

Subtest 5: Repeated Trials

The patient is asked to repeat 10 polysyllabic words three times each, e.g., "elephant". This measures whether production improves, deteriorates or remains unchanged with successive repetition of the same word.

Subtest 6: Inventory of Articulation Characteristics of Apraxia

Three types of speech behaviour are examined: spontaneous speech (by describing a picture), reading ("The Grandfather" passage) and automatic speech (counting). This measures the presence of apraxic speech behaviours.

3.3.3 Diagnostic criteria for AOS

We considered patients to have a diagnosis of AOS if they scored below the cutoff values in at least two of subtests 1,2,4 and 5 of the ABA II [22] as well as having three or more of the articulation characteristics of apraxia (subtest 6). We used these criteria as each subtest (1,2,4 and 5) of the ABA II is sensitive for AOS but not necessarily specific; patients with aphasia or dysarthria may obtain abnormal scores on some of these subtests yet not have AOS. Thus including any patient with a single abnormal subtest may over-estimate the prevalence of AOS. The more articulation characteristics of apraxia are present (subtest 6), the more likely the speech deficit is due to AOS. We decided therefore to specify at least two abnormal subtests as well as at least three of the articulation characteristics of apraxia to ensure that patients scored as having AOS definitely had AOS. We did not use the score from subtest 3 (limb and oral apraxia) in determining the presence of AOS as neither are necessary to make the diagnosis. However, subtest 3b was used to determine whether a patient had evidence of OFA.

3.3.4 Word / non-word repetition

One of the features of patients with AOS is that repetition of non-words is performed inferiorly to repetition of words [11, 30]. Non-word repetition is not assessed by the ABA II. For this reason we included a 40-item battery of words and non-words, part 7 of the Psycholinguistic Assessment of Language (PAL) devised by Caplan (Appendix 5, used

with permission) [99]. Both words and non-words occur in three syllable patterns: consonant-vowel-consonant (CVC), e.g., word "gauze"/non-word "roke", consonant-consonant-vowel-consonant-consonant (CCVCC), e.g., word "plant"/non-word "plart" or complex eg. word "stethoscope"/non-word "temesone".

The patient was asked to repeat each item after oral presentation by the examiner. The PAL supplies norms from 97 control subjects for comparison (Appendix 5b).

3.3.5 Prosodic tests

Stimulus materials (Appendix 10)

Stimuli consisted of auditory recordings of a human male voice enunciating phrases in standard English. The recordings were made in a sound-proofed room on a Compaq Presario 700 laptop computer using a microphone attachment. Each sentence was between 2 and 3 seconds long. Three sentence quartets were constructed (12 sentences in total). Each sentence quartet consisted of a string of lexical items, which were intoned as:

a) a question with a rising boundary tone, e.g., question (Q): "She was writing with a pen?"

b) a statement with a falling boundary tone, e.g., statement (S): "She was writing with a pen."

c) a question with word order change to denote the illocutionary intent resulting in a question with a falling boundary tone, e.g., statement question (SQ): "Was she writing with a pen?"

d) a question with word order change to denote the illocutionary intent but also with a rising boundary tone, e.g., question question (QQ): "Was she writing with a pen?"

Psycholinguistic methods

Discrimination:

An example was initially presented to the patient to ensure that they understood the concept of the test.

Twelve pairs of sentences were presented in a random manner. Each pair was of the same lexical structure: six were prosodically identical and six were prosodically different, e.g., Q "She was riding her new bike?" / S "She was riding her new bike." The patients' task was to indicate whether each sentence pair was the same or different, e.g., the correct response to the example above is "different".

After each pair the patient was asked to give a response. The patient could indicate their response either verbally or by pointing to a sheet of paper on which was written "same" and "different". If a patient scored full marks in this test, this test was not repeated on repeated assessments and the score was carried forward.

Identification:

An example was initially presented to the patient to ensure that they understood the concept of the test.

Twelve sentences were presented in a random manner. There were three of each sentence type. After presentation of each sentence the patient was asked to give a response. The patients' task was to indicate which type of sentence each was, e.g., S, Q, QQ, SQ. The patient could indicate their response either verbally or by pointing to a sheet of paper on which was written the various possibilities. If a patient scored full marks in this test, this test was not repeated on repeated assessments and the score was carried forward.

3.3.6 Aphasia assessment

Comprehension of yes/no questions was assessed in all patients (Appendix 4). Naming, reading and repetition were all assessed in subtests of the ABA II (Appendix 9) and repetition was also assessed by the PAL subtest 7 (Appendix 5a). In addition, the patients were assessed by a qualified speech and language therapist who had stroke experience during their hospitalisation. These records were reviewed to determine the presence or absence of associated aphasia.

3.4 Timing of assessments

3.4.1 Early post-stroke assessments:

Patients were assessed twice in the first week post-stroke: as soon as possible after admission to hospital, and a second time two to three days later. The initial speech evaluation was performed by the same neurologist at the same time as the neurological assessment. When possible the patient was examined in a quiet room, however, due to stroke severity or other medical reason, some patients were assessed at the bedside. These assessments consisted of a clinical assessment of stroke severity using the NIHSS [96](Appendix 6), the comprehension battery (Appendix 4) followed by the remainder of the speech and language battery. The entire assessment took approximately 40 minutes to complete.

3.4.2 Final assessment:

The final assessment took place approximately six months after stroke. It consisted of clinical assessment using the NIHSS (Appendix 6)[100], the speech and language battery as already described, and assessments of functional outcome using the modified Rankin Scale (mRS) (Appendix 8)[101] and the Barthel Index (BI) (Appendix 7)[102].

The BI measures performance in basic activities of daily living. It was used as it is a quick and simple score to evaluate a patient's functional independence. A higher score indicates a higher liklihood of the patient being able to live independently following discharge from hospital. It is considered reliable [103] but does, however, have the disadvantage of floor and ceiling effects. In addition, it is an ordinal scale meaning that parametric statistical

analyses cannot be used. The mRS [101] measures independence rather than performance of tasks. It is a continuous scale thus parametric analyses can be used; it is also reliable [104]. However, it is non-linear so that a change of one point has different implications depending on the specific score. The mRS has been shown to have prognostic value in terms of mortality, both when used acutely as well as at 3 months post-stroke [105, 106]. Although neither of these scales are perfect, they are both widely used and understood by clincians [107] and give an indication of a patient's functional outcome following stroke.

3.5 Imaging

All patients where possible had magnetic resonance imaging (MRI) on the same 1.5 T clinical scanner (GE systems, Milwalkee), which was protocolled for acute stroke. This protocol consisted of axial fast-spin echo (FSE) T2-weighted, diffusion weighted imaging (DWI), apparent diffusion coefficient (ADC) and axial T2 fluid attenuated inversion recovery (FLAIR) sequences. Computed tomography (CT) was performed if it was not possible to perform MRI. Imaging was performed early during the hospital admission.

3.5.1 Lesion volume measurement

Lesion volume was measured digitally using the FLAIR MRI image after identifying the area of interest (acute infarction) using the DWI image.

MRI data were transferred to a workstation and converted from *DICOM* (Digital Imaging and Communications in Medicine) into *Analyze* format using the software MRIcro [108]. Volume estimates were calculated using the Cavalieri principle, whereby a volume is sectioned into a series of two-dimensional slices, the position of the first slice being random with respect to the volume and with subsequent cuts at consistent intervals.

The Cavalieri principle states that the volume may be estimated by multiplying the area of each slice by the slice separation T. The area of each slice may be estimated by superimposing a grid of points on the slice (Figure 3.1) (each point has an area associated with it), and counting the number of points (P) that fall within the area of interest (Figure 3.2). By combining the information from sectioning and point counting, the volume of the structure may be estimated using the equation

$$V = T \frac{a}{P} \sum_{i=1}^{n} P_i$$

where P_i is the point count per slice, (a/P) is the area per test point, T is the slice separation and n is the total number of slices sampled (Figure 3.3).

Area stereological estimates were carried out using the specialised interactive software *Measure* developed at Johns Hopkins, Maryland [109]. Cavalieri volume estimates were carried out using *EasyMeasure* software (MARIARC Institute, University of Liverpool).

This technique has been demonstrated to give unbiased estimates of lesion volumes. In general, as slice number (n) increases, the coefficient of error (CE) decreases; however, the volume estimated from only three slices of a lesion gives a CE of <5% [110]. This technique has been used for measuring volumes of many different types of lesions including small lesions such as multiple sclerosis plaques [111] and pituitary glands [112].

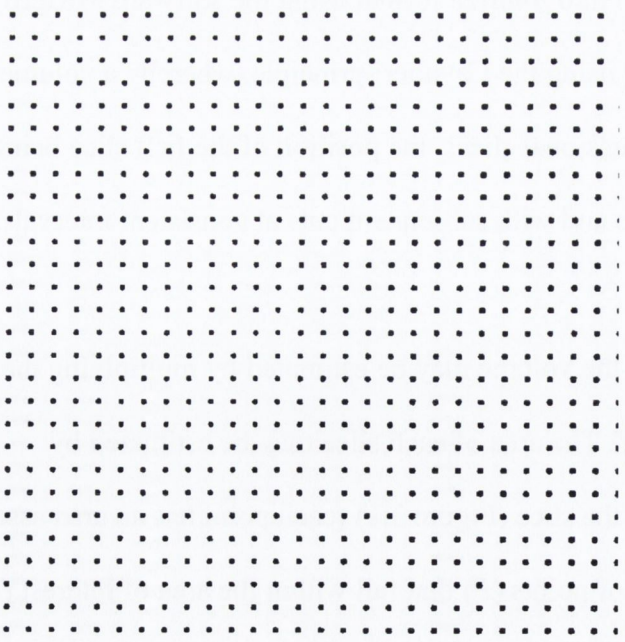


Figure 3.1 Representation of point counting grids used in stereological measurements

Each point has an area "a" associated with it

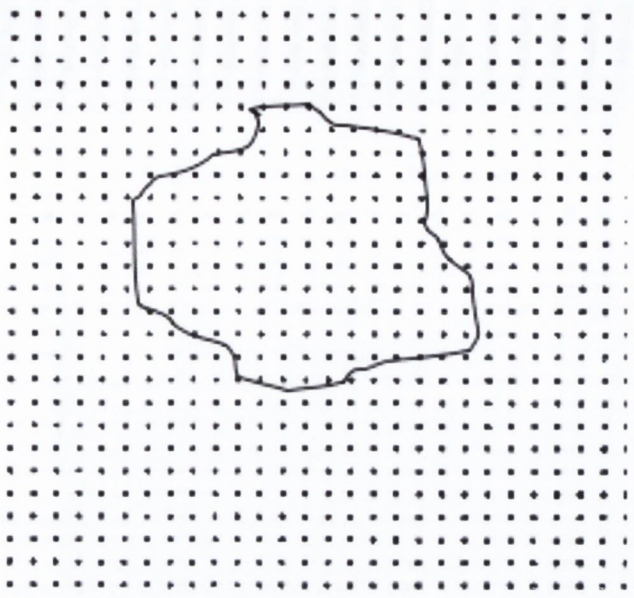


Figure 3.2: Area estimation of a slice of an object

Stereological estimate is made by counting all the points that fall within the region of interest (outlined in black). Summing up all points and multiplying by the area of each point "a" gives an estimate of the area of this slice of the object.

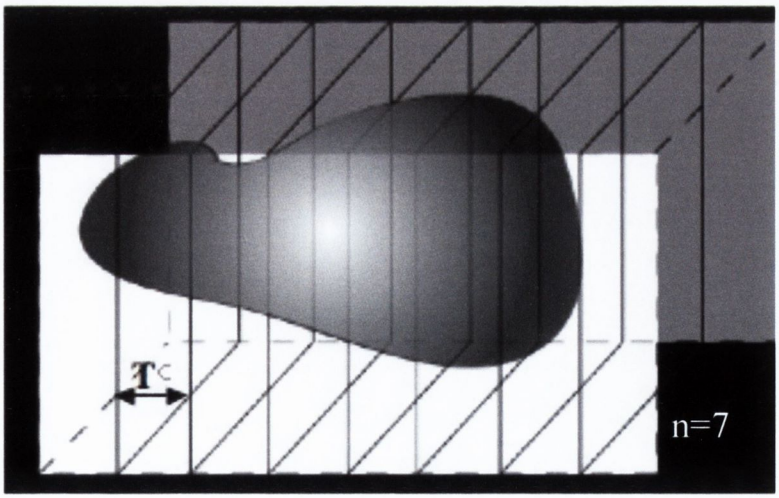


Figure 3.3: Sampling grid planes fixed at intervals through a 3-D object

T=slice separation; n=total number of slices sampled

An area estimate is generated for each sample slice (as in Figure 3.2) which is then summed and multiplied by slice separation T to estimate the object volume (as in Figure 3.3).

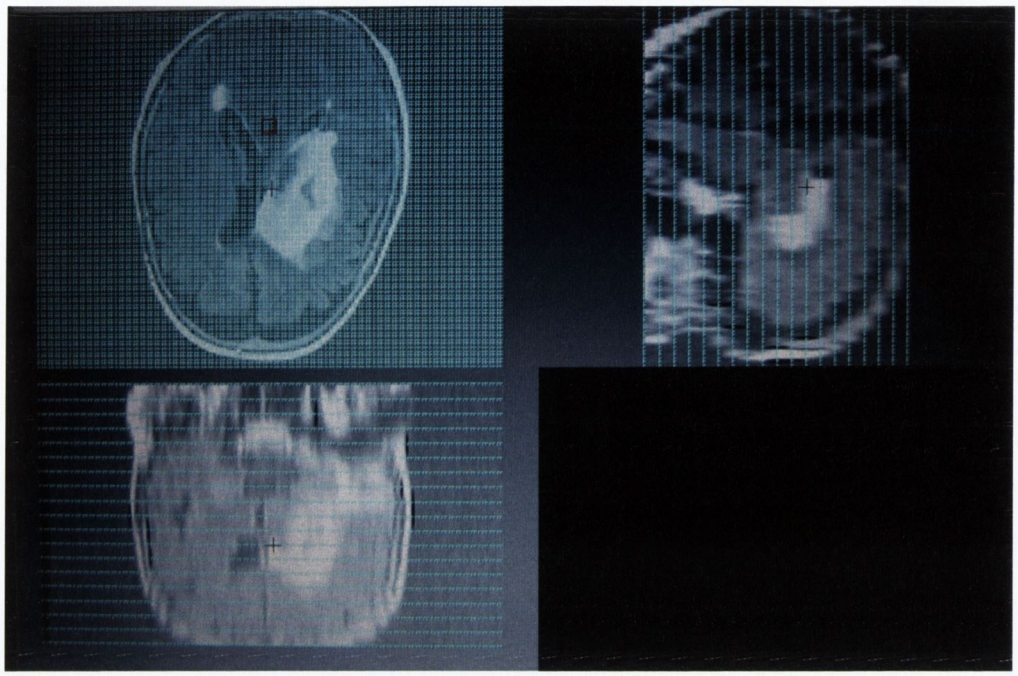


Figure 3.4: Example of the grid randomly placed on one slice of an MRI FLAIR image

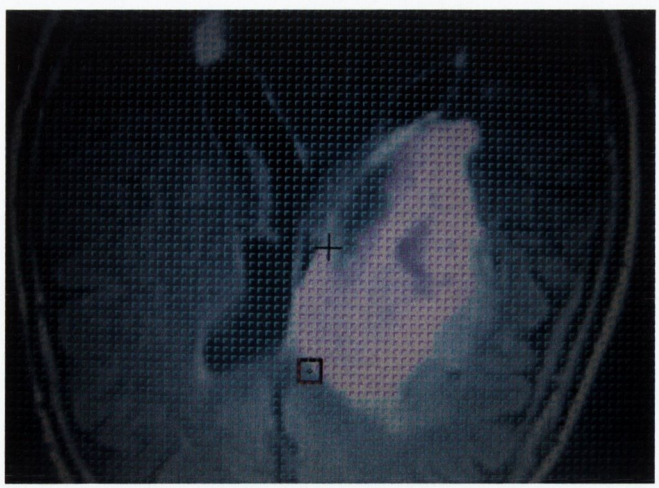


Figure 3.5: Example of the grid in place over the MRI slice with points within the area of interest selected (in pink)

Reliability of volume estimates

One rater (SM) measured lesion volume on all lesions. In order to assess the repeatability of stereological volume estimates, the same reader measured the volume of each lesion on a subset of 10 patients on two separate occasions at least two weeks apart.

For inter-rater agreement, two readers (SM and LR) each performed volume measurements on a subset of 10 patients. The readers had access to all MRI sequences to aid in identification of the acute lesion.

The intraclass correlation coefficient (ICC) (model 3) was used to assess repeated measures [113]. ICC values of >0.74 are considered excellent, 0.6-0.74 good, 0.4-0.59 fair and <0.4 poor.

Repeatability of measures was also demonstrated using agreement plots [114]. Results were considered acceptable if the standard deviation that defines the limits of agreement of the plots fell within the standard deviation of the population mean. The limits of agreement are ±1.96 standard deviations of the population mean. These tests were performed for both intra-rater and inter-rater measurements.

3.5.2 Identification of lesion location

Co-registration of images

SPM5 software [115] was opened and each patient's MRI data co-registered with a standardised T1 MRI image using the "Check Reg" function.

Creating lesion mask

When normalising MRI images, any lesions that are on the scan may distort the normalised image. For this reason a lesion mask must be created prior to the normalisation process [116]. A lesion mask was thus created for each image using MRIcro software [108]. The patient's MRI was opened and MRIcro's Region of Interest tool was used to create a region of interest (ROI) that accurately mapped the location and extent of the lesion.

A lesion image was then made: with the image and ROI open, 'Export ROI as Analyze image...' was selected from the 'ROI' menu. The option 'ROI is 1, background is 0' was chosen and the image saved with the prefix 'l' (for 'Lesion').

A masking image was then created: with the image and ROI open, 'Export ROI as smoothed Analyze image...' was chosen from the ROI menu. Full width half maximum (FWHM) smooth of 8mm, a 0.001% threshold and 'ROI is 0 (SPM object mask)' options were selected. The image was saved with the prefix 'm' for mask.

Normalisation of image data

In order to use lesion overlap techniques, all images must be standardised so that it will be possible to interpret the results relative to each other [117]. SPM5 was used to normalise image data using unified normalisation routine [117].

Creating region of interest (ROI)

MRIcro software was used [108]. The normalised image was opened from file. A region of interest was drawn, outlining the location of the infarct, on all relevant slices. This procedure was performed for all MRI scans after the image data had been normalised as described above.

Determination of lesions causing AOS

In order to determine whether a single brain region was involved in all patients with AOS, all ROI images of patients with AOS were overlapped using MRIcro's multiple ROI command. Digital images were compared with plates from a reference atlas to determine the locations involved [118].

In order to determine whether a lesion in a specific region always caused AOS, all ROIs of patients with AOS were overlapped and all ROIs of patients without AOS were overlapped. The MASK comparison was then used to determine whether there was any region that was exclusive to patients with AOS.

Determination of lesions causing dysprosody

Similarly, in order to determine whether a single brain region was involved in patients with linguistic dysprosody, ROI images of patients with each type of linguistic dysprosody (discrimination and identification) were overlapped using MRIcro's multiple ROI command.

In order to determine whether a lesion in a specific region always caused dysprosody, ROIs of patients with each type of linguistic dysprosody were overlapped and ROIs of patients without dysprosody were overlapped. The MASK comparison was then used to determine whether there was a specific region that was exclusive to patients with linguistic dysprosody.

3.6 Statistical analysis

An analysis to describe the patients with respect to their clinical characteristics was performed using means, proportions and frequency distributions. Patients who could not be assessed due to significant comprehension difficulty were excluded from analysis. To describe the natural history of AOS and linguistic dysprosody, only those patients who had at least two assessments performed were included.

Two standard deviations from the control group mean was used as the lower limit of normal for the purposes of determining an abnormal score on the prosody tests. Patients with AOS/linguistic dysprosody were then compared with the non-AOS/non-linguistic dysprosody patients with respect to variables. For categorical variables, this was performed by comparing distribution using Chi-square (χ^2) tests, *z* tests or Fisher's exact tests where numbers were small. For continuous variables, student's *t*-test was used to compare means between two groups. ANOVA was used to make comparisons between multiple groups. To assess and allow for confounding among clinical characteristics in the group comparisons and to assess the relative importance of potential variables, logistic regression was used.

To determine whether lesion volume correlated with the severity of AOS, the Spearman correlation coefficient was used. ANOVA was used to compare means of multiple groups (e.g., AOS vs. no AOS vs. unable to assess). Multiple regression was used to determine the importance of predictor variables (e.g., NIHSS, age, lesion volume) in explaining the severity of AOS.

XL-Stat software (Addinsoft, New York) was used and a p value of <0.05 was considered significant.

3.7 Ethics approval

The study was approved by the Beaumont Hospital Ethics (Medical Research) Committee and informed consent was obtained from patients or their next of kin before inclusion in the study. The aims of the study and examination required were explained and individuals given an information sheet (Appendix 1) as well as time to ask questions before signing a standardised consent form (Appendix 2).

Chapter 4: Frequency and natural history of AOS following acute ischaemic hemispheral stroke, its association with orofacial apraxia and use of the Psycholinguistic Assessment of Language subtest 7 in AOS

4.1 Introduction

AOS has been reported most frequently following stroke, but is also seen in neurodegenerative diseases such as motor neuron disease [23] and progressive supranuclear palsy [119]. Because of its wide associations AOS frequently occurs with both dysarthria and aphasia [11, 32] and differentiating these can be difficult as discussed previously (see Chapter 1.7, 1.8).

The frequency of AOS in the acute period following stroke is unknown. In most studies, there was a variable interval, often of some years, between onset of the neurological insult and patient assessment [4, 32]. As a result, the speech and language deficit had largely stabilised and was unlikely to change further and that, importantly, significant recovery may have already occurred. Functional brain reorganisation may well have occurred, with resultant implications for lesion studies.

Similarly, the course of AOS is unknown, particularly in the early post-stroke period. Differing views have been published, without any more than case reports or small series as evidence. Some suggest that AOS has a poor prognosis for recovery [24, 30]. There have

been reports, however, of patients initially mute following stroke showing a rapid resolution of their speech deficit in the early post-stroke period, despite evidence of established brain infarction [45, 51]. These patients' deficits have been postulated to be due to AOS, the mechanism of their rapid recovery unknown.

Orofacial apraxia (OFA) is the inability to perform volitional movements of the orofacial apparatus on command, such as protruding the tongue, licking the lips etc. even though the same patient may carry out these actions in an involuntary reflexive manner. Among the many challanges of AOS assessment is the fact that it often coexists with OFA [11, 45, 46]. The association between AOS and OFA is not well understood as AOS has also been reported occurring without OFA [9, 12, 120]. In addition, functional data from healthy individuals suggest that speech and non-speech movements recruit different parts of the brain [60]. The fact that they can occur independently argues against the theory that AOS results from impaired orofacial control.

There is no gold standard or universally accepted test for diagnosing AOS and thus different studies have used varying methods. In addition, although validated batteries are available for testing of AOS, these have not been used extensively in the acute stroke population. Most studies of patients with AOS have been performed a long time after the acute insult, when the patient is medically well, the speech and language deficit has stabilised and patients are able to perform lengthy and detailed assessments. Reports of patients with AOS in the acute stroke period have mainly relied on descriptive accounts of the speech and language deficit as standardised batteries are often time consuming and inappropriate for bedside testing of patients with acute stroke. The Apraxia Battery for Adults II (ABA II) [22] was used in this study as it comprises the majority of tasks suggested by Duffy [121] and those of the MSE, which are considered necessary to diagnose AOS.

Patients with AOS perform worse at non-word repetition than at word repetition [6-8, 29]. The ABA II includes word repetition (subtest 2), however, it does not include non-word repetition. The Psycholinguistic Assessment of Language (PAL) is a psycholinguistically oriented language assessment battery comprising 27 subsets to assess different components of the language processing system. The PAL is predominantly used as a research tool. Subset 7 (Appendix 5) tests word and non-word repetition. It consists of 20 words and 20 non-words of differing degrees of complexity, e.g., CVC word "boat", non-word "dipe"; CCVCC word "plant", non-word "plart"; complex word "stethoscope", non-word "pensafon". This subtest can be performed in a few minutes at the bedside, has been validated against controls and may provide useful information in the assessment of patients with AOS.

4.2 Specific aims

As discussed in more detail in Chapter 2, the specific aims of this study were to determine the frequency and natural history of AOS in patients hospitalised with acute ischaemic hemispheral stroke, and to evaluate the PAL subtest 7 in the assessment of patients with AOS. I also sought to determine the association between AOS and OFA and the association between AOS and stroke severity.

4.3 Results

4.3.1 Subjects

Two hundred and eleven patients were admitted to Beaumont Hospital with suspected stroke during the course of the study (one year). Of these, 159 patients met exclusion criteria (Table 4.1) and two patients declined to take part. Fifty consecutive patients with acute ischaemic hemispheral stroke who fulfilled inclusion criteria were recruited. There were 28 males and 22 females, their mean age was 66 ±12 years and their age range 21-90 years. All but two (48/50, 96%) were right handed. Initial assessment was performed a median of four days post stroke, the second assessment a median of seven days post symptom onset and the third assessment a median of six months later.

Table 4.1: Patients excluded from study

Reason for exclusion	Number
Prior stroke	64
Posterior circulation/brainstem stroke	25
Intubated/Low GCS	6
Symptoms resolved or patient discharged before assessment	10
Not native English speaker	5
Co-existing neurological diagnosis	11
Pre-existing deafness or speech disturbance	3
Not ischaemic stroke	35

GCS=Glasgow Coma Scale

4.3.2 Frequency of AOS

See figure 4.1 for a flow chart of patient recruitment. At the first assessment, 9 of the 50 patients were not able to complete the test battery due to significant comprehension difficulties. Of the remaining 41 patients, 14 (34.1%) had evidence of AOS.

At the second assessment, four patients had deteriorated clinically and were not assessed for this reason (two of these four had had significant comprehension difficulties at the first time point). Five patients were not able to complete the test battery due to significant comprehension difficulties (all five had had significant comprehension difficulties at the first assessment). Of the original 9 patients unable to complete the test battery due to significant comprehension difficulties, two had improved sufficiently to complete the assessment. Of the remaining 41 patients, 15 (37%) had evidence of AOS.

At the third assessment, two patients still had significant comprehension difficulties, one patient had withdrawn from the study, five patients had died, one patient had moved out of the country and six patients had been lost to follow-up. Of the remaining 35 patients, 11 (31.4%) had evidence of AOS.

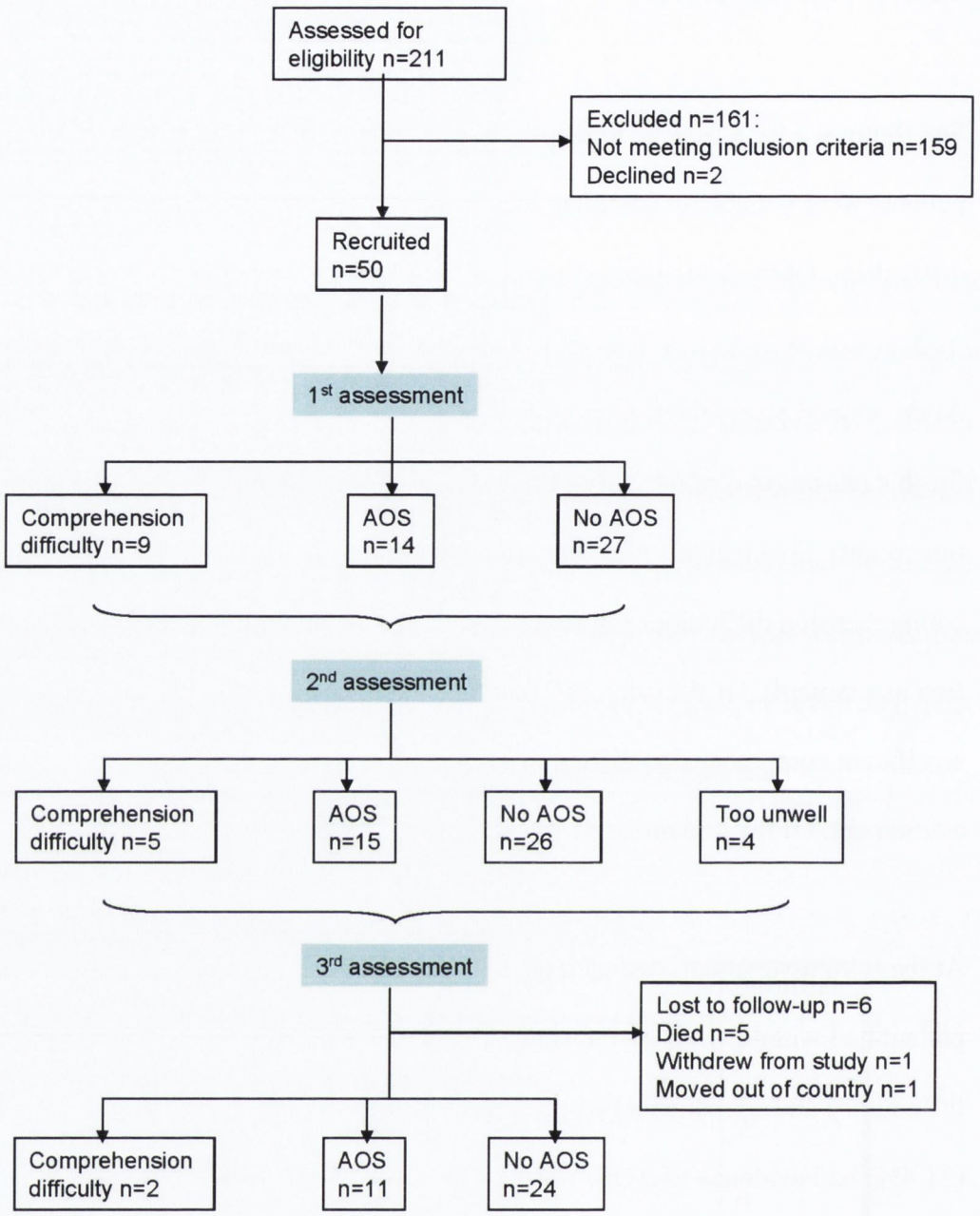


Figure 4.1: Flow chart of patient recruitment

All patients who scored <20/30 on the screening comprehension test due to significant aphasia had left hemisphere infarction. In total, over the course of the study there were five patients who could not complete the test battery at any time point due to significant comprehension difficulties ("Unable to assess" group in Table 4.2). In these five patients, there was a non-significant trend to be older and have more vascular risk factors than the

other 45 patients who could complete assessment. However, there was a statistically significant difference in the NIHSS score between the two groups (mean 18.4 versus 7.7, p=0.04) suggesting that this group of patients had larger and more severe strokes. There were no significant differences in demographics or vascular risk factors between the patients with AOS and those without (Table 4.2).

In total, throughout the course of the study, 18 individuals of 45 tested (40%) had evidence of AOS at some time following stroke.

Table 4.2: Patient demographics and clinical characteristics

	AOS group n=18	No AOS group n=27	Unable to assess n=5
Mean age (yr ± sd)	61.1 ± 12.5	67.3 ± 10.5	76.2 ± 12.9
Sex (Males)	10 (55.6%)	15 (55.6%)	3 (60%)
Smoking history	12 (66.7%)	16 (59.3%)	3 (60%)
Hypertension	9 (50%)	12 (44.4%)	5 (100%)
Hypercholesterolaemia	11 (61.1%)	14 (51.9%)	3 (60%)
Atrial fibrillation	6 (33.3%)	5 (18.5%)	3 (60%)
Diabetes mellitus	2 (11.1%)	5 (18.5%)	0 (0%)
Mean NIHSS ± sd	10.6 ± 5.6 §	5.9 ± 3.5	18.4 ± 7.7 *
Mean NIHSS excluding language component ± sd	8.7 ± 5.2	5.8 ± 3.6	15.6 ± 7.2 *
L hemisphere affected	18 (100%) $	12 (44.4%)	5 (100%)

Yr=years, sd=standard deviation, L=left, AOS=apraxia of speech, NIHSS=National Institute of Health Stroke Scale

*=$p<0.05$ compared to the other two groups as a whole

§=$p=0.001$ AOS versus no AOS group

$=$p<0.0001$ AOS versus no AOS group

4.3.3 Association between AOS and OFA

Only data from the initial two assessments was used to determine the association between AOS and OFA. Eleven of the patients with AOS also had evidence of OFA while none of the patients without AOS had evidence of OFA. All 11 patients with OFA also showed evidence of AOS, indicating a significant association between the two (Fisher's exact test $p<0.0001$). However, five patients had AOS without any evidence of OFA (Table 4.3). Thus, AOS occurred with or without OFA, but OFA only occurred in the presence of AOS.

Table 4.3: Association between OFA and AOS

	OFA	No OFA
AOS	11	5
No AOS	0	27

$p<0.0001$

4.3.4 Association between AOS, stroke severity and hemisphere

Thirty-five (70%) patients had left hemisphere infarcts in the group as a whole. One hundred percent of patients with AOS had left hemisphere infarcts compared to 44% of those without AOS ($\chi^2= 15$, $p<0.0001$).

Mean NIHSS in patients with AOS was 10.6 (range 2-21) compared to 5.9 (range 2-15) in those without AOS ($p=0.001$). Even when the language component of the NIHSS was excluded, the difference between groups remained significant (8.7 vs. 5.8, $p=0.0003$) (Table 4.2).

Multiple regression analysis demonstrated that NIHSS and hemisphere significantly predicted the presence of AOS ($r^2=0.51$, $p<0.00001$). Multiple regression analysis

demonstrated that patient age did not, however, predict the presence of AOS (p=0.3). The NIHSS also correlated with the severity of AOS (Pearson correlation coefficient r=0.79, p=0.001).

4.3.5 Association between AOS and aphasia

Details of aphasia testing were available on all of the 18 patients with AOS. Of these, as well as AOS, nine patients had some evidence of receptive dysphasia and all had some evidence of expressive dysphasia, ranging from very mild to severe.

The majority of patients with AOS (14/18, 78%) gave consistent yes/no responses. Six patients had more marked expressive dysphasia than receptive dysphasia; these all had either moderate or severe AOS. Twelve patients had word finding difficulty; of the six patients that were able to name ≥90% of words tested, four had mild AOS and two moderate AOS. Eleven patients with AOS had difficulty repeating words; these all had moderate or severe AOS. Thus AOS and aphasia were frequently associated. However, although patients with more marked AOS tended to have more marked expressive dysphasia, this was not always the case; two patients with moderate AOS did not have word finding difficulty.

It is notable that two patients who were completely mute at the first assessment - unable to name, repeat or read - were able to answer yes/no questions correctly by nodding/shaking their head and when asked to name objects were able to mime how to use each object and selected the correct name out of a list by indicating appropriately. One of these patients was able to name objects by writing, although he made some minor spelling errors suggesting an additional mild aphasia. The other patient was unable to write due to severe

limb weakness. This suggests that a significant contribution to their muteness was indeed AOS rather than aphasia.

4.3.6 Natural history of AOS

These results refer specifically to the 18 patients with AOS following stroke. At the first assessment, four patients had comprehension difficulty and could not complete the assessment. Two of the four patients with significant comprehension difficulties at the first time-point had improved sufficiently to allow assessment at the second time-point. One patient who had AOS at the first assessment deteriorated medically and subsequently died. By the third assessment, another patient had died and two had been lost to follow up. Overall, 10 patients with AOS had assessment at all three time-points, and five patients had assessments at two time-points. Thus, 15 patients with AOS had at least two assessments and could be analysed for the purposes of describing natural history. These 15 patients are described further below.

Of 13 patients who had AOS at the first assessment, three showed an improvement in the severity of AOS between the first and second assessments: from moderate to mild. One patient showed a deterioration in the severity of AOS from moderate to severe and in 9 patients the severity of AOS did not change between the first and second assessments.

Between the second and third assessments (approximately six months apart) one patient died and two were lost to follow-up. Of the remaining 12 patients with AOS, in two patients the severity of AOS remained unchanged, and in 10 patients the severity of AOS improved (in three cases there was no evidence of AOS at six months). See Table 4.4. Regression analysis demonstrated that initial AOS severity predicted severity at the final assessment (r^2=0.75, p=0.0003).

Patients with severe AOS at the first assessment (n=3) still had evidence of AOS at the six month assessment (two moderate and one mild). Two of the three patients with mild AOS at the first assessment had no evidence of AOS at the six month assessment (the third patient died). Thus in this patient sample there was improvement in the severity of AOS with time in the majority of cases, however no evidence of rapid early recovery.

For individual ABA II subtests scores for patients with AOS see Appendix 11.

Table 4.4: Change in AOS over time in the 15 patients with at least two assessments

Patient ID	T1	T2	T2
1	moderate	mild	none
4	unable	moderate	mild
5	mild	mild	none
10	severe	severe	moderate
13	moderate	severe	mild
15	moderate	mild	mild
16	moderate	moderate	mild
20	mild	mild	mild
23	unable	severe	moderate
25	mild	mild	RIP
26	severe	severe	moderate
30	moderate	moderate	no follow up
37	severe	severe	mild
39	mild	mild	none
44	moderate	mild	no follow up

T1=first assessment; T2=second assessment; T3=third assessment; RIP=patient deceased

4.3.7 Usefulness of the PAL subtest 7 in AOS assessment

Comparison between word / non-word repetition in patients with AOS versus patients without AOS

Results of the PAL subtest 7 are presented in tabular form on pages 81 and 82. Both the AOS and the no-AOS groups scored lower in repetition of non-words than in repetition of words, as did controls (Tables 4.5-4.8). The patient group with AOS scored significantly worse than the group without AOS in all subtests (52.1 vs. 92.6 for CVC words, 56.4 vs. 92.6 for CCVCC words and 45.7 vs. 94.8 for complex words; 42.1 vs. 83.7 for CVC non-words, 35.7 vs. 76.3 for CCVCC non-words and 25.7 vs. 77.8 for complex non-words, $p \leq 0.01$ for all comparisons, see table 4.5). Between the first and final assessments there was an improvement in scores in both groups. However, the group with AOS still scored significantly worse than controls at the final assessment and there remained a significant difference between the AOS and the no-AOS groups in most subtests (84.3 vs. 97.1 for CVC words and 71.4 vs. 97.1 for complex words; 66.4 vs. 91.4 for CVC non-words and 47.1 vs. 82.9 for complex non-words, $p < 0.05$ for all comparisons, see table 4.6). Note should be made, however, of the large standard deviation in the group with AOS.

When patients were grouped by hemisphere, those with left hemisphere stroke performed worse than patients with right hemisphere stroke for words and non-words, similarly to patients with AOS (Table 4.9).

4.3.8 Comparison between repetition of high- and low-frequency words and non-words in patients with AOS

There was a significant difference in repetition of words between patients with and without AOS, both for high-frequency and for low-frequency words (61.7 vs. 96.3 and 58.3 vs. 91.5 respectively, $p<0.0001$). There was also a significant difference in repetition of non-words between groups (42.5 vs. 80.6, $p<0.0001$) at the first assessment (Table 4.7). Although patients with AOS tended to score lower on repetition of non-words than for words, this did not reach statistical significance.

By the final assessment, there remained a significant difference between the patients with and without AOS in repetition of high-frequency (89.3 vs. 98.1, $p=0.03$) and low-frequency words (76.4 vs. 95.2, $p=0.001$). There also remained a significant difference in repetition of non-words (61.1 vs. 84.8, $p=0.03$).

Thus patients with AOS tended to score lower on both word and non-word repetition than patients without AOS. Again, note should be made of the large standard deviations in the AOS group scores.

Table 4.5: PAL Subset 7- Word / non-word repetition in AOS: first assessment

	WORDS			NON-WORDS		
	CVC	CCVCC	Complex	CVC	CCVCC	Complex
Controls n=97 #	98.5 (5.3)	99.2 (4)	97.1 (7.1)	91.3 (16.4)	88.5 (15)	87.6 (17.9)
AOS n=12	52.1 (45.3)	56.4 (45.7)	45.7 (42.6)	42.1 (41.2)	35.7 (35.2)	25.7 (33.7)
No AOS n=27	92.6 (12.6)	92.6 (20.1)	94.8 (13.1)	83.7 (21.3)	76.3 (29.9)	77.8 (27.4)
ANOVA p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
p AOS vs controls	0.005	0.008	0.002	0.001	0.0002	<0.0001
p no AOS vs controls	0.03	0.1	0.4	0.09	0.05	0.09
p AOS vs no AOS	0.003	0.01	0.001	0.0006	0.001	<0.0001

Table 4.6: PAL Subset 7- Word / non-word repetition in AOS: final assessment

	WORDS			NON-WORDS		
	CVC	CCVCC	Complex	CVC	CCVCC	Complex
Controls n=97 #	98.5 (5.3)	99.2 (4)	97.1 (7.1)	91.3 (16.4)	88.5 (15)	87.6 (17.9)
AOS n=14	84.3 (21.4)	92.9 (12.7)	71.4 (30.1)	66.4 (31.3)	62.9 (30.2)	47.1 (37.3)
No AOS n=21	97.1 (5.6)	96.2 (8)	97.1 (7.2)	91.4 (11.1)	80 (24.5)	82.9 (23.1)
ANOVA p	<0.0001	0.001	<0.0001	<0.0001	<0.0001	<0.0001
p AOS vs controls	0.02	0.08	0.006	0.01	0.007	<0.0001
p no AOS vs controls	0.3	0.1	1.0	1.0	0.1	0.4
p AOS vs no AOS	0.05	0.4	0.007	0.009	0.09	0.004

Values given are mean percentages with standard deviation in parentheses.

AOS=Apraxia of Speech, CVC=consonant vowel consonant, CCVCC=consonant consonant vowel consonant consonant

Control values were taken from the PAL norms table (Appendix 5b)

Table 4.7: PAL Subtest 7- Repetition of high-frequency, low-frequency words and non-words in patients with AOS: first assessment

	HIGH-FREQUENCY WORDS	LOW-FREQUENCY WORDS	NON-WORDS
AOS n=12	61.7 (42.8)	58.3 (41.3)	42.5 (36.6)
No AOS n=27	96.3 (6.9)	91.5 (13.8)	80.6 (23.3)
p	0.007	0.01	0.002

Table 4.8: PAL Subtest 7- Repetition of high-frequency, low-frequency words and non-words in patients with AOS: final assessment

	HIGH-FREQUENCY WORDS	LOW-FREQUENCY WORDS	NON-WORDS
AOS n=14	89.3 (15.9)	76.4 (22.7)	61.1 (27.0)
No AOS n=21	98.1 (4.0)	95.2 (6.8)	84.8 (16.2)
p	0.03	0.005	0.004

Table 4.9: PAL Subtest 7- Words / non-word repetition by hemisphere: first assessment

	WORDS			NON-WORDS		
	CVC	**CCVCC**	**Complex**	**CVC**	**CCVCC**	**Complex**
Controls n=97	98.5 (5.3)	99.2 (4)	97.1 (7.1)	91.3 (16.4)	88.5 (15)	87.6 (17.9)
Left hemisphere n=24	71.5 (39.9)	71.2 (41.4)	68.5 (40.1)	60.8 (39.3)	54.6 (39.4)	50 (40.5)
Right hemisphere n=15	91.3 (13)	96 (8.3)	94.7 (5)	84.7 (20.3)	76 (28.5)	77.3 (28.1)
ANOVA p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
p L vs controls	0.003	0.003	0.002	0.001	0.0004	0.0002
p R vs controls	0.06	0.2	0.1	0.2	0.1	0.2
p L vs R	0.03	0.008	0.004	0.02	0.06	0.02

4.4 Discussion

In this study, I documented the prevalence of AOS following acute ischaemic hemispheral stroke and its natural history over a six-month follow-up period. I investigated the association between AOS and clinical features including stroke severity and OFA. In addition, I investigated the usefulness of the PAL subtest 7 in the assessment of patients with AOS.

4.4.1 Frequency of AOS following acute ischaemic hemispheral stroke

Hitherto the prevalence of AOS following stroke was unknown. Few studies had investigated the prevalence of speech and language disorders following stroke, in particular with regard to AOS. This may be because patients with speech and language deficits are an inherently difficult group of patients to assess. AOS may occur in association with either dysarthria and/or aphasia [11, 24, 122] and it may be difficult to distinguish among them (see Chapter 1.7, 1.8).

AOS was diagnosed as the primary speech pathology in only 9% of the patients with motor speech disorders seen in the Department of Speech Pathology in one series, with 58% caused by stroke [11]. Another study found that dysarthria or AOS was present in 6% of patients with speech disturbance attending rehabilitation [48]. However, AOS also occurs as a secondary diagnosis in patients with aphasia (i.e., aphasia is considered to be the primary pathology and AOS a less important feature) [11], and in some patients may occur only transiently following stroke [45, 51]. Direct comparisons of prevalence of AOS following stroke between studies are difficult due to differences in methods of diagnosis

[4, 33] as well as variable timings of assessment following stroke [4, 32, 33]. However, it is likely that AOS occurs more frequently following stroke than has been thought in the past.

Forty percent of this cohort of consecutive patients hospitalised with acute ischaemic hemispheral stroke had evidence of AOS at some time following their stroke. This is significantly higher than the 10% suggested in one of the few studies of speech and language deficits following acute stroke; the test battery used in this study was designed specifically for aphasia rather than for AOS and thus may have under-estimated the frequency of AOS [123]. In addition, Trapl's study assessed patients within three days of acute stroke as a once-off assessment; if a patient had significant aphasia at this assessment, co-existing AOS may have been missed.

Left hemisphere strokes were over-represented in our patient group, making up 70% of the sample; the relatively small numbers in our patient group make this likely to have occurred by chance. While the predominance of patients with left hemisphere stroke may have resulted in a higher frequency of AOS in our sample, it should be noted that the five patients who were exluded from analysis due to severe comprehension impairment all had left hemisphere infarction and these patients may also have had AOS if it had been possible to assess their speech initially. In fact, two patients who were unable to complete testing at either the first or second assessment due to significant comprehension impairment scored >20 on the yes/no comprehension screening test at the six-month visit and had evidence of AOS (moderate and mild) at this assessment, suggesting an even higher frequency of AOS than we have shown. In addition, the median time to the first assessment was four days, during which time it is possible that some patients with AOS may have had resolution of their deficit.

There was no significant difference in baseline demographics between those with AOS and those without. The only significant difference between the groups was the side of infarction, which was left hemisphere in 100% of the AOS group versus only 44% of the non-AOS group. It has long been recognised that AOS results from left hemisphere damage and there are only rare case reports of right hemisphere damage causing AOS [30]. Functional MRI and PET data in normal controls has also shown left lateralised activation during speech production [60, 124]. Our findings that 100% of our patients with AOS had left hemisphere infarction is in keeping with the literature and not inconsistent with the current understanding of the functional anatomy of motor speech planning.

4.4.2 Natural history of AOS following acute ischaemic hemispheral stroke

There was an improvement in the severity of AOS over time, but only three patients showed an early improvement between the first and second assessments (over the course of the first week post-stroke) and this improvement was only modest. Between the second and third assessments the severity of AOS improved in the majority of patients: however, in only three cases had AOS fully resolved at the six month follow-up.

There is a potential for a learning effect to occur when a test is presented to patients on repeated occasions. However, it is unlikely that the learning effect was responsible for the improvement seen over time in this study as there was little improvement between the first and second assessments (when a test-retest learning effect might be expected) and there was six months in between the second and third assessments.

Dramatic early resolution of AOS has been described in some case reports [45, 51]. Nagao et al described a patient presenting with acute speech disturbance due to a small infarct in the left precentral gyrus of the insula, she was aphonic on admission, started to speak

within 12 hours demonstrating evidence of AOS, yet had fully recovered to baseline within 48 hours [45]. Mohr described three patients with what he called "motor aphasia", and which seem to resemble AOS, in whom the deficit in speaking aloud rapidly improved following acute stroke. In all three cases postmortem showed established infarction in the left inferior frontal region including Broca's area and underlying white matter [51]. Such rapid early recovery of AOS is one feature that suggests that the underlying pathophysiology of AOS may be disruption of functional anatomic connections.

We did not witness such dramatic and rapid recovery in our patients with AOS. Our results suggest a more gradual improvement over time, with a significant proportion of patients still having residual AOS at six months. This recovery is more like that seen in aphasia recovery post-stroke, where language improves gradually over months [125, 126]. One potential reason that we did not document rapid early recovery of AOS may be that the median time to first assessment was four days; it is possible that we missed recruiting patients whose deficits had already resolved. Patients with AOS have been described, however, who continued to improve several years after onset of their language deficit [24], thus it is possible that there will be continued improvement for the patients with evidence of AOS at the six month assessment.

4.4.3 Association between AOS and OFA

Although many patients had both AOS and OFA, there was evidence of a dissociation between the two. All patients with OFA had AOS; however, there was a group of patients that had AOS without any evidence of OFA. Previous studies have shown that many patients with AOS also exhibit OFA [11]. Jackson (cited here by Buckingham) was the first to describe such patients [13]. However, AOS has also been reported occurring without OFA [9, 12, 120, 127]. The fact that they can occur independently argues against

the theory that AOS results from impaired orofacial control. An fMRI study of normal subjects performing speech and non-speech oral movements found that non-speech oral movements recruited greater bilateral activity in traditional motor areas while speech movements recruited the left inferior frontal gyrus, bilateral middle frontal gyrus, left middle and inferior temporal gyri, caudate and thalami [60], providing one explanation of why OAS and OFA can occur independently. Our results confirm previously reported findings and again imply that AOS does not simply result from OFA or from disruption of a "praxis centre".

4.4.4 Factors predicting severity and recovery of AOS

We found evidence of an association between the presence of AOS and clinical stroke severity. Patients with AOS had significantly higher NIHSS than those without. In addition, NIHSS correlated with the severity of AOS. Ogar found an association between more severe AOS and increasing stroke volume; however, the clinical stroke severity was not examined [32]. Clinical measures such as the NIHSS correlate modestly well with infarct volume on CT [100] and MRI [61]. In addition, patients with left hemisphere strokes score on average four points higher than those with right hemisphere strokes [62]. Thus it is to be expected that patients with AOS, all of whom had left hemisphere strokes, would have higher NIHSS than patients without AOS, many of whom had right hemisphere strokes. However, the difference in NIHSS remained significant even when controlled for hemisphere, and when the language component of the NIHSS was excluded. Interestingly, patient age did not predict the presence of AOS. Studies of patients with aphasia following stroke have demonstrated that older patients are more likely to develop aphasia and aphasia severity is greater with increasing age [128].

Initial AOS severity predicted final outcome, just as initial aphasia score predicts final score in studies of aphasia recovery [125, 126]. Initial AOS severity explained 75% of the variance. Given the relatively small numbers in this analysis, however, the potential for a type II error is high. These results echo studies of aphasia recovery after stroke which showed that initial aphasia severity only accounted for 32-41% of the variance [125]. A multiple regression analysis that combined patient age and NIHSS with initial AOS severity did not account for a greater proportion of the variance than initial AOS severity alone (76% vs. 75%), indicating that there are other, as yet unknown, factors contributing to recovery.

4.4.5 Usefulness of PAL subtest 7

We used subtest 7 of the PAL which investigates word versus non-word repetition and provides norms from 97 controls. This battery is primarily used for research and has not been systematically used in studies of AOS or aphasia, thus we did not use the results from this test to diagnose the presence or absence of AOS. However, one of the reported characteristics of AOS is that repetition of non-words is inferior to repetition of words [7, 11]. Patients with AOS scored significantly worse than those without AOS in repetition of words and non-words. In addition, repetition of non-words was worse than repetition of words for patients with AOS; however, this did not reach statistical significance. Standard deviations within the AOS patient group were large, suggesting a wide range of scores within this group: thus, individual patients scored within normal limits in this test despite having AOS. When patients were grouped by hemisphere, those with left hemisphere stroke performed worse than patients with right hemisphere stroke for words and non-words. Thus, impaired word/non-word repetition may simply reflect left hemisphere damage rather than being specific for AOS. Accordingly, the results of this test should be viewed with caution as it does not appear to be sensitive enough to reliably distinguish patients with AOS from those without. This may be in part due to small sample size; a *post hoc* calculation performed to determine the sample size required to detect a significant difference showed that a minimum sample size of 102 would be required.

Repetition of words in normal controls has been demonstrated to cause bilateral activation of superior and middle temporal gyri, medial frontal gyrus, precentral gyrus and insula as well as the left cingulate gyrus and the right middle frontal gyrus and superior frontal gyrus [129]. Despite this, patients with right hemisphere stroke in our study performed within normal limits on word repetition, which suggests that it is predominantly mediated by the left hemisphere.

4.4.6 Strengths and limitations

There are several strengths to this study. Firstly, patients were assessed in the acute period after stroke, before significant functional adaptation could have occurred and before clinical deficits may have resolved, in contrast to other studies [4, 32]. In addition, the longitudinal design ensured that we were able to recruit patients who initially had severe comprehension deficits precluding detailed assessment but later were found to have AOS. No other study to date has performed longitudinal follow-up of patients with AOS following stroke, thus our study is unique in this regard, and provides useful information on the natural history of AOS. This study included 18 patients with AOS which compares well with other studies [4, 32, 33].

There are a number of limitations in this study that should be highlighted. Firstly, the scope of the assessment we performed on these patients, many of whom were acutely unwell, was necessarily limited. For instance we did not perform a detailed specific aphasia battery. Most aphasia batteries do not specifically test for AOS and are time consuming, often requiring several hours, which is impractical in the acute period following stroke. Although we did not perform a detailed aphasia battery, our test battery included assessment of comprehension, naming, reading and repetition. In addition, we documented speech and language therapists' assessment of the presence or absence of associated aphasia. This information was available for all subjects with AOS, and while nine had evidence of some receptive difficulties, all had evidence of expressive dysphasia. These results are not surprising, as the anatomic and vascular characteristics of AOS and dysphasia are similar as are the disorders that cause them. In addition, it is uncommon for AOS to occur in the absence of some degree of dysphasia [8, 19, 24, 25]. In Ogar's study of 18 patients with AOS, only two did not have evidence of dysphasia [32].

As already mentioned, there is no gold standard or universally accepted test for diagnosing AOS. Although clinical characteristics are agreed, there has been a lack of uniform diagnostic criteria in studies investigating AOS, with anything from elaborate checklists to simple speech description [4] [33]. Hillis' study on 80 patients with or without left insular stroke used a battery consisting of verbal picture description, repetition, oral reading and naming of pictures and objects. The authors defined AOS as >10% total errors in each oral task, variable off-target attempts at articulating words, distorted groping articulation and impaired speech prosody [33]. Duffy suggested using a list of tasks adapted from Wertz, LaPointe and Rosenbek and used by the Mayo Clinic which includes repetition of phonemes, monosyllabic and polysyllabic words, sentences, increasing length of words, automatic speech, singing and description of spontaneous speech and reading aloud [121]. The motor speech evaluation (MSE) has also been used in studies of AOS [32].

There are only two published measures for assessment of AOS, the Apraxia Battery for Adults (ABA II) [22] and the Comprehensive Apraxia Test [130]. Both have good face validity and can be administered in a standardised fashion. However, both have the limitation of a lack of normative data [121]. Hill et al used the ABA II to diagnose the presence and severity of AOS in a study of telerehabilitation in AOS and demonstrated good inter- and intra-rater agreement [131].

The ABA II [22] has been shown to differentiate between patients with AOS versus aphasia [29]. When it was used to assess patients with AOS, aphasia, dysarthria or normal speech, those with AOS scored lower than all other subgroups on subtests 1, 2, 3, 4, 5 as well as having more of the articulation characteristics of apraxia (subtest 6) [29]. The ABA II includes most of the tasks suggested by Duffy, although it does include one subtest which perhaps should be excluded when determining whether a person has AOS (i.e., the presence of limb/oral apraxia). It also comprises seven of the 9 subtests of the MSE.

Importantly for this study of AOS following acute stroke, the ABA II can be completed within 20 minutes and can be performed at the bedside.

The ABA II [22] was used in this study as it comprises the majority of tasks suggested by Duffy [121] and those of the MSE, which are considered necessary to diagnose AOS. Although the ABA II is not a perfect test due to a lack of published normative data; it is standardised, has been shown to be reliable [29] and has demonstrated good inter- and intra-reliability [131]. We did not use results from subtest 3 (oral and limb apraxia) as part of our diagnostic criteria as neither are necessary for a diagnosis of AOS. We think that it can be considered a valid test for assessing AOS as the subtests included (in particular subtests 2, 5 and 6) measure characteristics which are integral to AOS.

Other studies have demonstrated high levels of inter-rater agreement of the diagnosis of AOS, even without the use of any diagnostic battery. In Mumby's paper, four speech and language therapists were asked to watch video clips of 42 individuals with/without AOS/aphasia and without any predetermined diagnostic criteria had to diagnose the presence/absence and severity of AOS based simply on their clinical judgement. The video clips showed spontaneous speech as well as repetition of polysyllabic words. It was found that inter- and intra-rater agreement was very high and that diagnosis of the presence/absence and severity of AOS agreed well with the original diagnosis which was made using criteria based on Wertz and McNeil [132].

Secondly, the mean time between onset of stroke and initial assessment was four days. Some of the rapid recovery described previously [45] [51] could have occurred within this time and therefore earlier assessments might have given an even higher rate of AOS. In addition, the patients whose comprehension difficulties precluded them completing the

language assessment all had left hemisphere infarcts and may well have had AOS if it had been possible to assess for it.

Thirdly, left hemisphere strokes were over-represented in our patient sample. Our patient sample was relatively small and therefore the difference is likely to have occurred by chance. This over-representation of left hemisphere pathology may thus over-estimate the prevalence of AOS.

4.5 Conclusion

In conclusion, we found that AOS occurred frequently following stroke, affecting 40% of our patient sample. We demonstrated an improvement in AOS during the six month follow-up period, with initial severity predicting final outcome. We did not, however, demonstrate the rapid resolution of AOS that has been described previously. Thus, patients with less severe AOS at onset are more likely to make a full recovery in their speech and language deficit with time. There was an association between AOS and OFA, as well as with initial clinical stroke severity.

Our results help to understand the natural history of AOS and suggest that it does not simply result from OFA or from disruption of a "common praxis centre". However, our findings suggest that there are probably other factors which impact on recovery from AOS. Establishing what these factors are may help better predict prognosis for patients with AOS and indicate those who may benefit more from therapy.

In addition, although the PAL subtest 7 gave useful qualitative information about patients' speech and language abilities post stroke, it did not discriminate adequately between patients with and without AOS. However, this study was not powered adequately to specifically answer this question. Impaired word and non-word repetition occurred in patients with AOS and in patients with left hemisphere stroke (regardless of AOS status). This test did not pick up a significant difference between non-word repetition and word repetition in patients with AOS.

Chapter 5: AOS: association with lesion location and volume

5.1 Introduction

5.1.1 Lesion location and AOS

AOS is thought to be due to a disruption of speech production at an intermediate level, i.e., below aphasia (high level) and above dysarthria (low level). Darley proposed a motor speech programmer (MSP) which is responsible for programming all the muscles important for speech to activate at the proper time, in the appropriate order and for the correct duration to produce the desired speech sounds in the desired sequence. He proposed that the MSP was located in Broca's area and may project directly to the motor cortex [19].

A more complex model of speech production, the Direction Into Velocities of Articulators (DIVA) model, has been proposed by Guenther and Perkell [133]. This suggests a complex neural loop feeding back on itself to produce speech. Projections from premotor cortex to primary motor cortex are involved in feed-forward control of the articulators. Other projections from the premotor cortex to higher order auditory cortex in the superior temporal gyrus and orosensory areas in the somatosensory cortex and supramarginal gyrus carry target sensations associated with motor plans in the premotor cortex. The incoming auditory information from the primary auditory cortex is compared to the auditory targets from the premotor cortex and any difference between the two implies an error, which prompts a signal to travel via the cerebellum to rectify the error. The authors also implicate the anterior insula, suggesting that it has similar functional properties to the premotor and

motor cortices. This model is based on studies that have shown activation of auditory cortex in speech production [134] as well as studies implicating the insula [4, 135].

Many different brain regions have been implicated in causation of AOS. One study using computer reconstructions and lesion overlap technique in 25 patients with longstanding AOS showed that all patients had lesions within the left precentral gyrus of the insula [4]. However, another study examined 40 patients with and without left insular infarction and found no association between AOS and damage to the left insula, but did show an association between AOS and damage to the left posterior inferior frontal gyrus (Broca's area) [33]. A PET study of normal controls, however, found a strong association between the left insula and planning of articulation and found no role for Broca's area [135]. Other reports have implicated subcortical frontal white matter and basal ganglia lesions in AOS [46]. An fMRI study of normal subjects performing speech and non-speech oral movements found that non-speech oral movement recruited greater bilateral activity in traditional motor areas while speech movements recruited the left inferior frontal gyrus, bilateral middle frontal gyrus, left middle and inferior temporal gyri, caudate and thalami [60]. One caveat here is that while the frontal gyri are functionally distinct, depending on the imaging modality used, anatomical distinction of the gyri may be difficult.

A case series of three patients with very small lesions near the left face representation of the primary motor cortex found that all presented with a speech and language deficit similar to AOS with slow, effortful, aprosodic speech without aphasia or orofacial apraxia [136]. The authors suggested that cortico-cortical fibres connecting this region with Broca's area are important for articulatory control.

Some authors have shown that Broca's area is not involved in production of single words [137] but is activated during verbal fluency tasks [138]. Kent proposed that single words

can be produced via automatic motor plans while longer or more complex sentences require activation of Broca's area, probably in combination with other areas such as the insula and premotor cortex [139].

One PET study of eight normal control subjects showed increased regional cerebral blood flow (rCBF) in bilateral precentral gyri and left supplementary motor area during tongue movement, phoneme sequence and reciting months of the year, i.e., during oromotor movements and automatic speech, but showed increased rCBF in Broca's area only when a more complex automated task was assessed (reciting the Pledge of Allegiance) [140]. Another PET study showed that although Broca's area was activated during reading of nouns and verb generation, with practice, the rCBF in this area decreased suggesting that as a task becomes automatic, alternate pathways are used [141].

A family with an inherited form of AOS has been reported with significant differences in grey matter volume [142]: increased grey matter in the anterior insula bilaterally, left inferior frontal gyrus, bilateral putamen and motor cortices, posterior lobe of right cerebellum and left medial occipito-parietal cortex, and less grey matter in the left inferior frontal cortex dorsal to the operculum, head of caudate bilaterally and supplementary motor area. Many of these areas have been implicated in acquired AOS [4, 33, 58, 90].

In summary, multiple different brain regions have been proposed as being integral to motor speech planning/programming and damage to multiple different brain regions has been shown to cause AOS by various authors.

The difficulty with most reports in the literature is that varying methods of defining and diagnosing AOS have been used by each group. This means that the patients in different studies may not have exactly the same deficit, thus any conclusions drawn only relate to

the group of patients tested and cannot necessarily be extrapolated to other patients who have AOS defined using differing criteria. In addition, different methods of localising lesions have been used by different groups, some using lesion overlap and CT or MRI [4, 32, 136], others using PET or other methods of indicating perfusion [31, 33, 143]. Many of the studies assessing production of speech in normal controls have used fMRI or PET [135, 138, 140, 141, 144].

The other caveat is that localising a lesion does not necessarily localise a brain function, although most papers using the above lesion localising techniques have implied this.

Rather than there being one single brain region that is responsible for motor speech programming or planning, it may be more likely that a neural network is responsible, with different areas having a very specific function within motor programming. AOS may, as a result, be caused by a lesion anywhere within the network [145]. This theory implies that it may be possible to subcategorise AOS depending on where in the network the lesion occurs. If this is the case, a small lesion within the network may cause a relatively mild deficit, while a larger lesion knocking out many parts of the network would cause a much more severe disturbance in speech. This has been proposed previously [32], when descriptions of AOS in patients with lesions of the left superior precentral gyrus of the insula were reported.

Apraxias are often thought of as being due to a disconnection between functionally related areas, e.g., ideomotor apraxia is thought to be due to a disruption in the system between processing a command, accessing stored information about tools/gestures, and translating these into a motor output. As AOS is an apraxia, and given the disparate results of lesion studies, then it seems likely that it too is caused by a disconnection between functionally related areas. A disconnection may also be more amenable to recovery/reorganisation than

if the deficit was due to infarction of a vital region containing a "speech motor programming centre", thus this may explain the potential for rapid recovery of AOS following acute stroke.

5.1.2 Lesion volume and AOS

There is only one study which examined the relationship between lesion size and severity of AOS [32]. The authors examined 18 patients with AOS and 8 patients with left hemisphere stroke but without AOS. The motor speech examination (MSE) was used and two speech and language pathologists rated the presence and severity of AOS using videotapes of the patients' performances. The authors found a significant difference in lesion size between the two groups (mean 141.5cm^3 in those with AOS versus 68.3cm^3 in those without AOS) as well as a correlation between AOS severity and lesion volume. The same study used lesion overlap technique to show that all patients with AOS had lesions involving the superior prefrontal gyrus of the left insula (56% of the patients with AOS in this study had also been included in the original lesion-overlap study [4] thus it is not surprising that the two studies found the same results with regard to lesion location). However, a major limitation of this study is that the patients were examined a long time after stroke onset, range 10-251 months, with a mean of six years post stroke. After this long interval it is likely that patients would have had significant improvement in their speech and language deficit from onset and the lesion size may therefore not reflect the initial severity of the deficit.

If the association between lesion volume and AOS severity can be confirmed, it may support the hypothesis that AOS is due to disconnection of functionally related areas. It may also be that larger lesions may result in more persistent speech deficits due to less potential for functional reorganisation within that region.

5.2 Specific aims

To determine the neuroanatomical substrate of AOS in patients following acute ischaemic hemispheral stroke, and thus how regional abnormalities may explain the concept of rapid recovery.

5.3 Results

As discussed in more detail in Chapter 4, 50 consecutive patients with acute ischaemic hemispheral stroke who fulfilled inclusion criteria were recruited. There were 28 males and 22 females, their mean age was 66 ±12 years and their age range 21-90 years. All but two (48/50, 96%) were right handed.

In total, throughout the course of the study, 18 individuals of 45 tested (40%) had evidence of AOS at some time following stroke. Five patients could not complete the test battery at any time point due to significant comprehension difficulties.

5.3.1 Lesion location

The following pages demonstrate the lesion location in patients with and without AOS, as well as the location of lesions in patients who could not complete assessment.

Figures 5.1-5.18: ROIs of all patients with AOS
Figures 5.19-5.44: ROIs of all patients without AOS
Figures 5.45-5.49: ROIs of patients unable to complete assessment

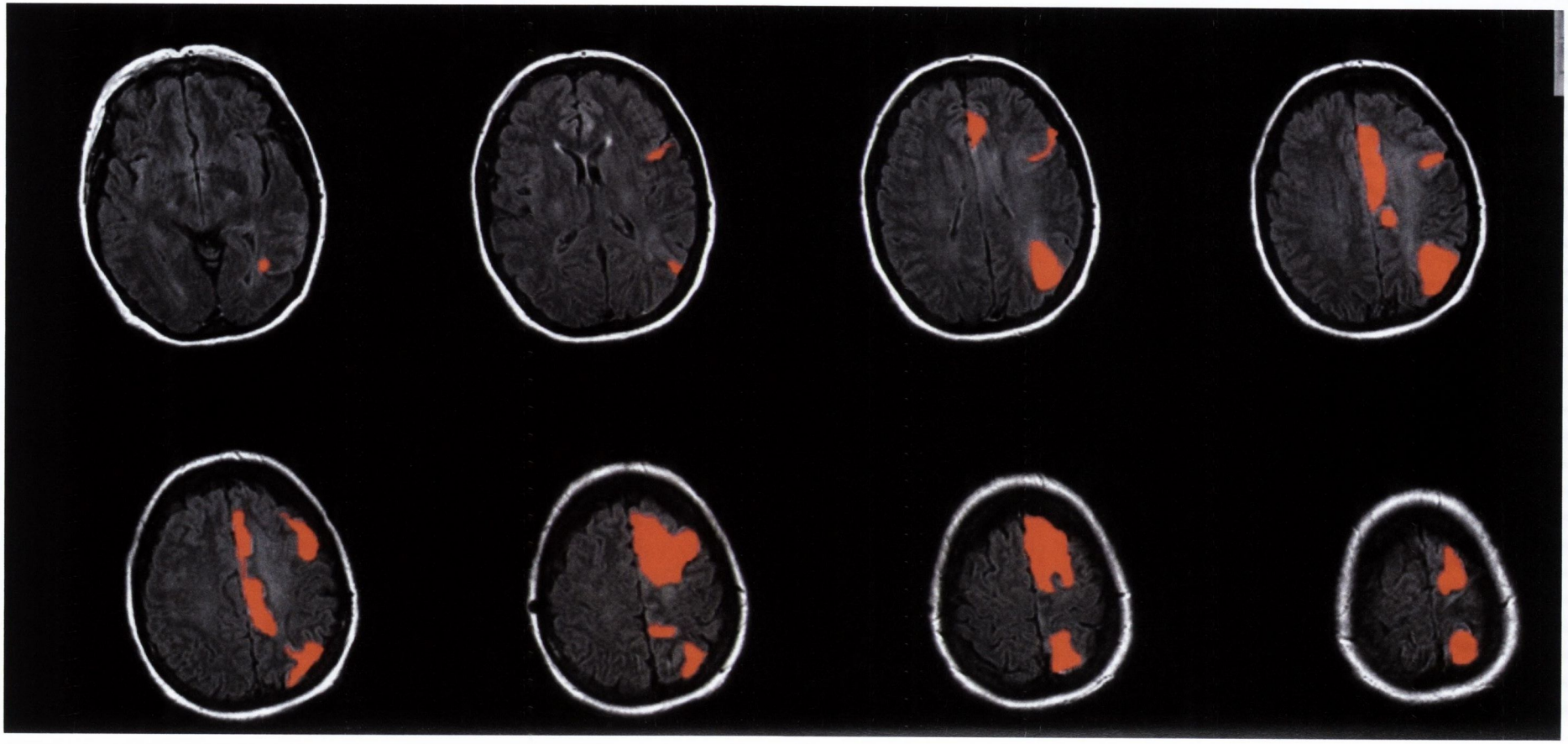


Figure 5.1: Patient 1 (AOS)

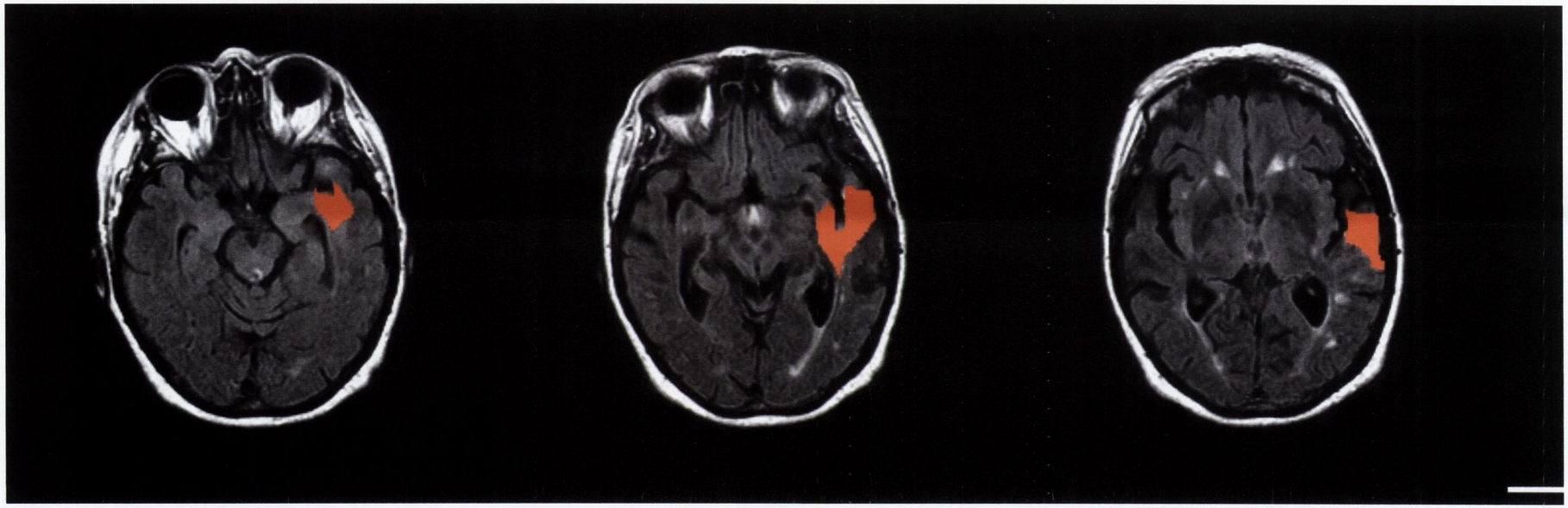


Figure 5.2: Patient 4 (AOS)

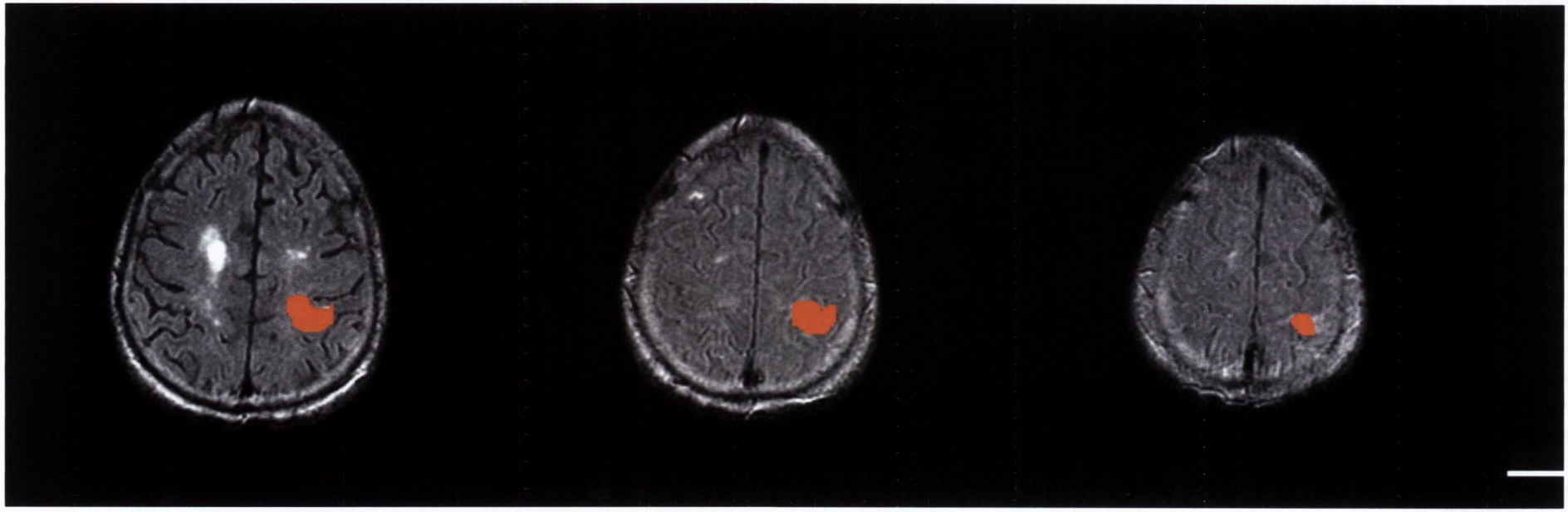


Figure 5.3: Patient 5 (AOS)

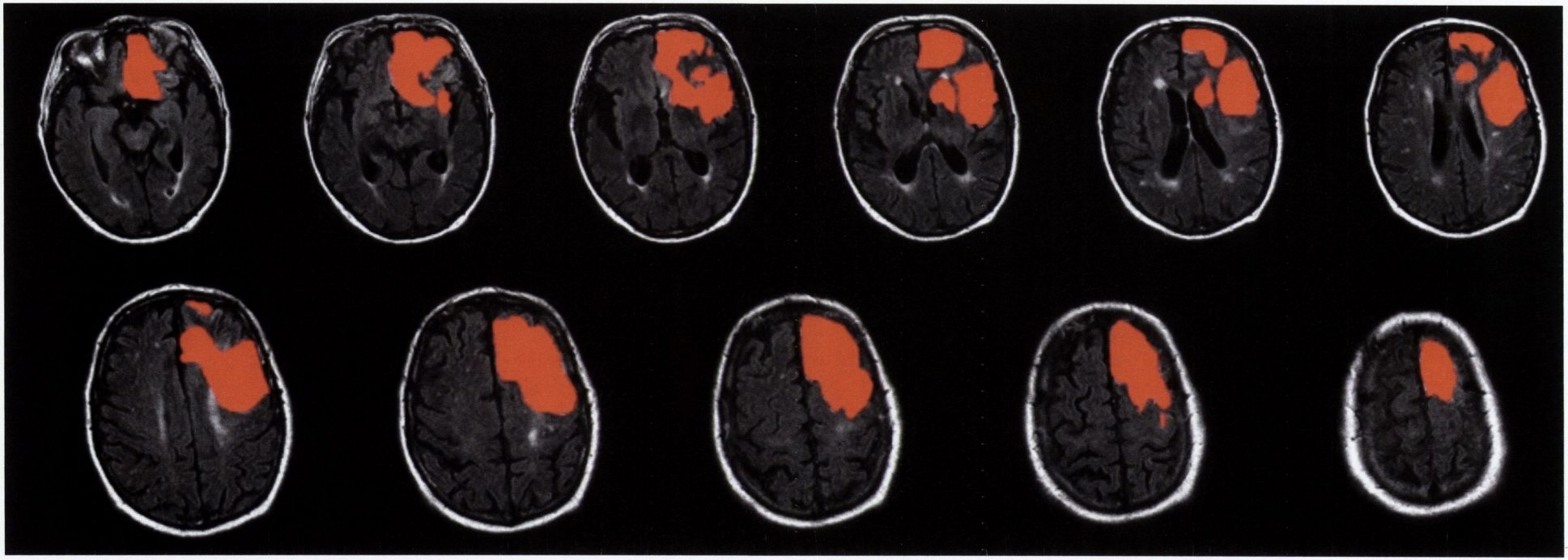


Figure 5.4: Patient 7 (AOS)

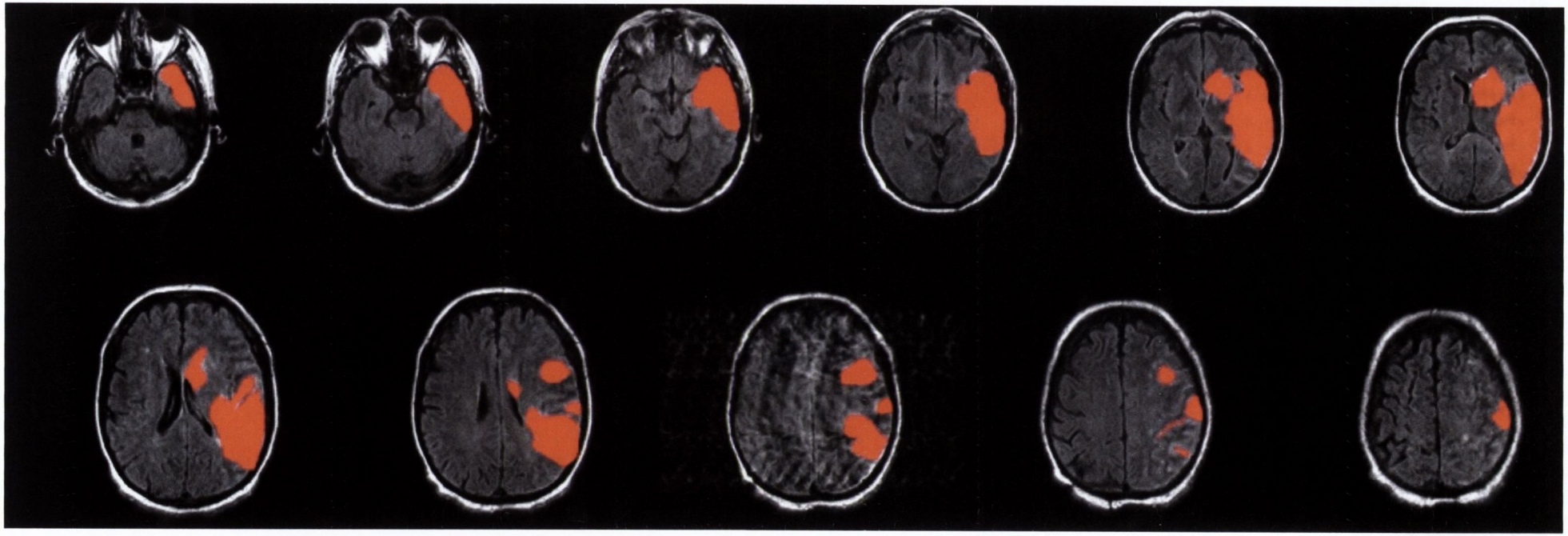


Figure 5.5: Patient 10 (AOS)

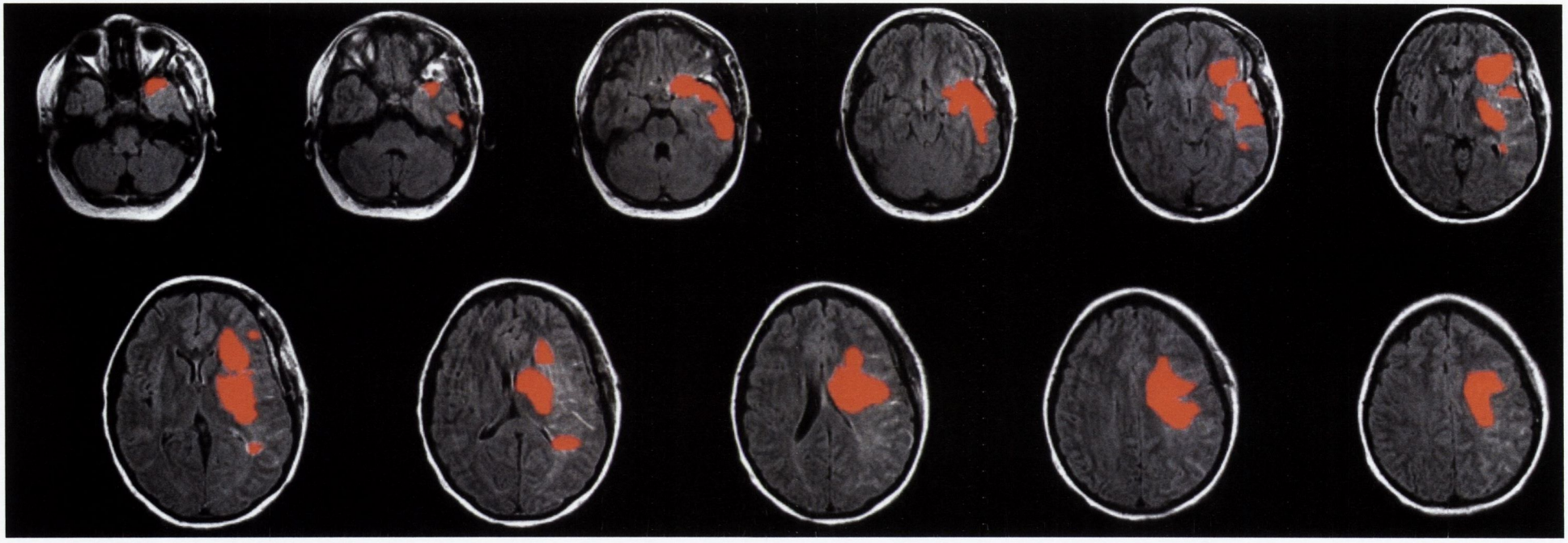


Figure 5.16: Patient 13 (AOS)

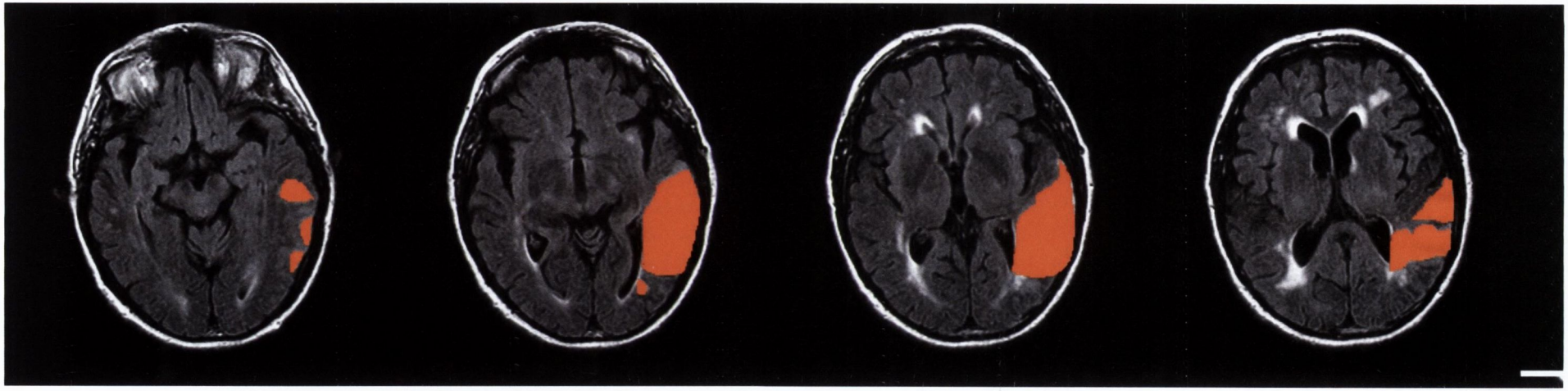


Figure 5.7: Patient 15 (AOS)

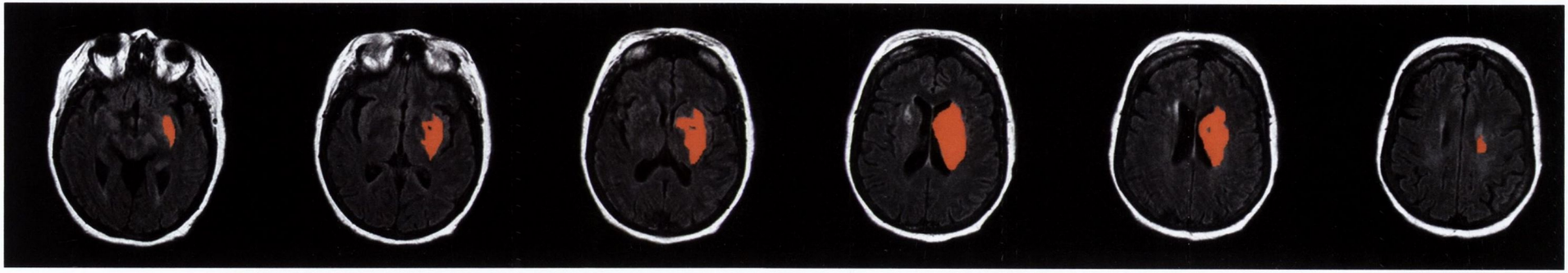


Figure 5.8: Patient 16 (AOS)

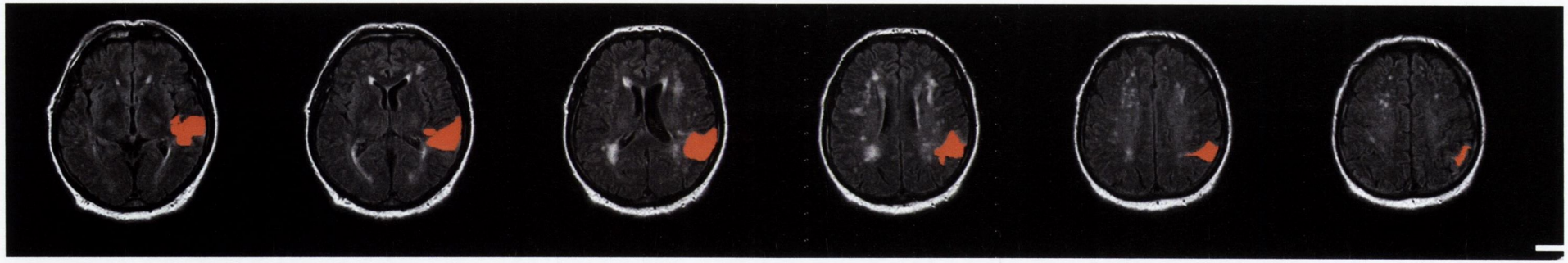


Figure 5.9: Patient 20 (AOS)

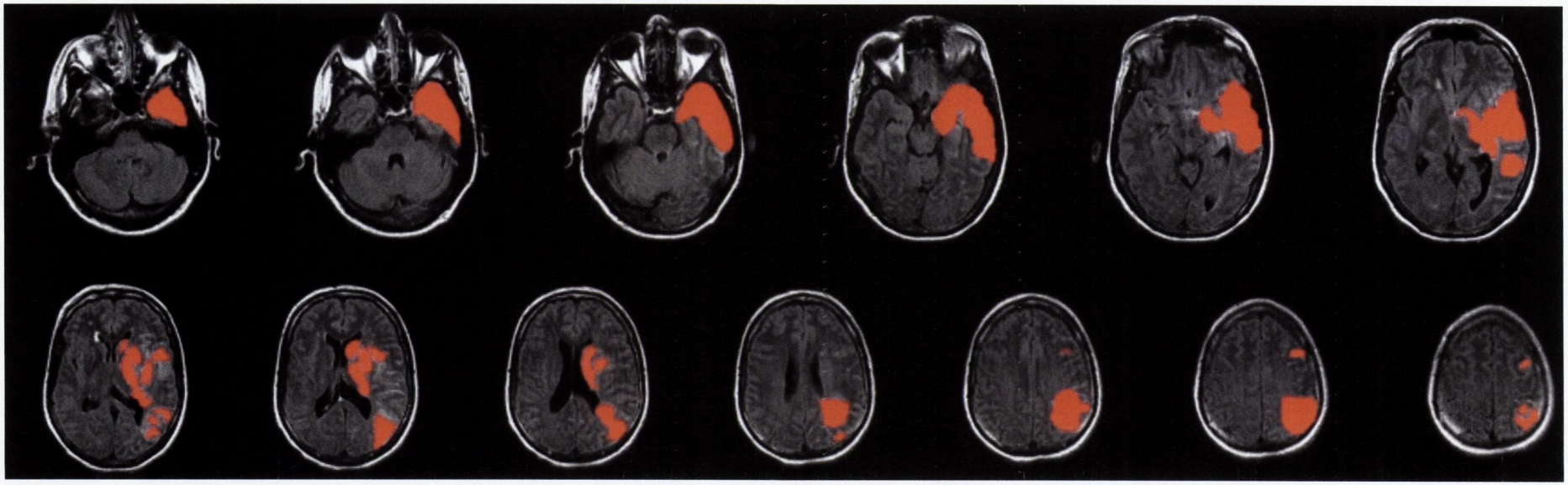


Figure 5.10: Patient 22 (AOS)

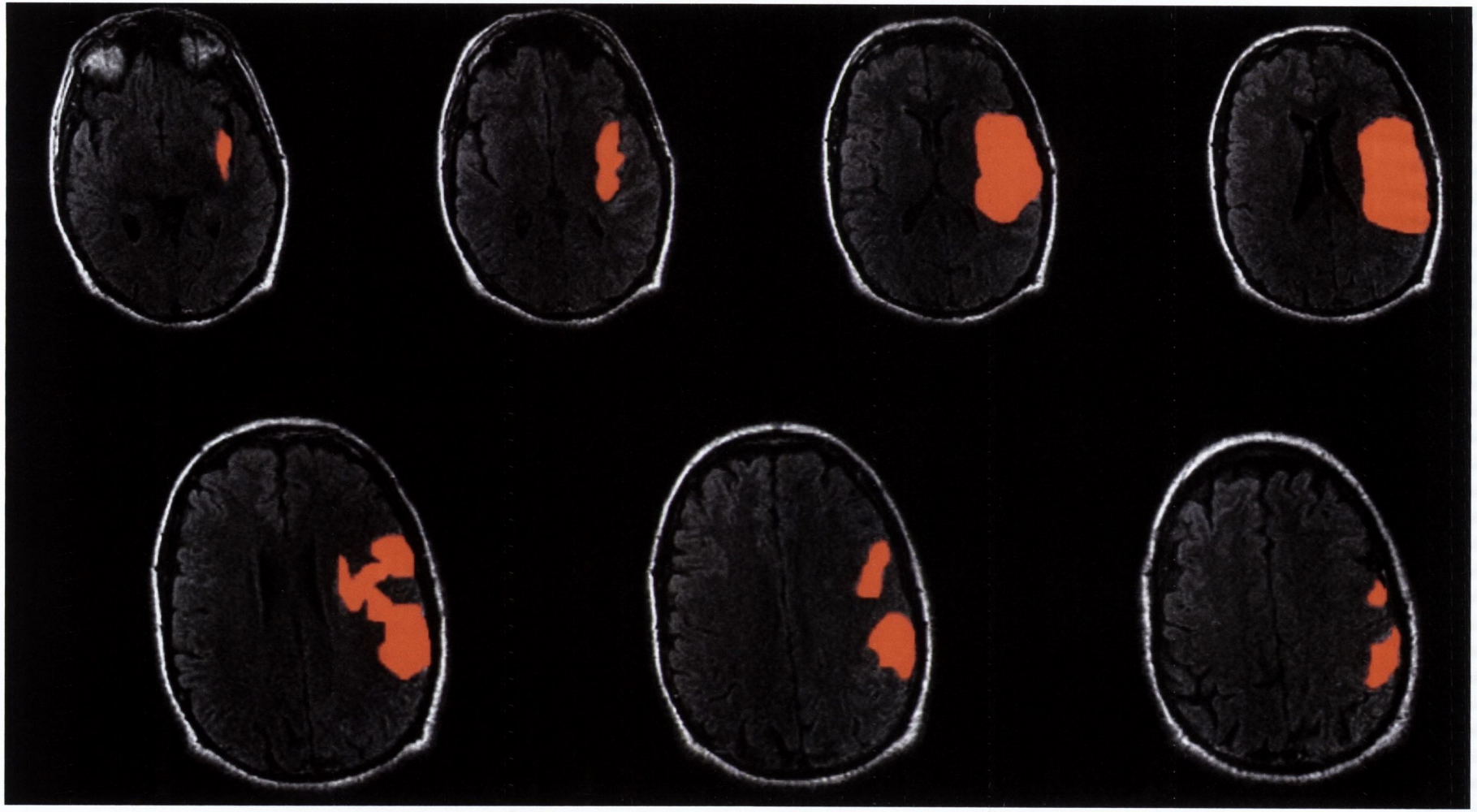


Figure 5.11: Patient 23 (AOS)

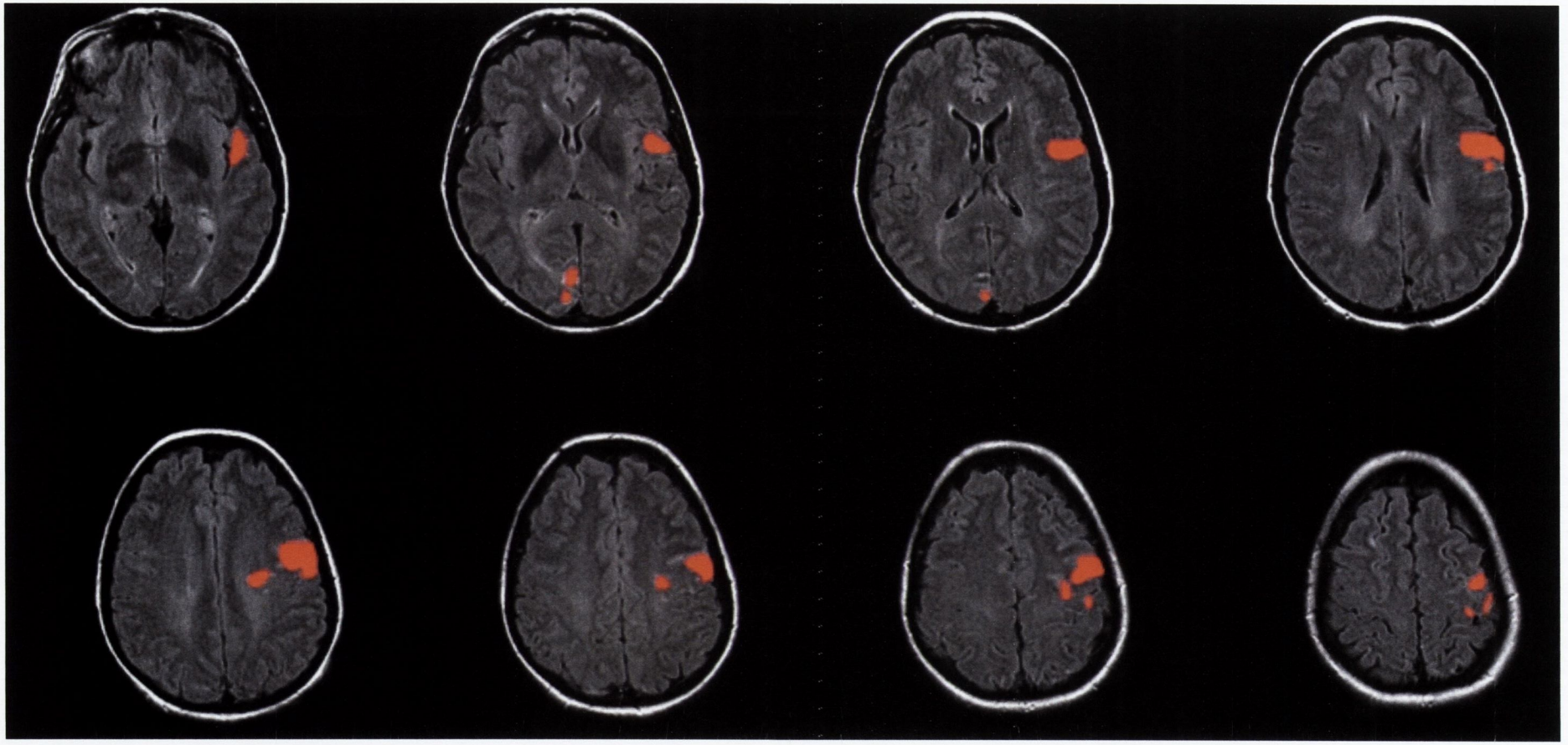


Figure 5.12: Patient 25 (AOS)

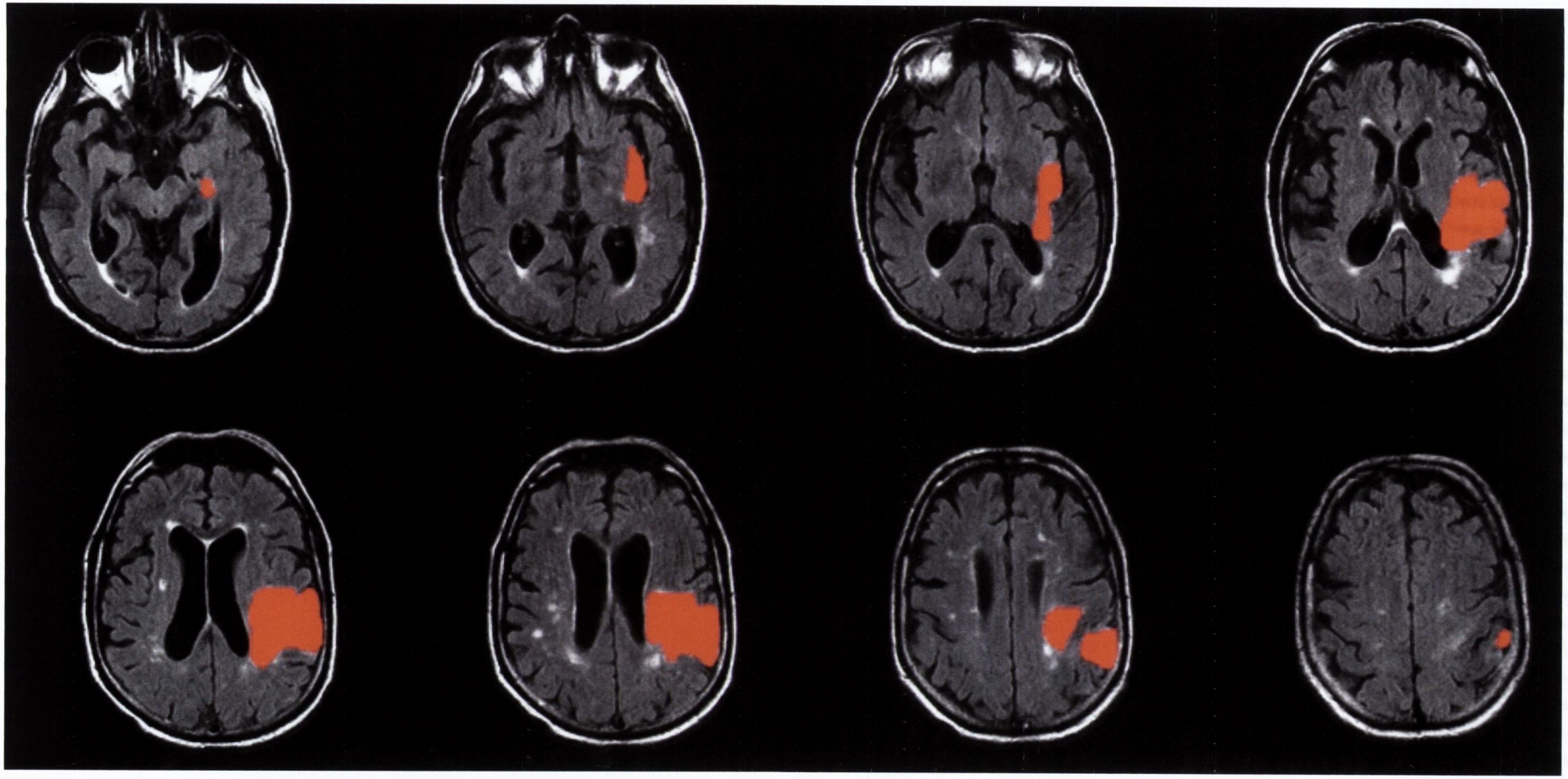


Figure 5.13: Patient 26 (AOS)

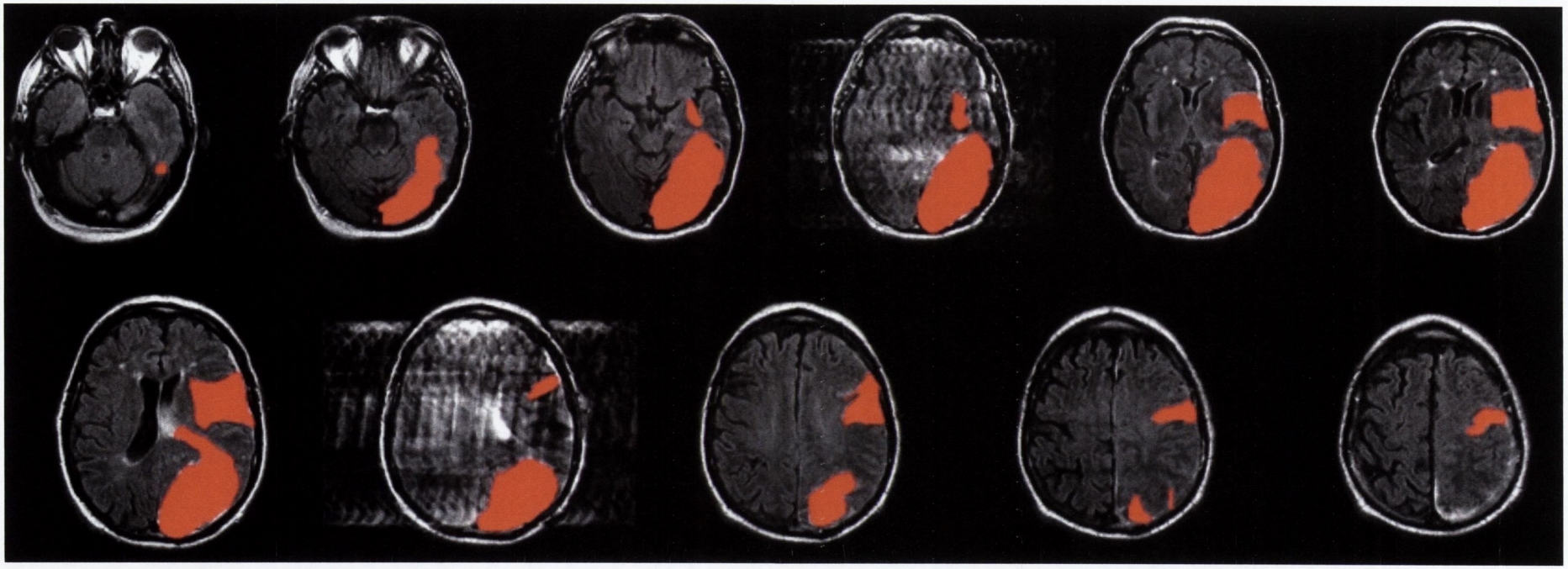


Figure 5.14: Patient 30 (AOS)

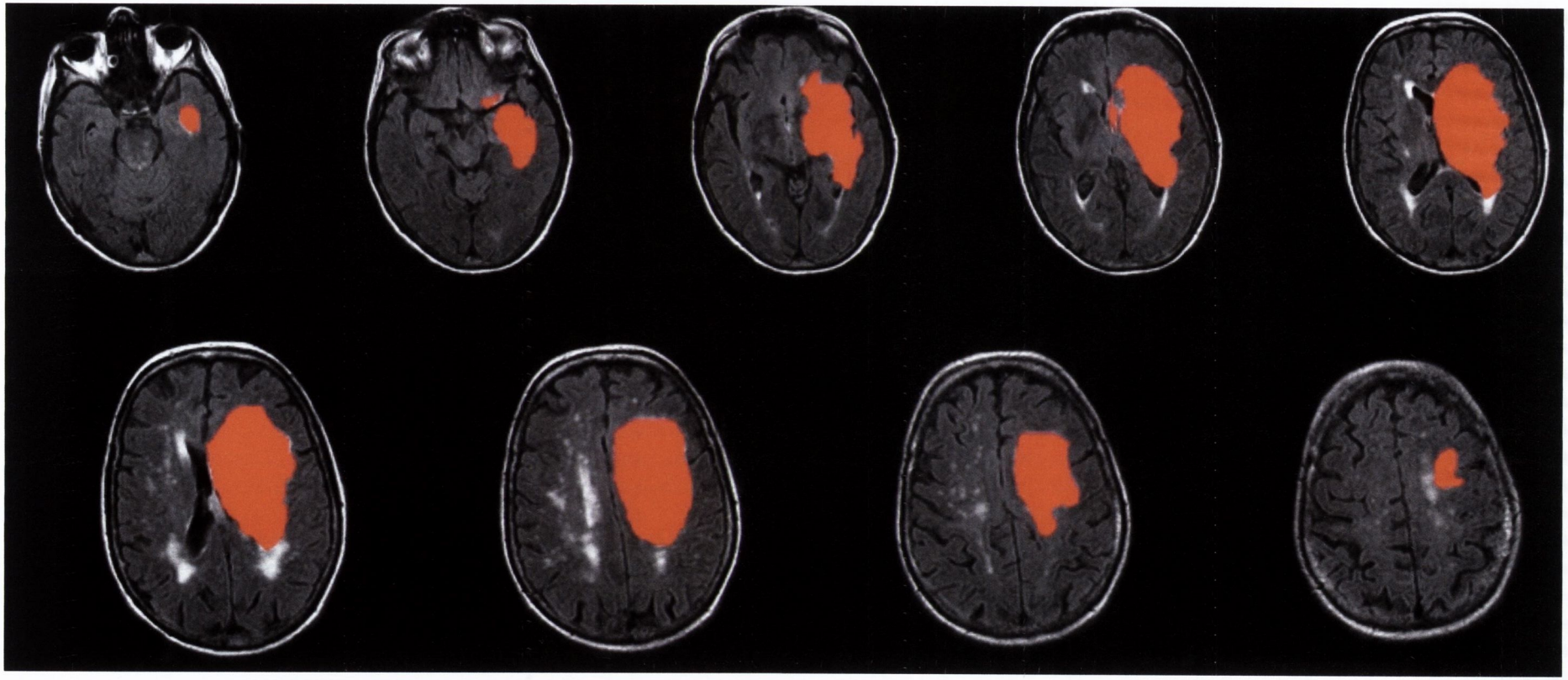


Figure 5.15: Patient 37 (AOS)

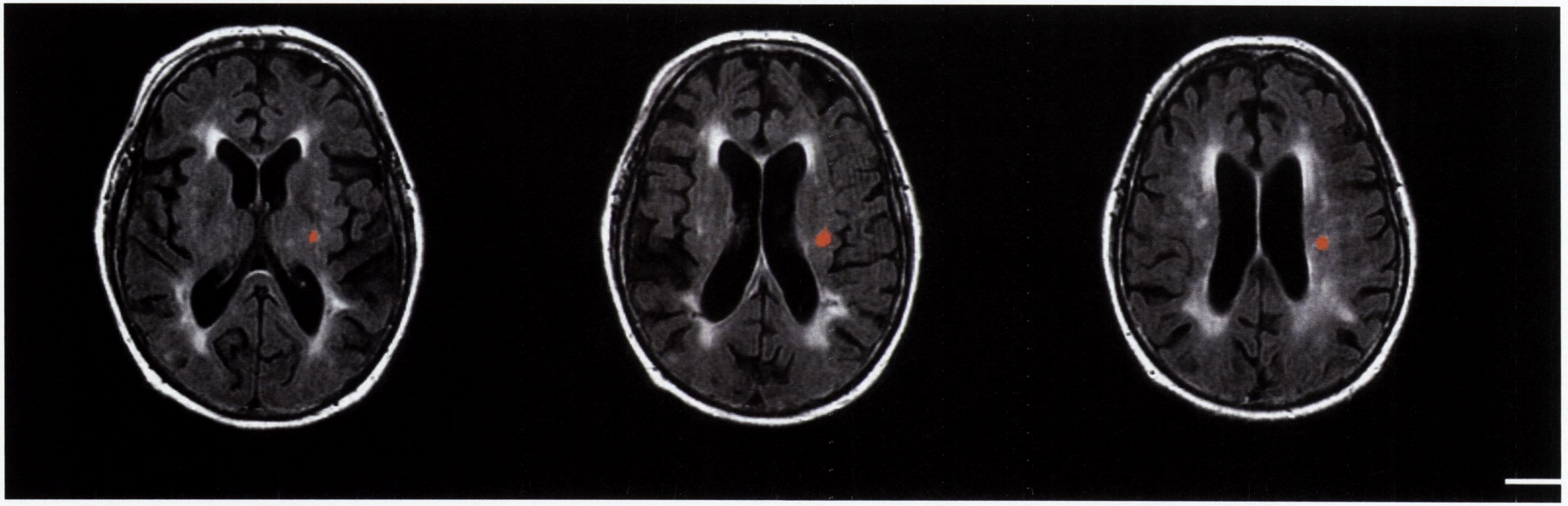


Figure 5.16: Patient 39 (AOS)

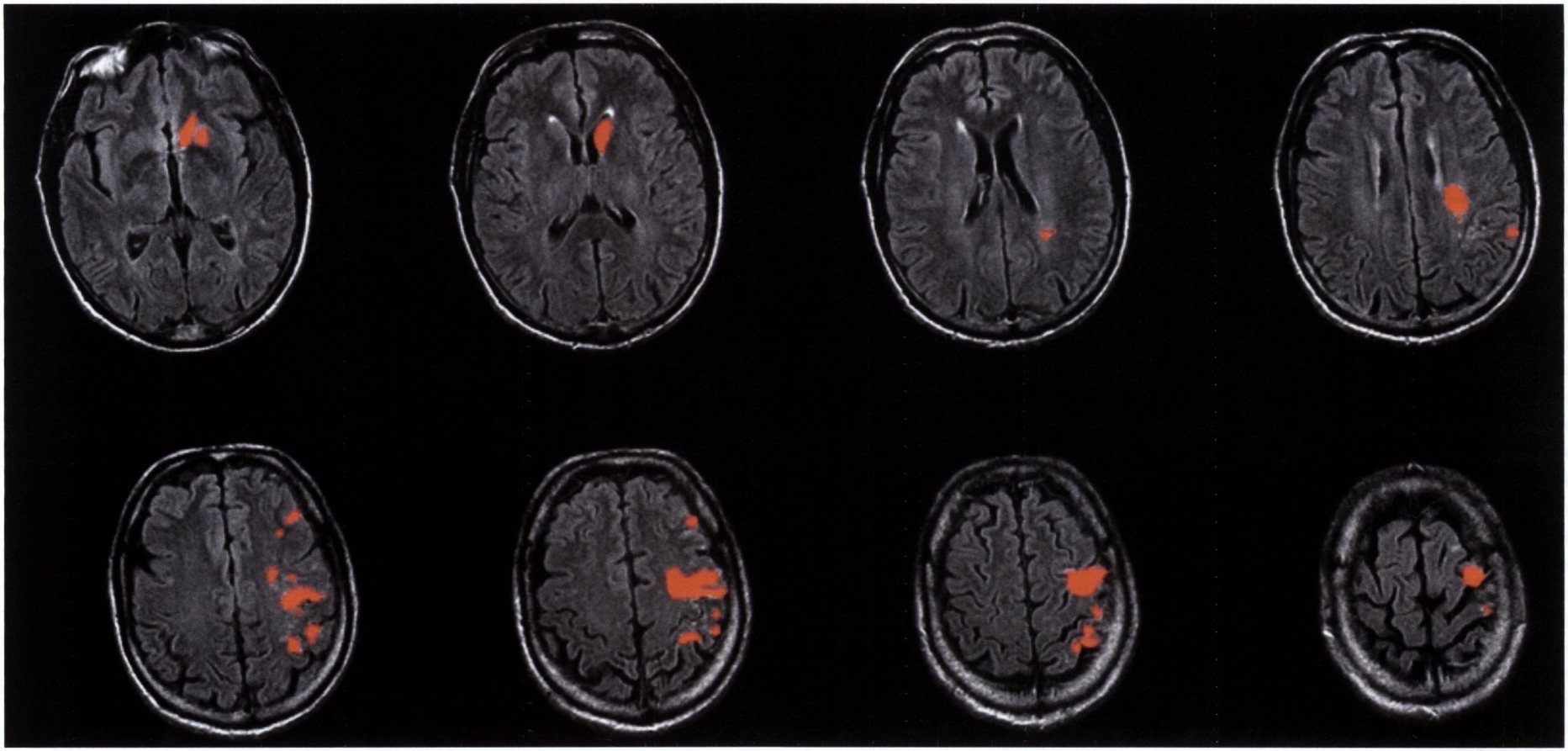


Figure 5.17: Patient 44 (AOS)

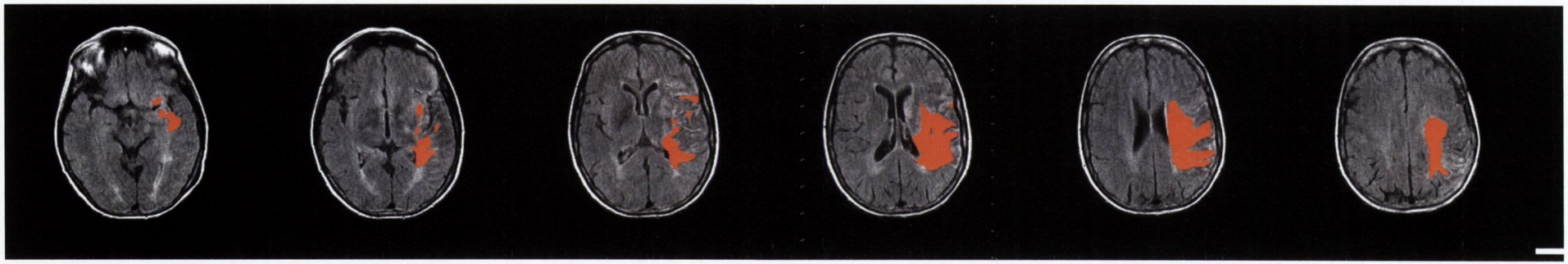


Figure 5.18: Patient 50 (AOS)

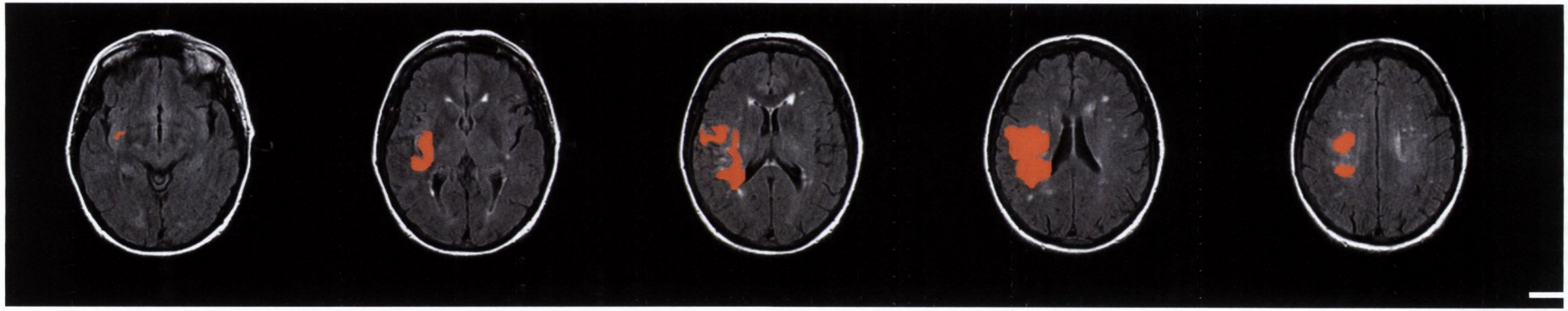


Figure 5.19: Patient 2 (No AOS)

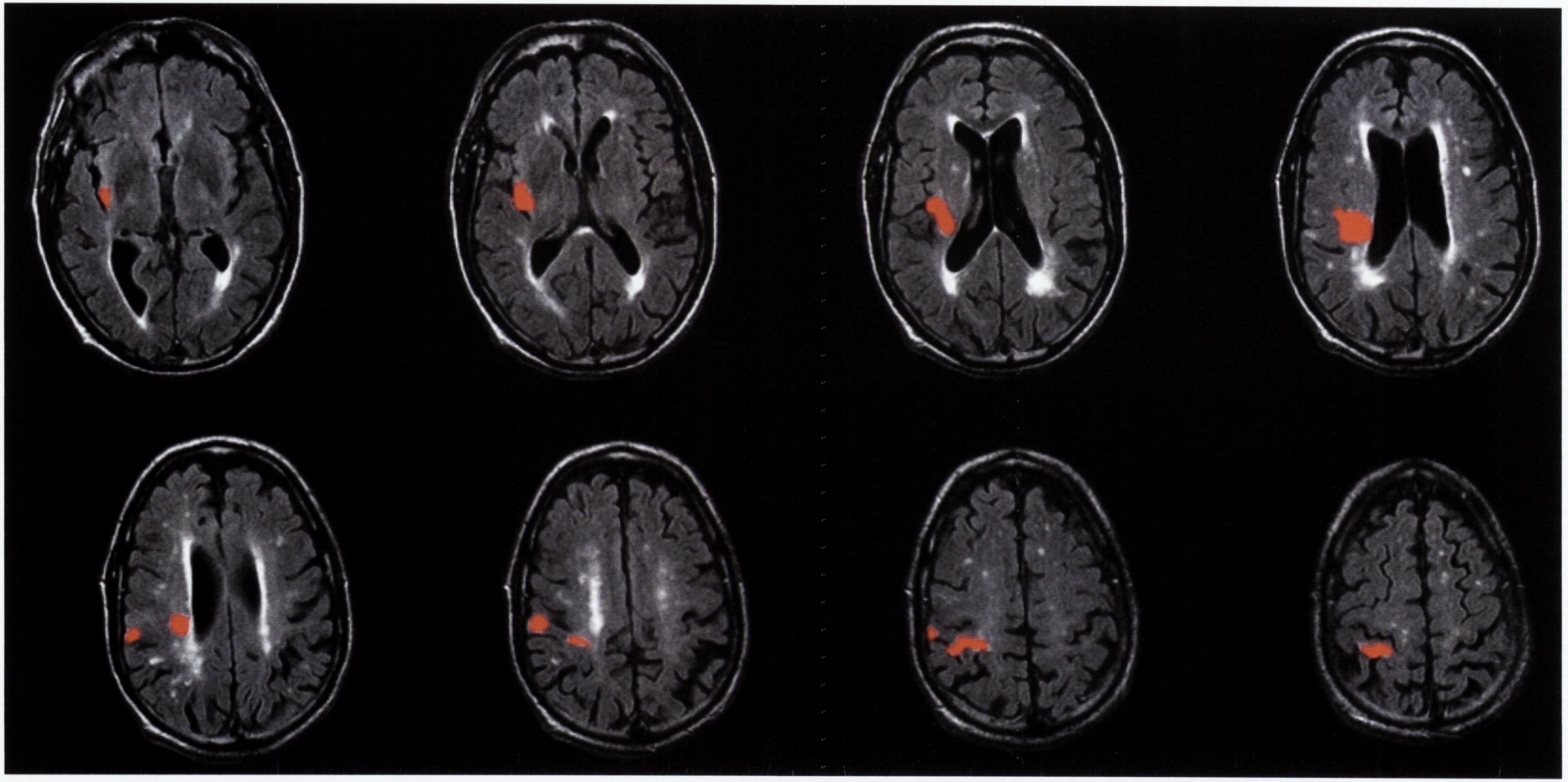


Figure 5.20: Patient 3 (No AOS)

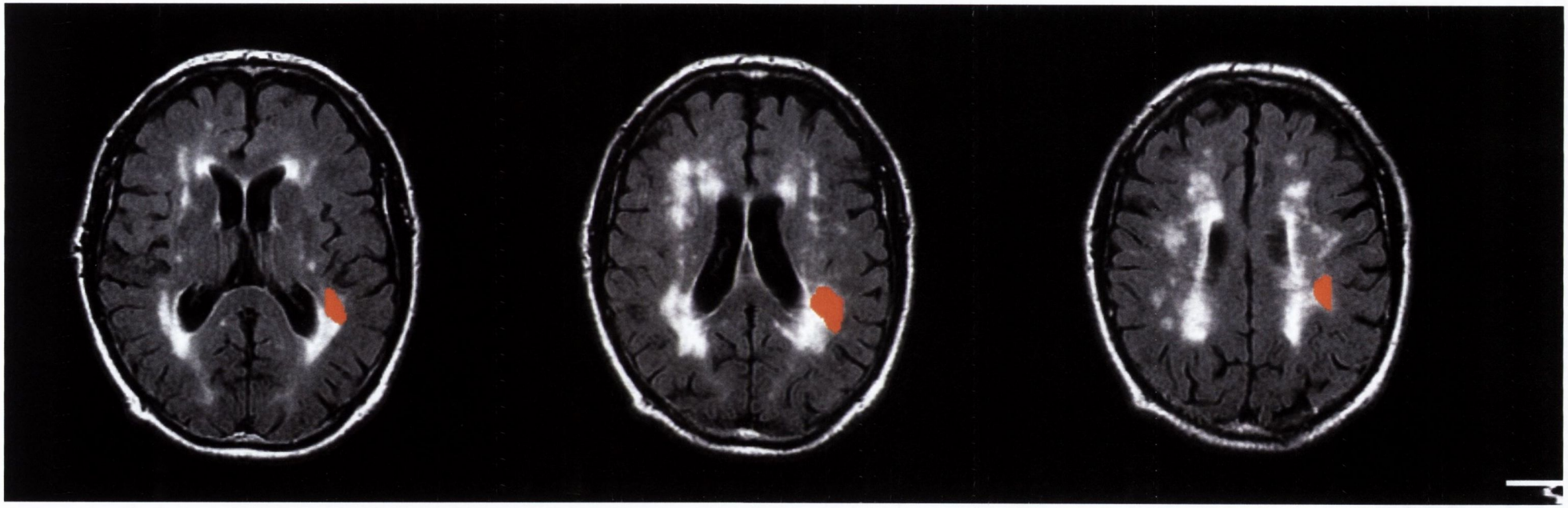


Figure 5.21: Patient 8 (No AOS)

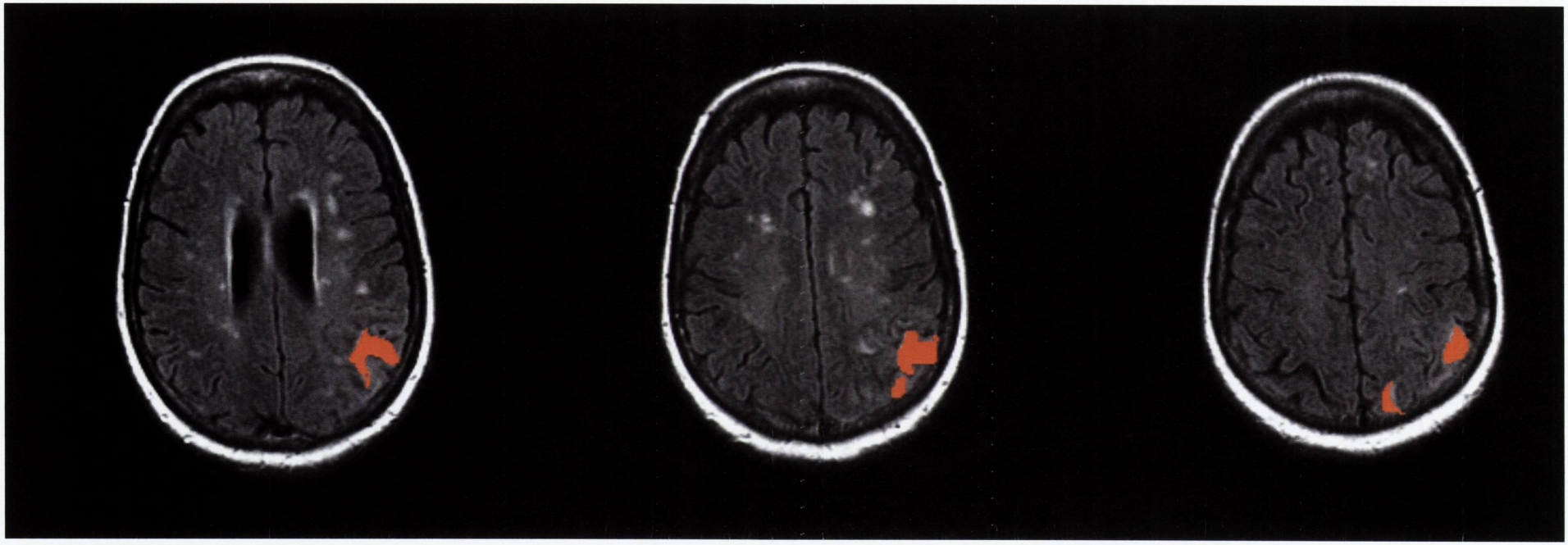


Figure 5.22: Patient 11 (No AOS)

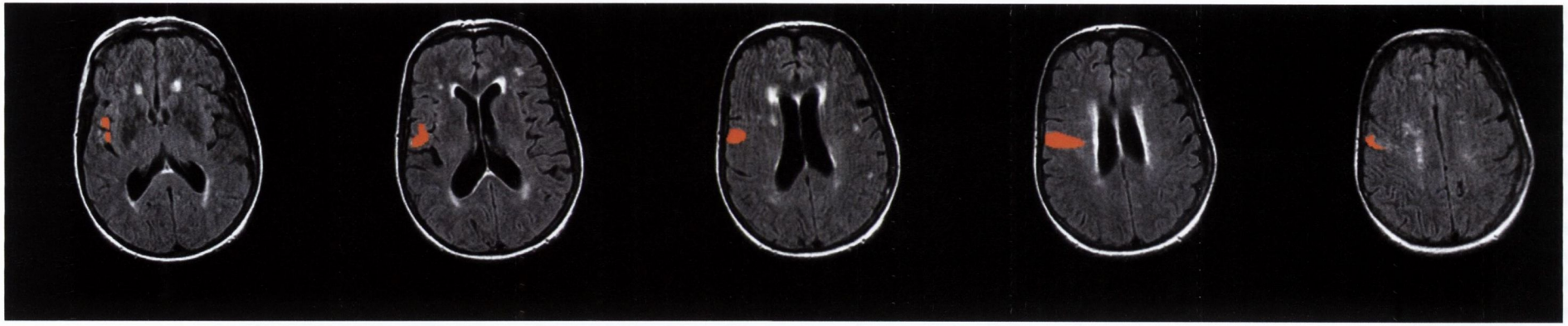


Figure 5.23: Patient 12 (No AOS)

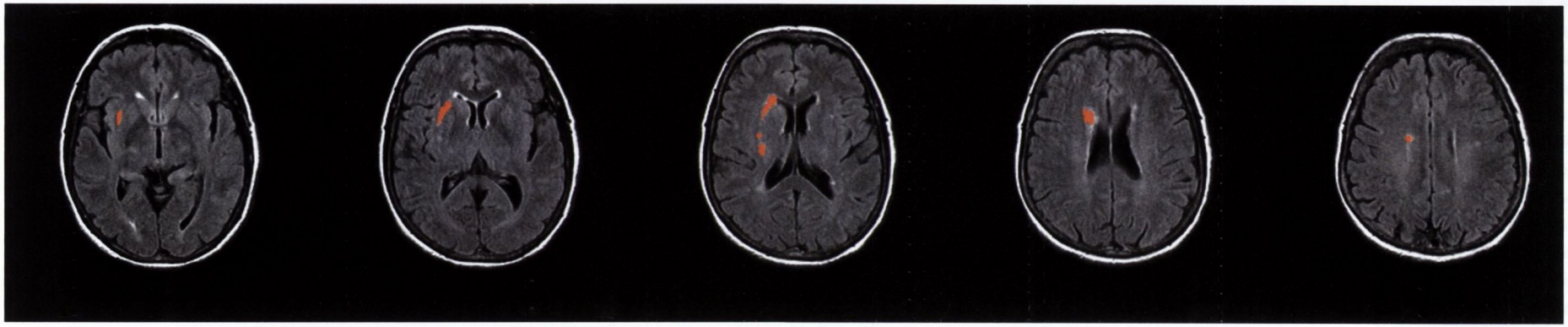


Figure 5.24: Patient 14 (No AOS)

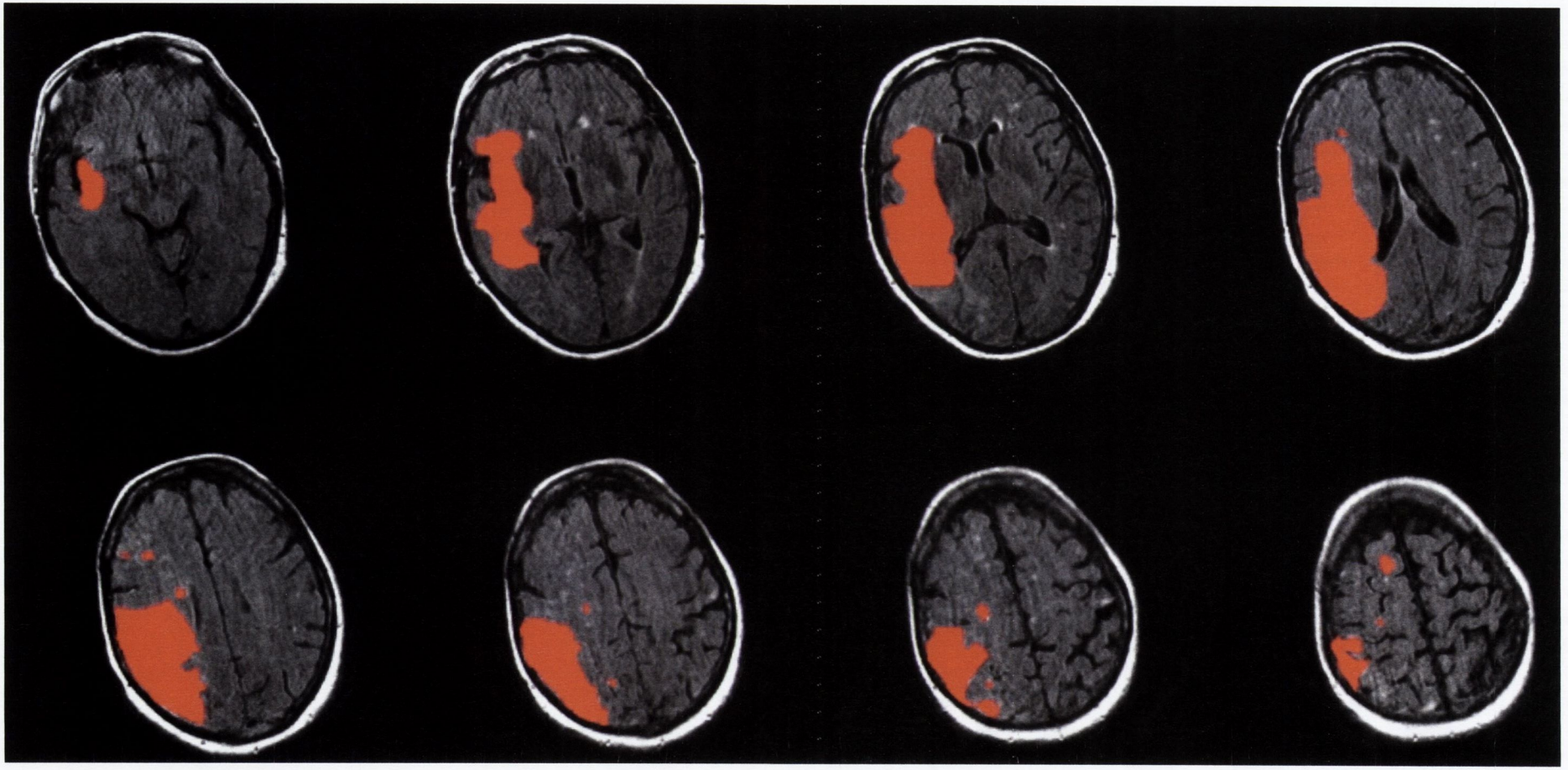


Figure 5.25: Patient 17 (No AOS)

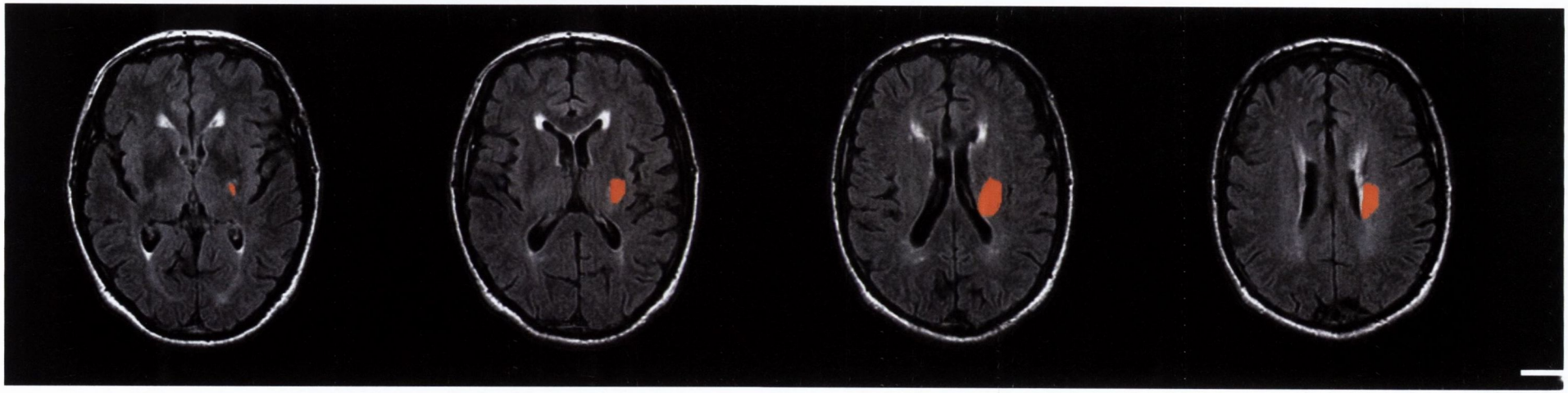


Figure 5.26: Patient 21 (No AOS)

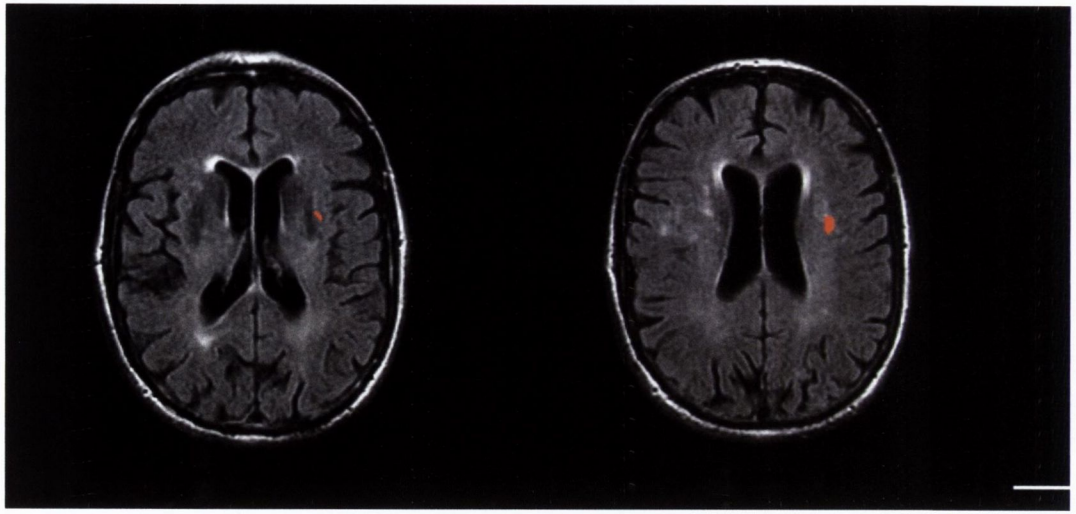


Figure 5.27: Patient 24 (No AOS)

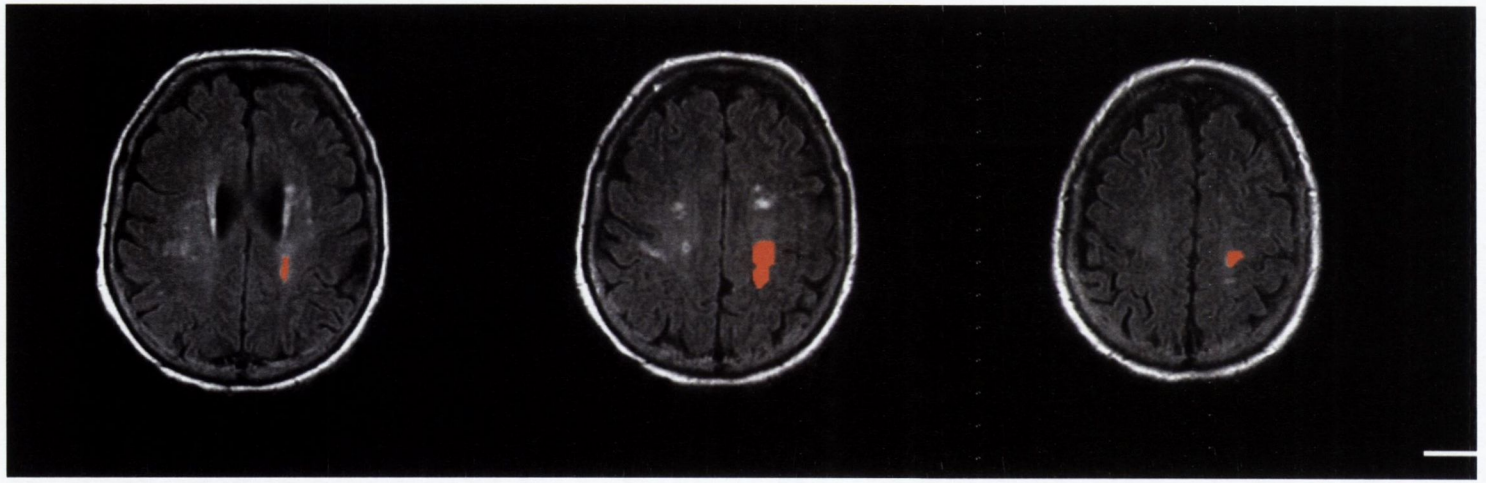


Figure 5.28: Patient 28 (No AOS)

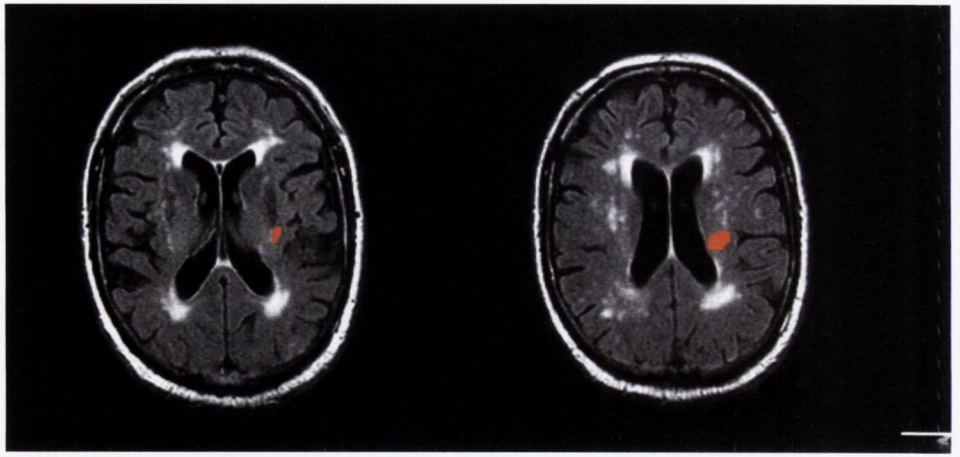


Figure 5.29: Patient 29 (No AOS)

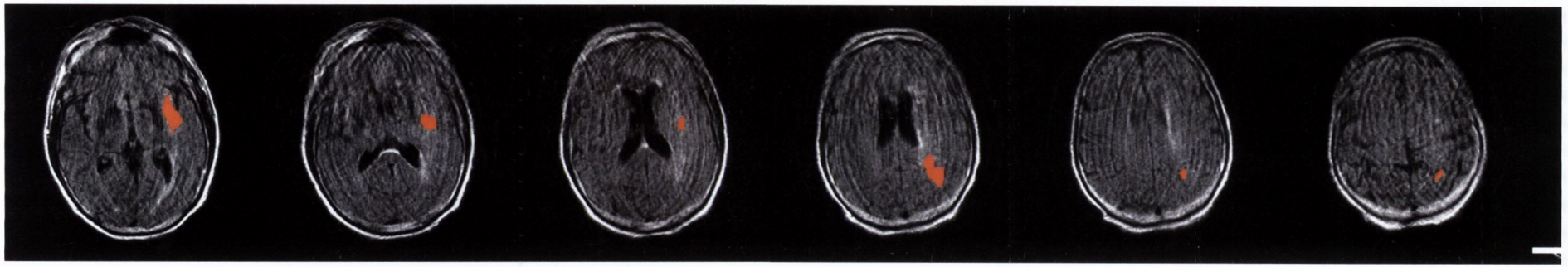


Figure 5.30: Patient 31 (No AOS)

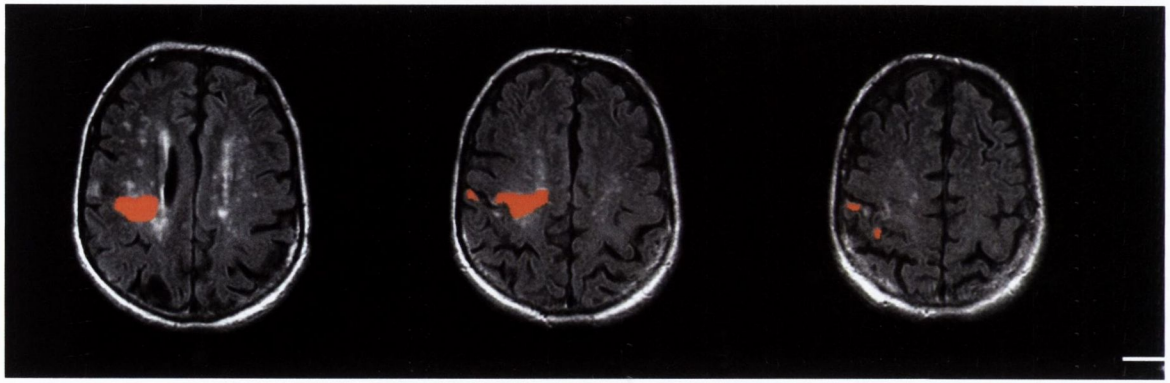


Figure 5.31: Patient 32 (No AOS)

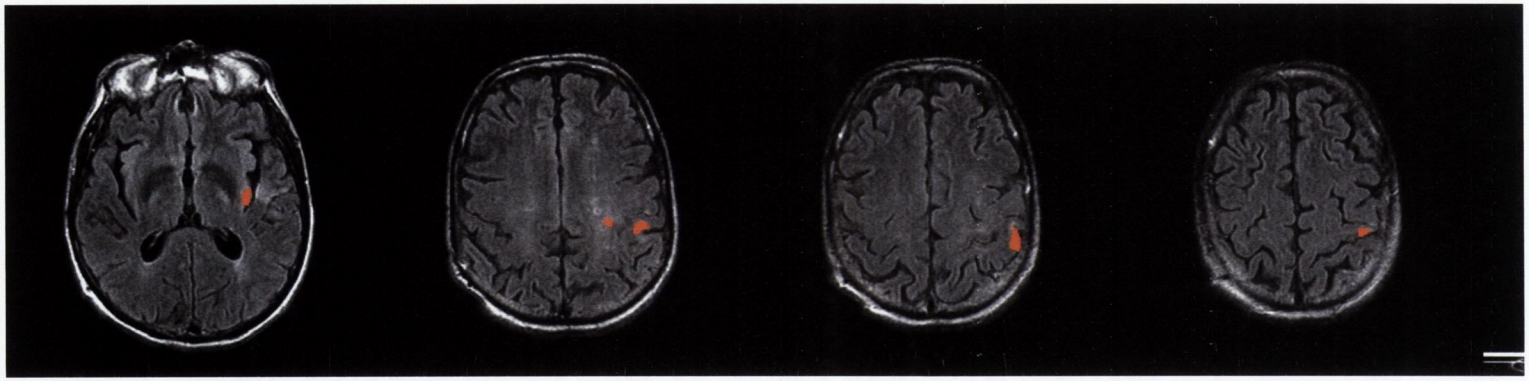


Figure 5.32: Patient 33 (No AOS)

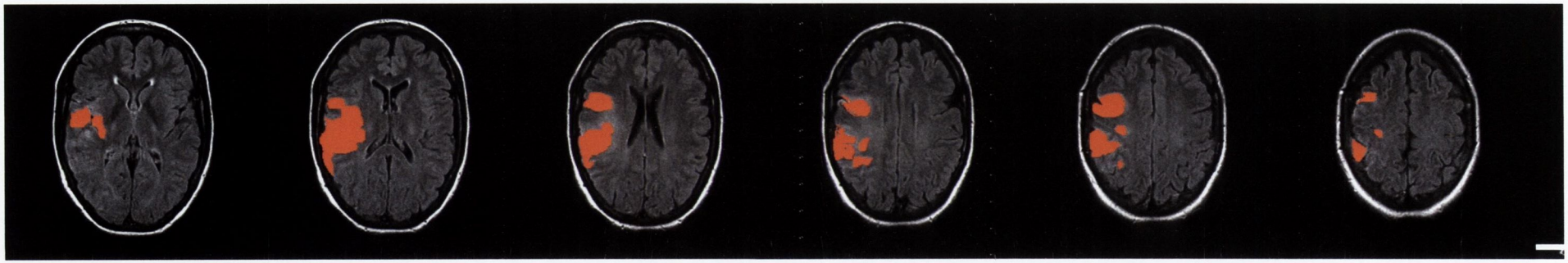


Figure 5.33: Patient 35 (No AOS)

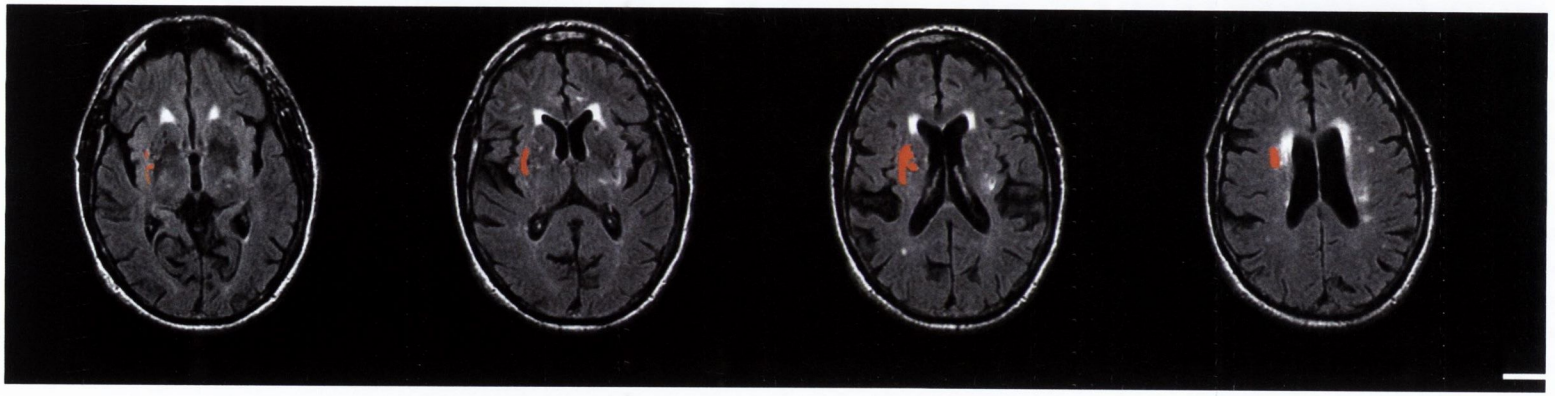


Figure 5.34: Patient 36 (No AOS)

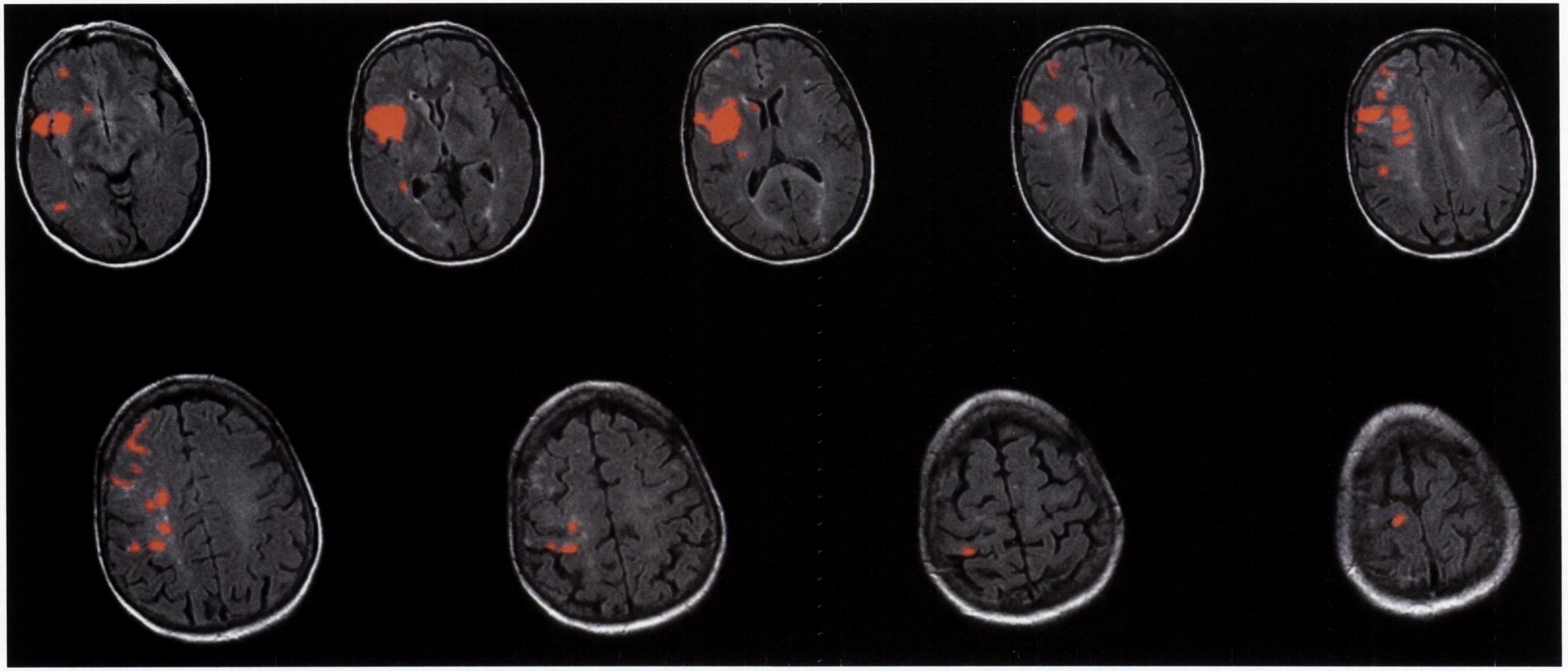


Figure 5.35: Patient 38 (No AOS)

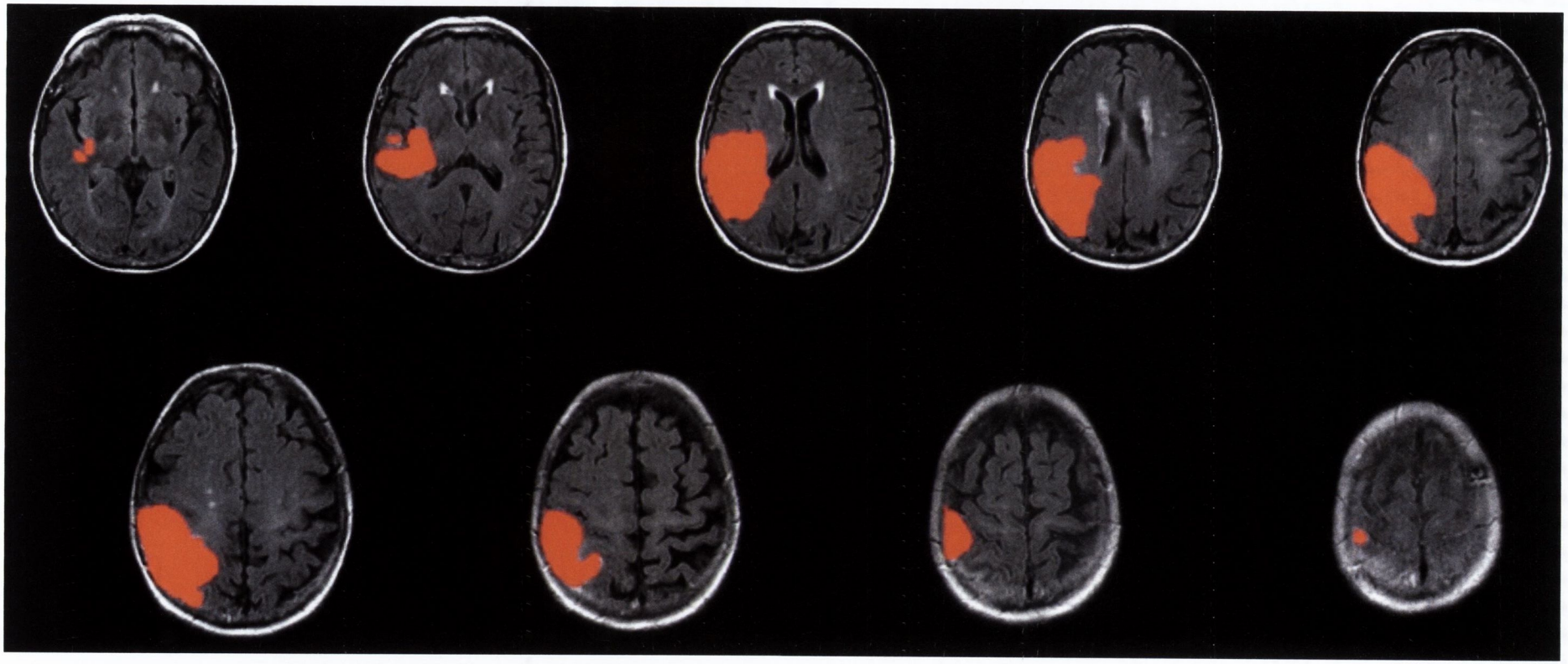


Figure 5.36: Patient 40 (No AOS)

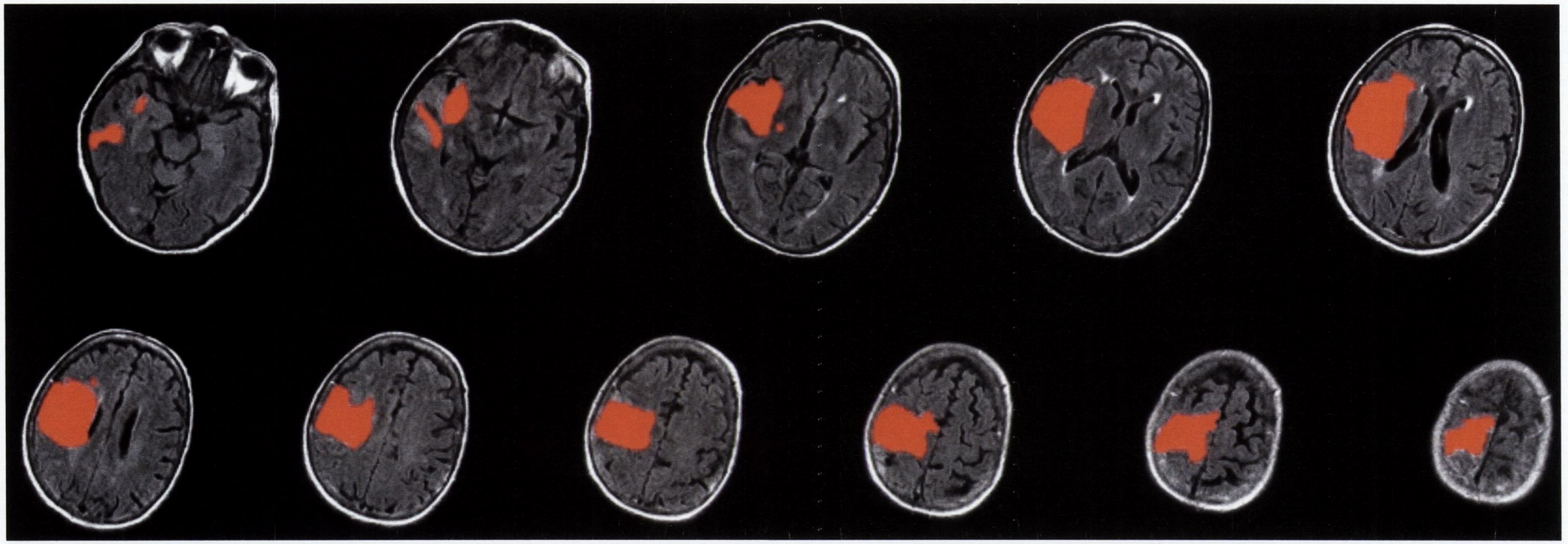


Figure 5.37: Patient 41 (No AOS)

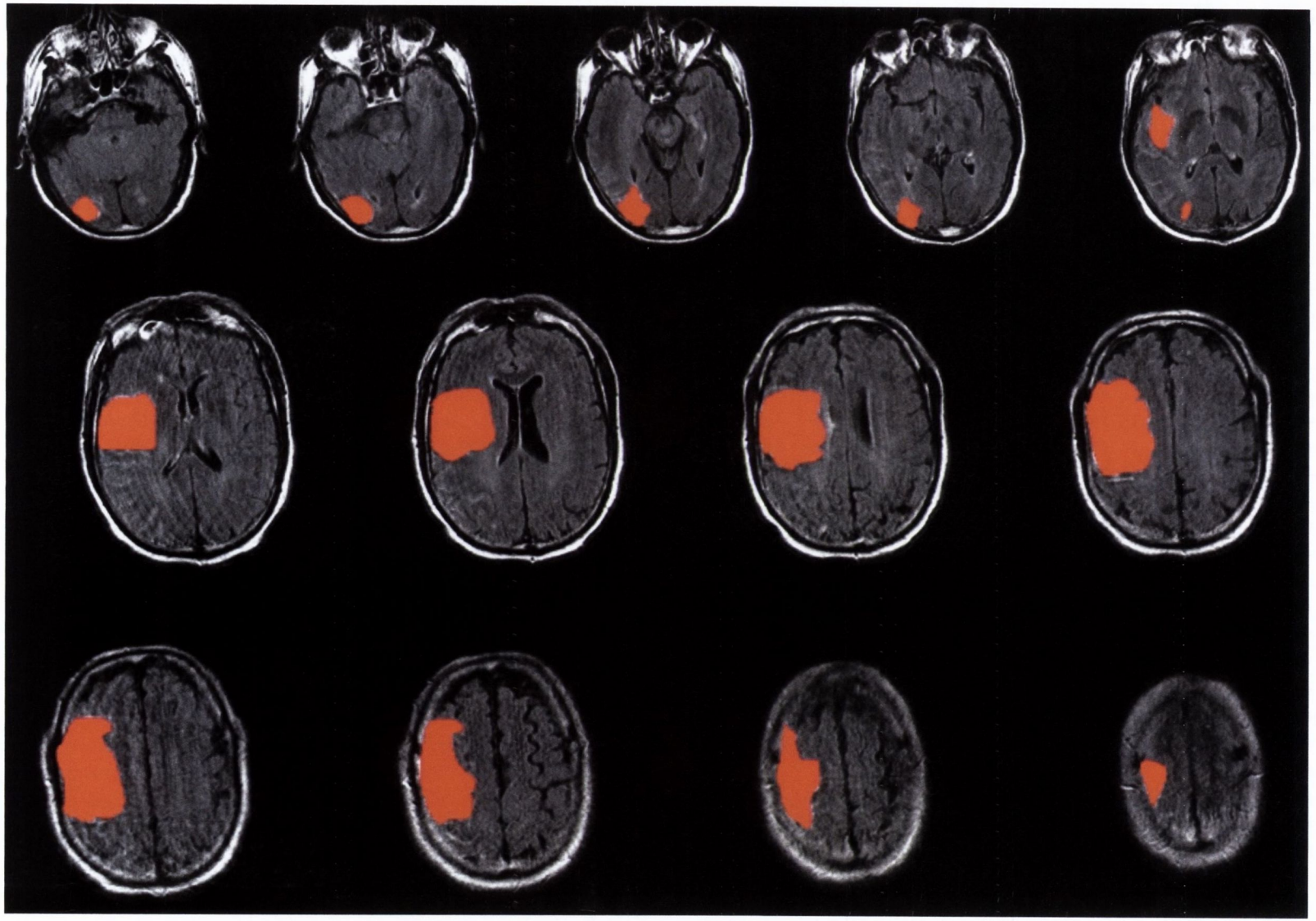


Figure 5.38: Patient 42 (No AOS)

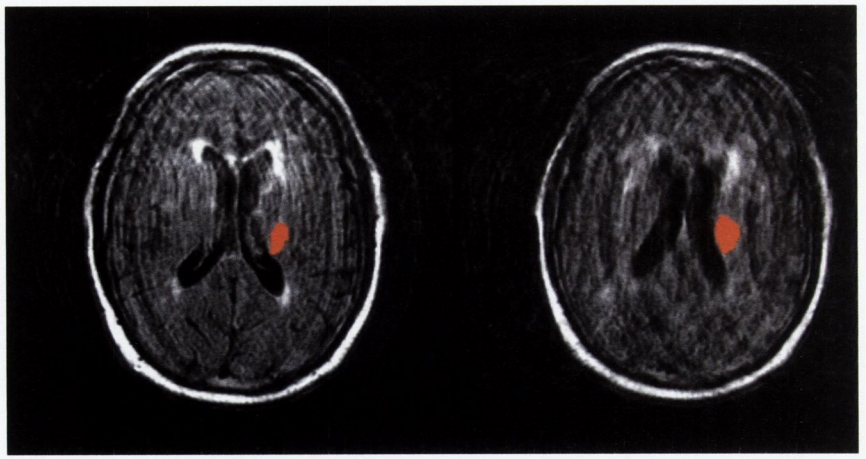


Figure 5.39: Patient 43 (No AOS)

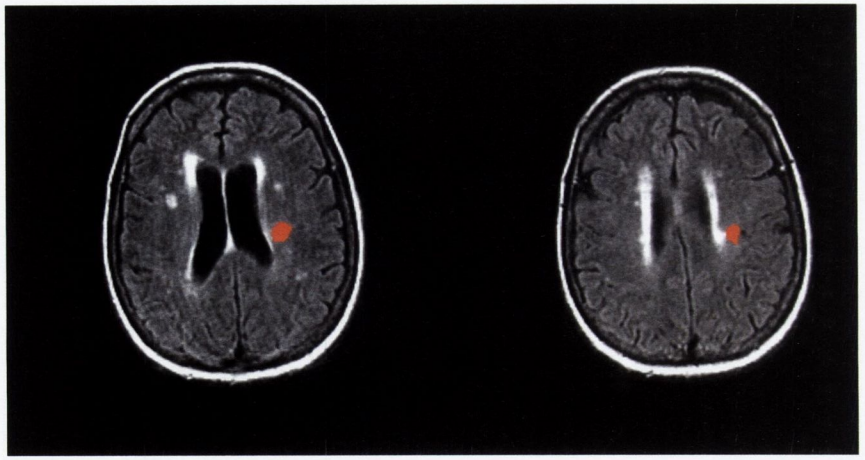


Figure 5.40: Patient 45 (No AOS)

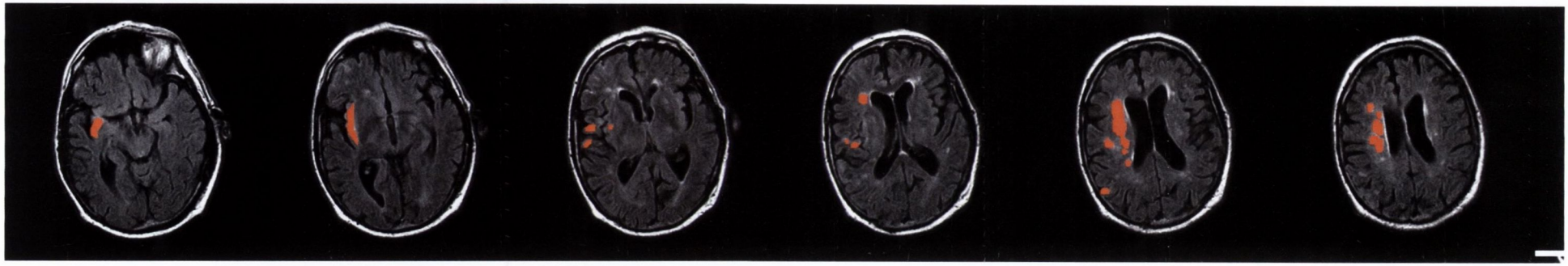


Figure 5.41: Patient 46 (No AOS)

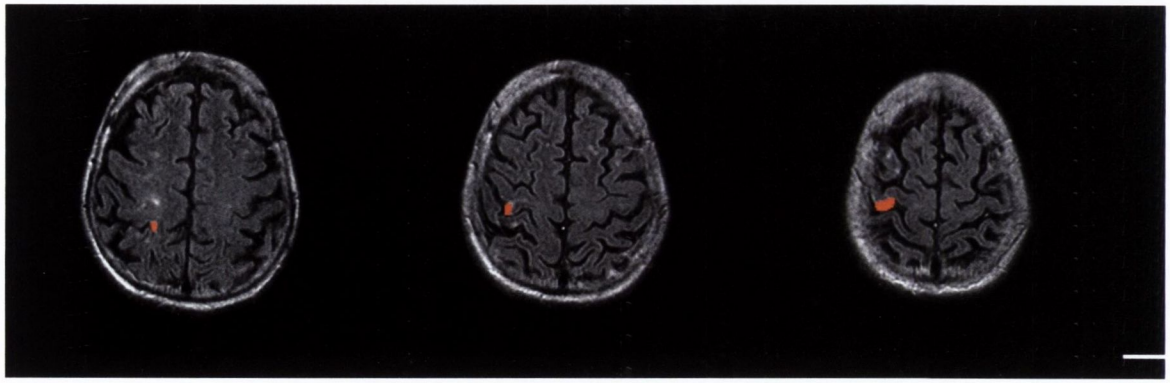


Figure 5.42: Patient 47 (No AOS)

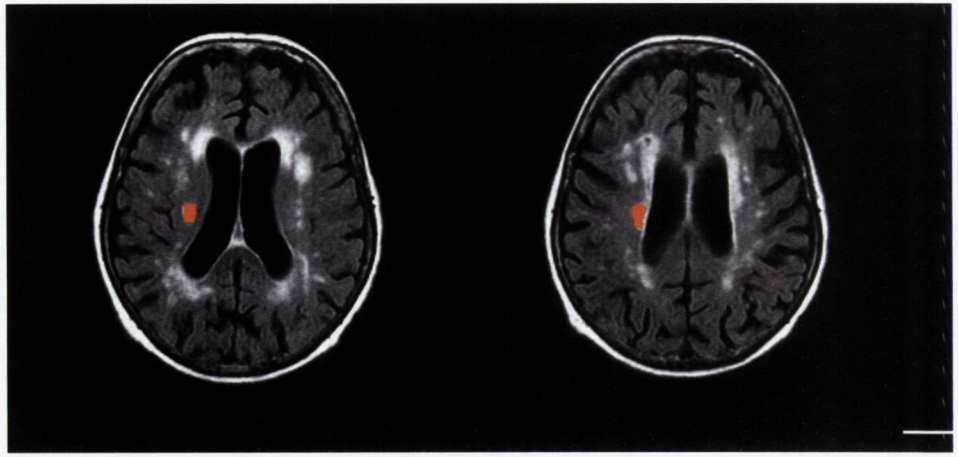


Figure 5.43: Patient 48 (No AOS)

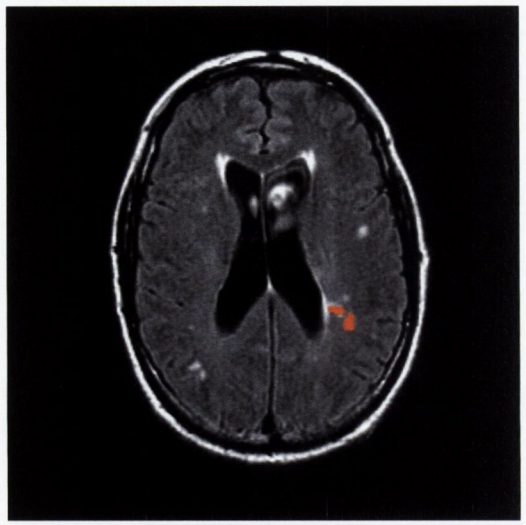


Figure 5.44: Patient 49 (No AOS)

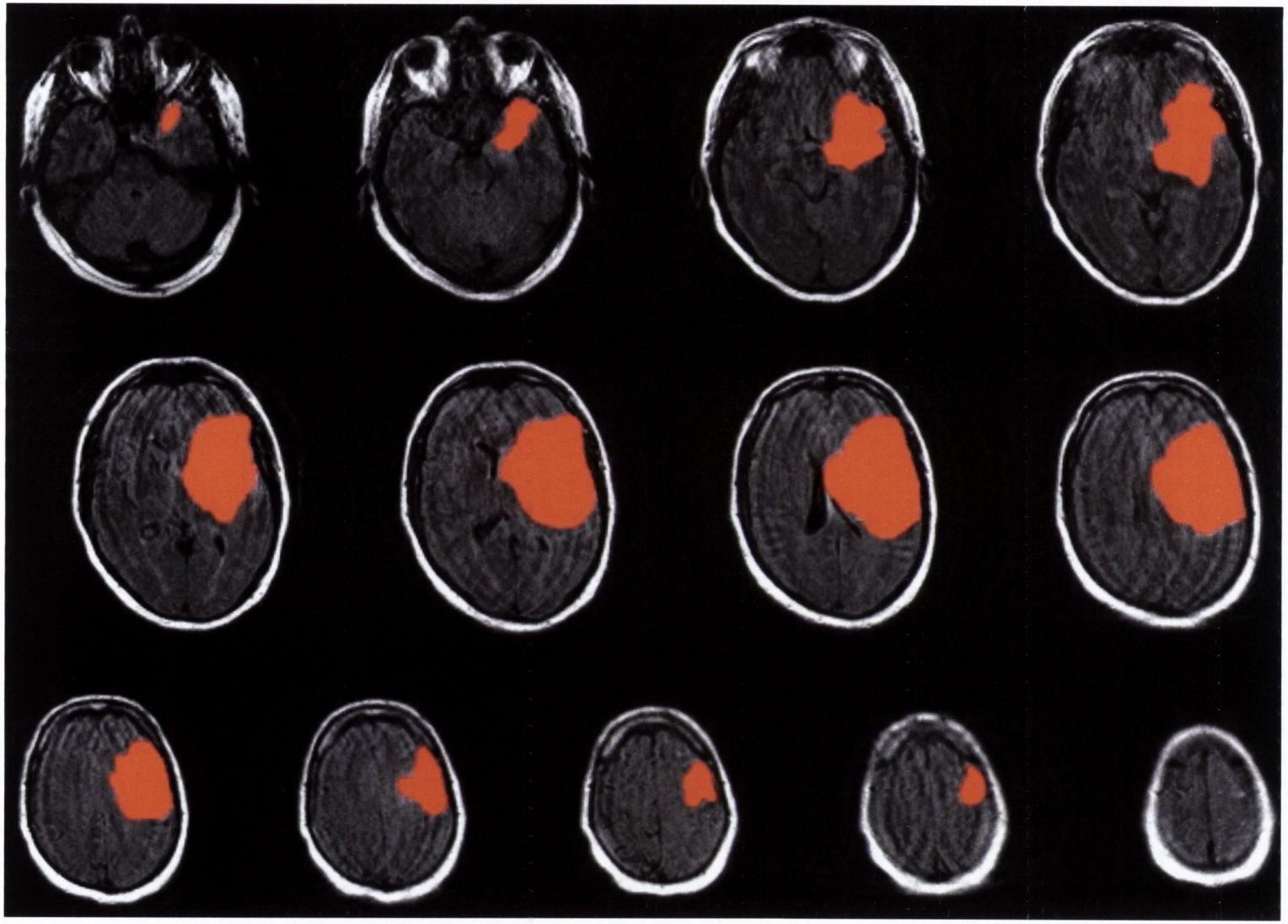


Figure 5.45: Patient 6 (Unable to complete assessment)

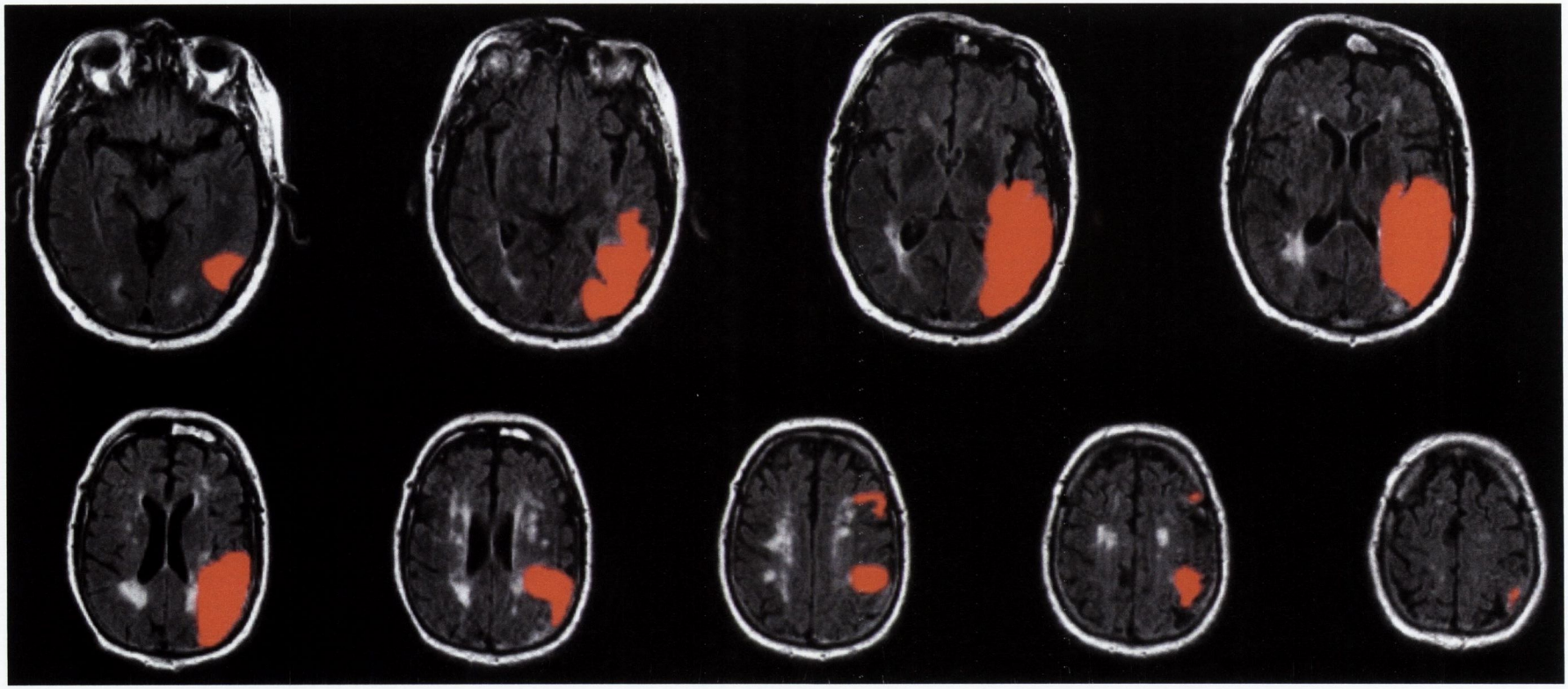


Figure 5.46: Patient 9 (Unable to complete assessment)

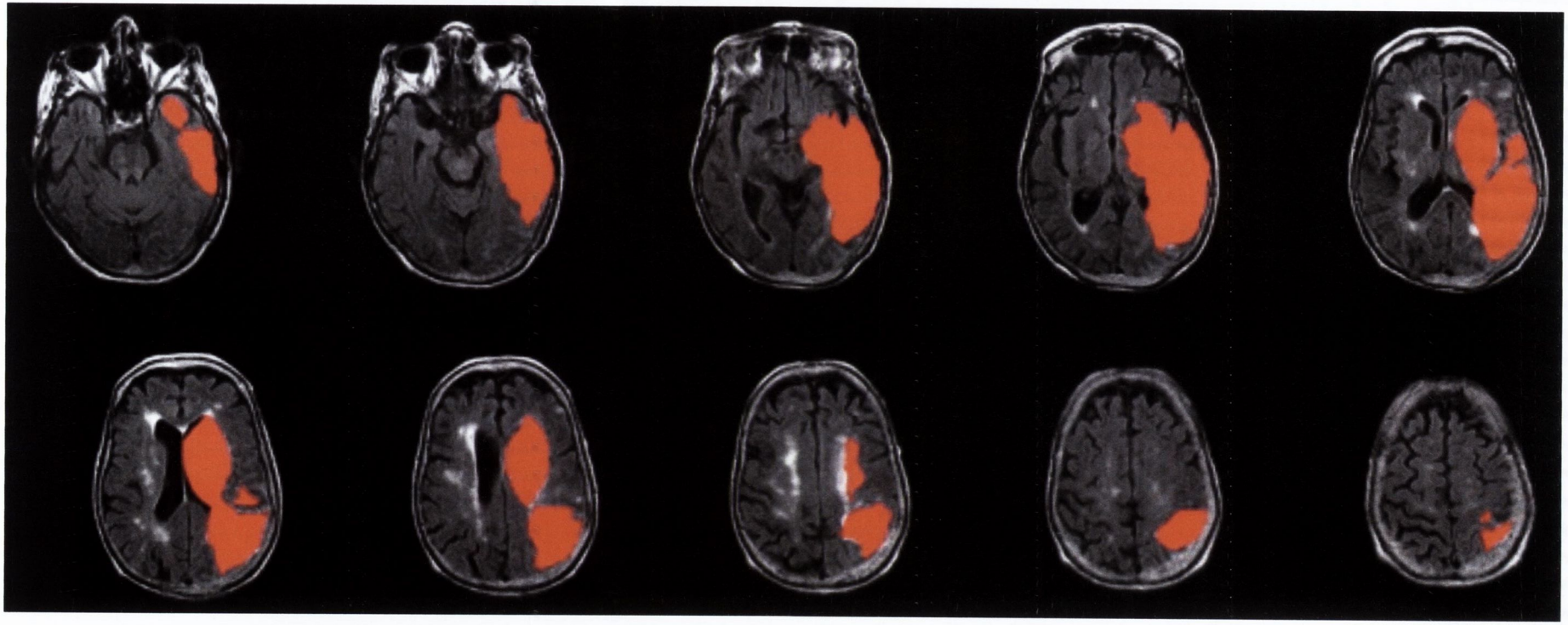


Figure 5.47: Patient 18 (Unable to complete assessment)

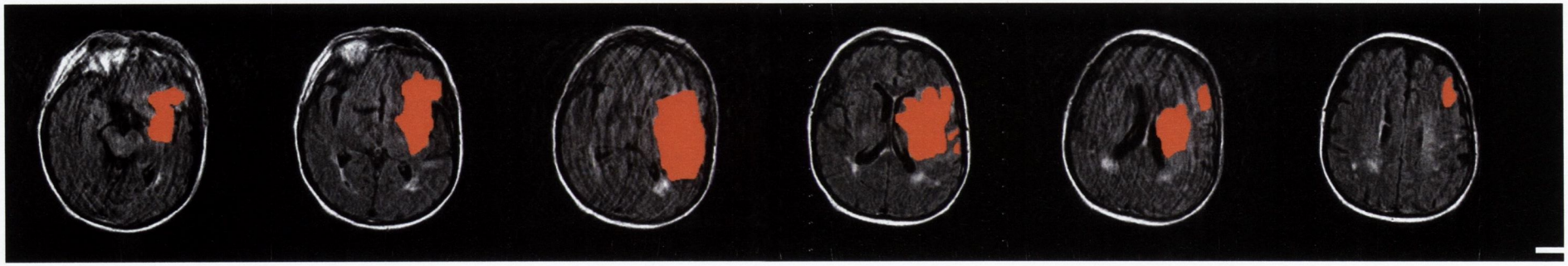


Figure 5.48: Patient 19 (Unable to complete assessment)

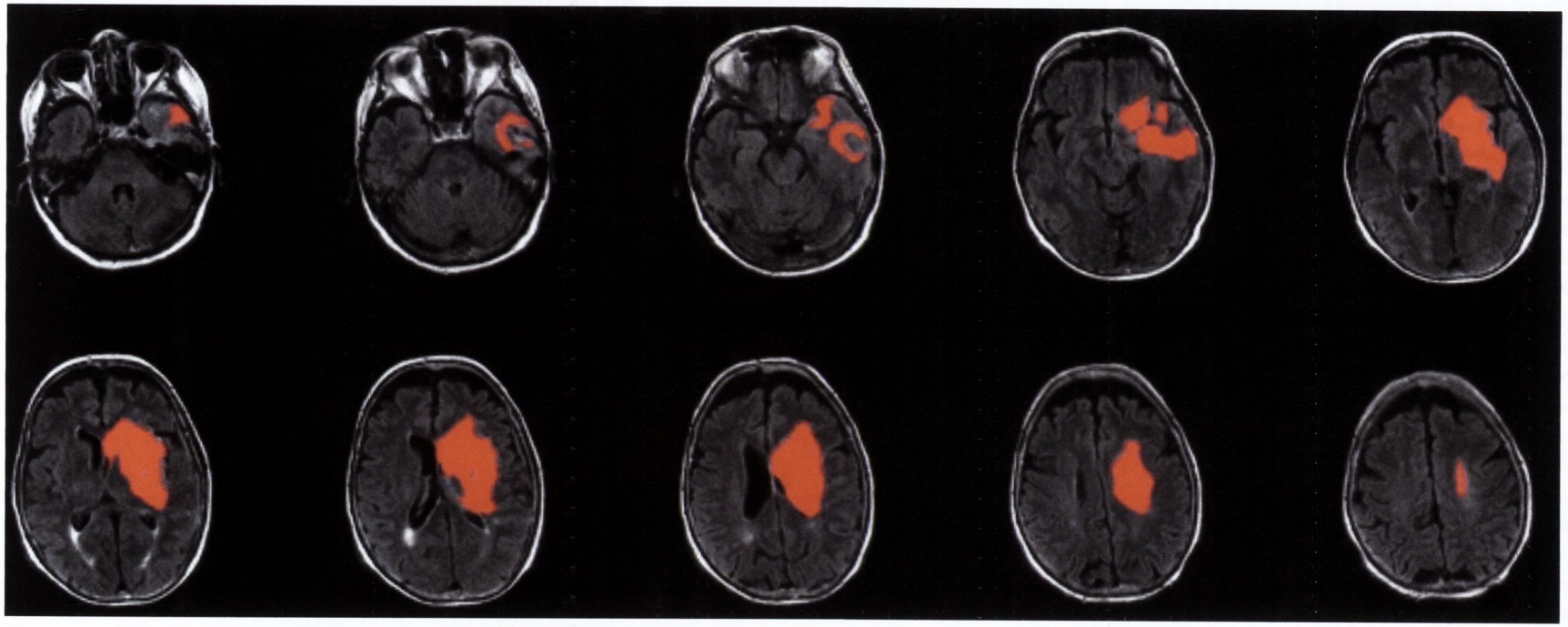
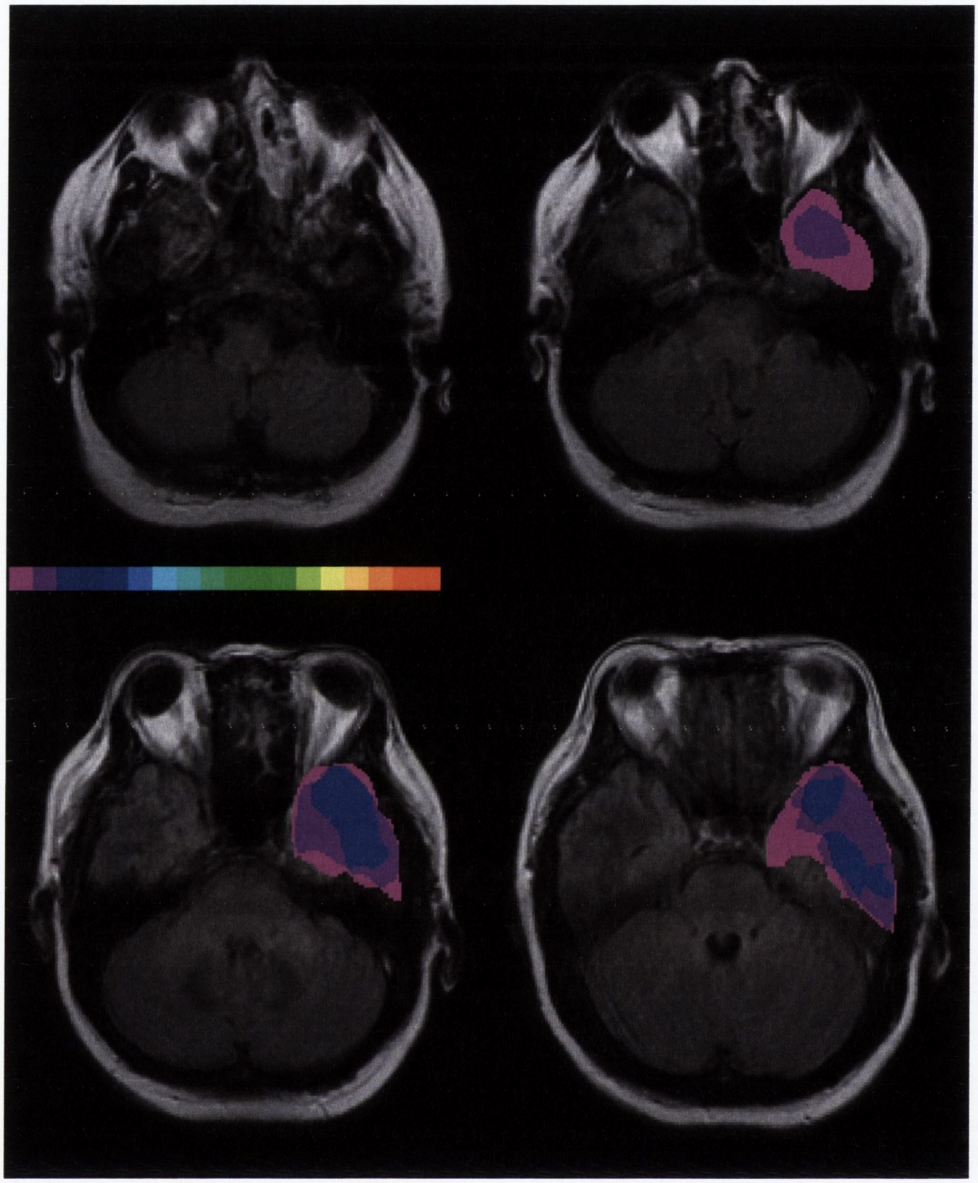
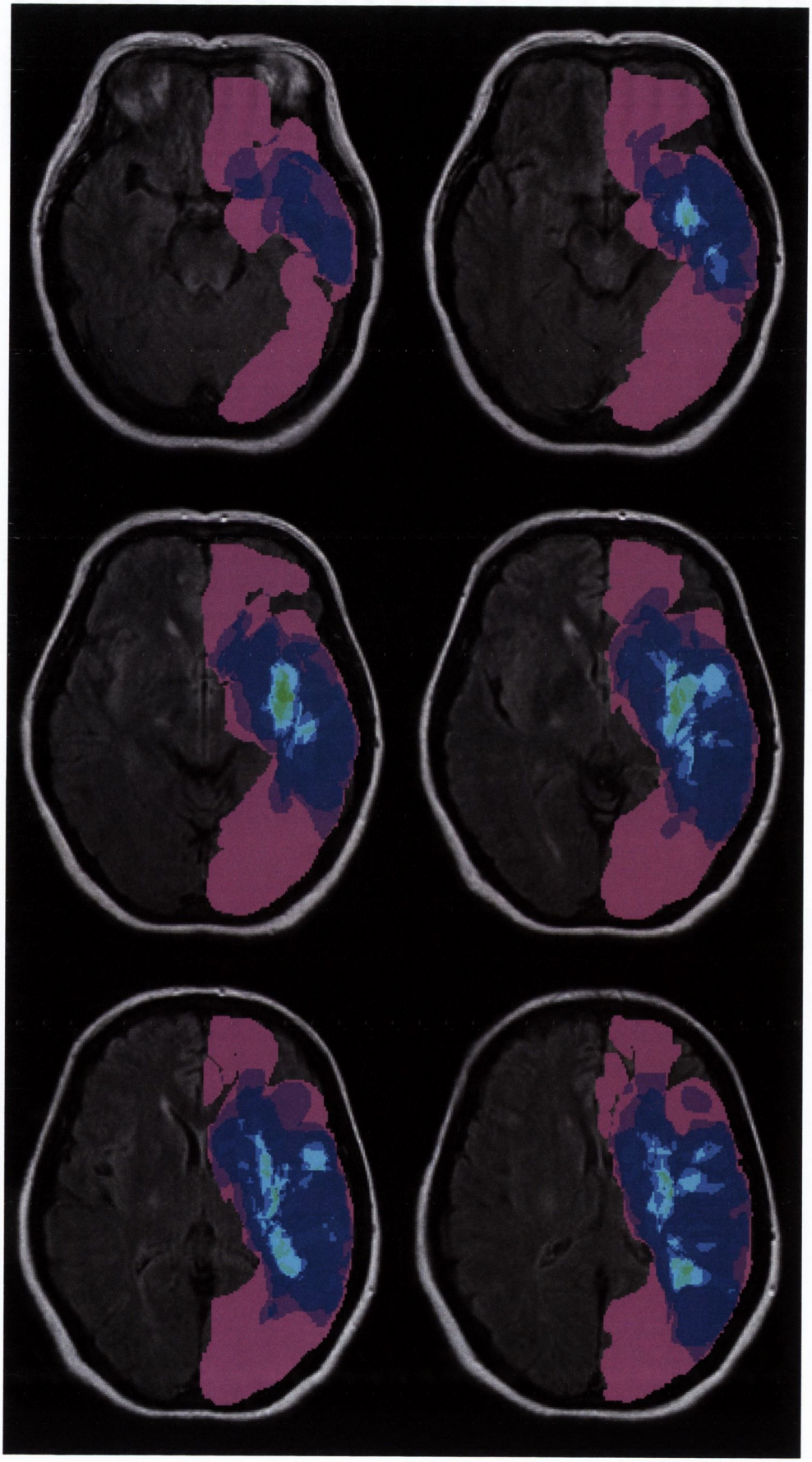
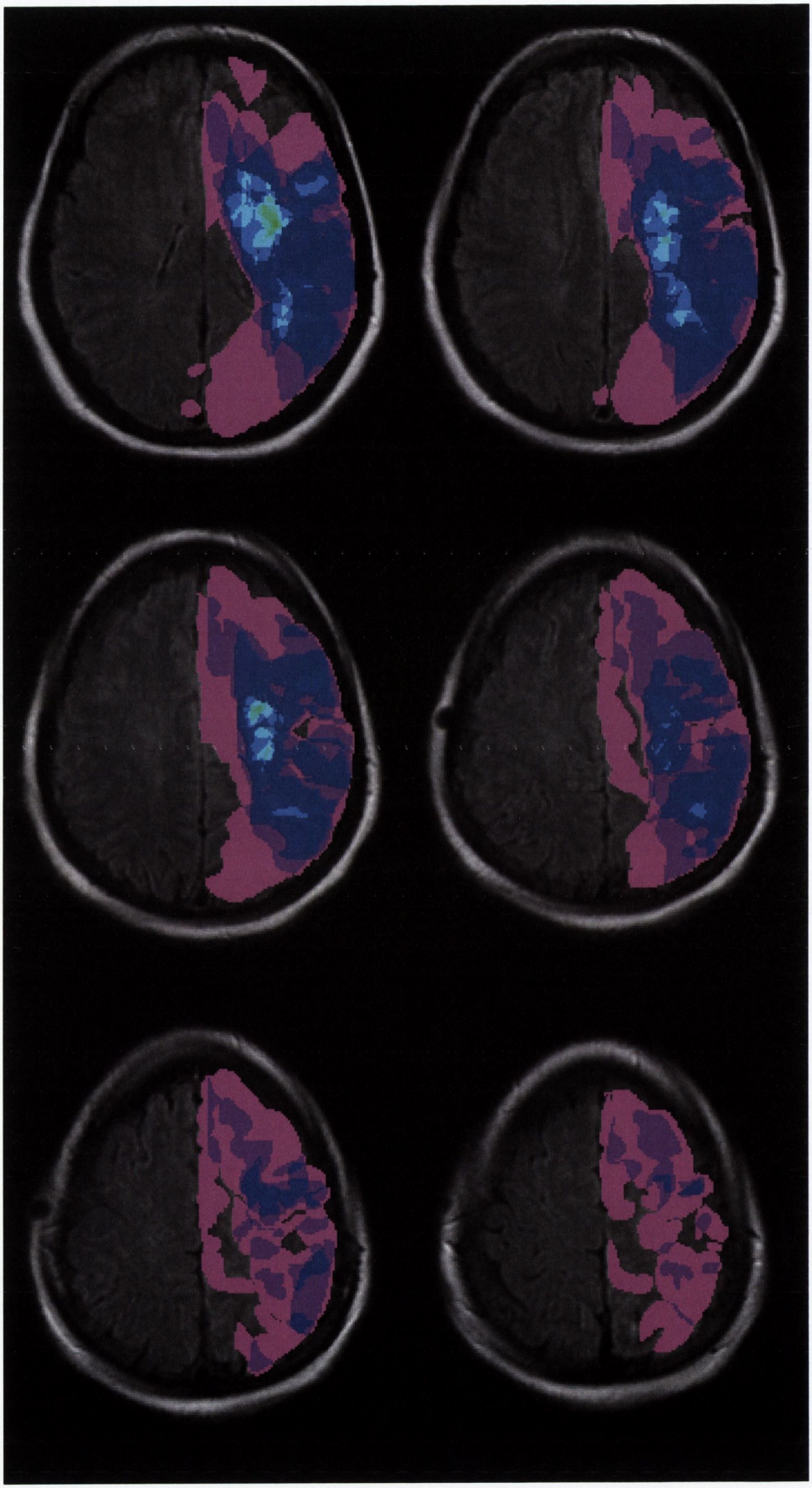


Figure 5.49: Patient 27 (Unable to complete assessment)

Lesion location in patients with AOS







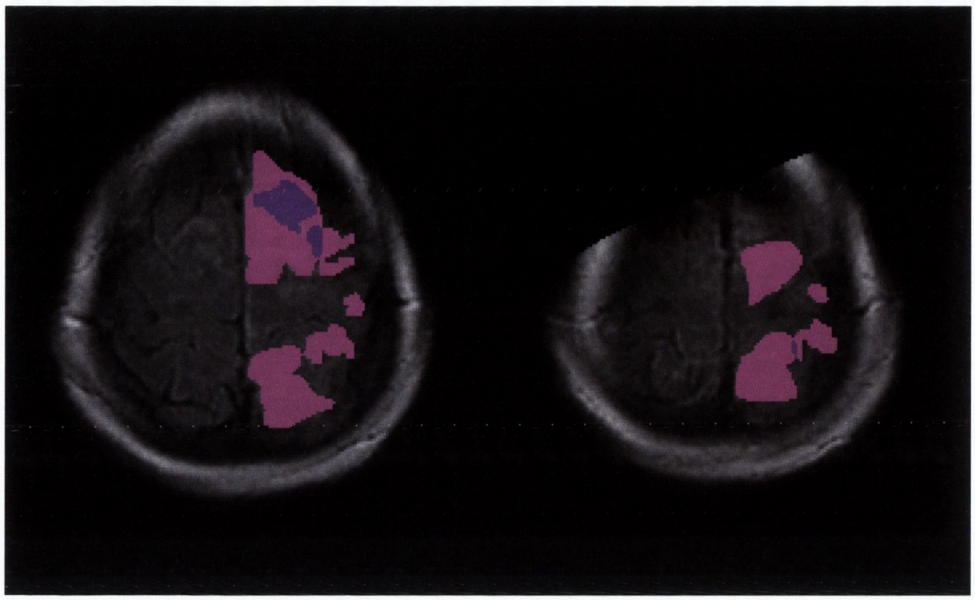
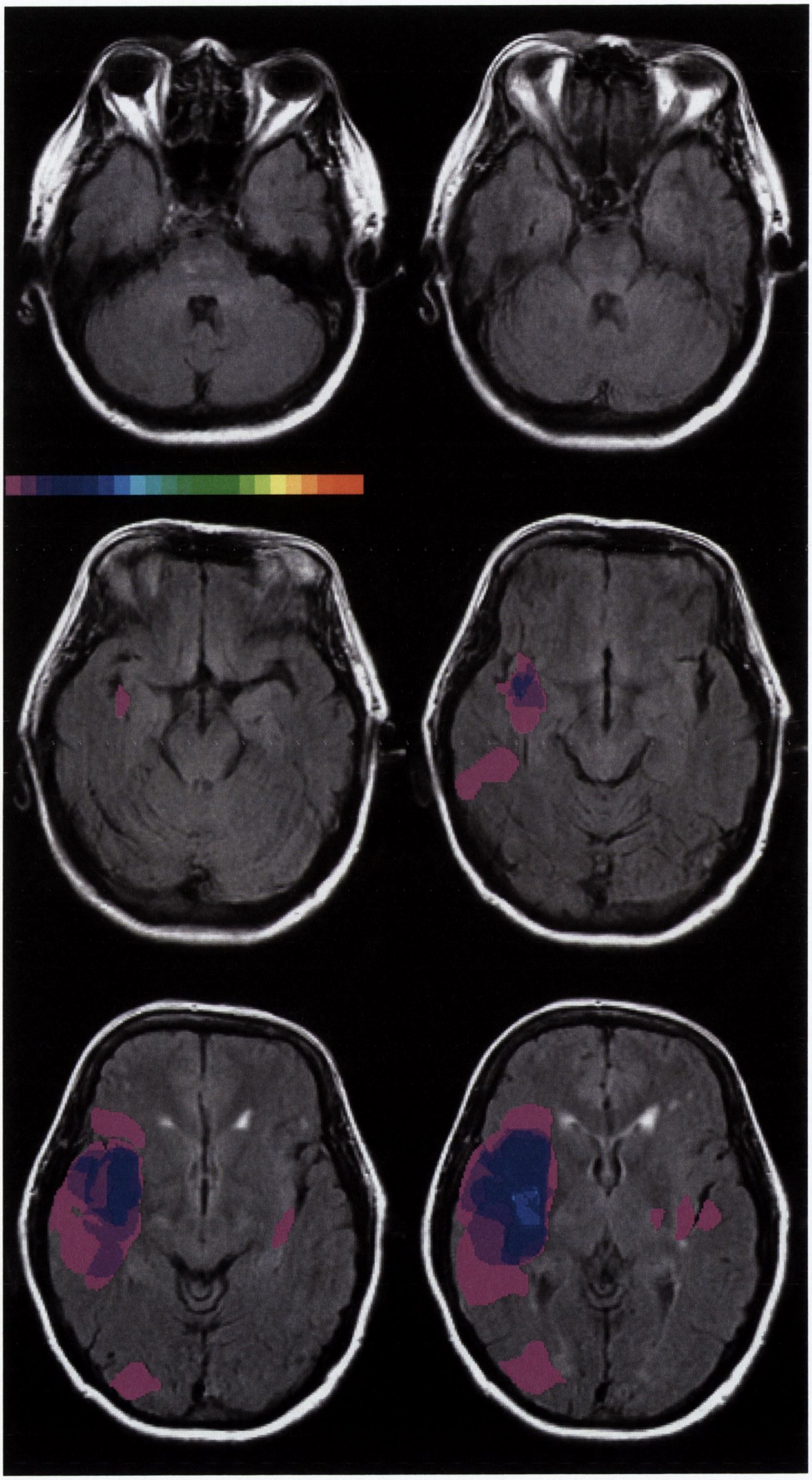
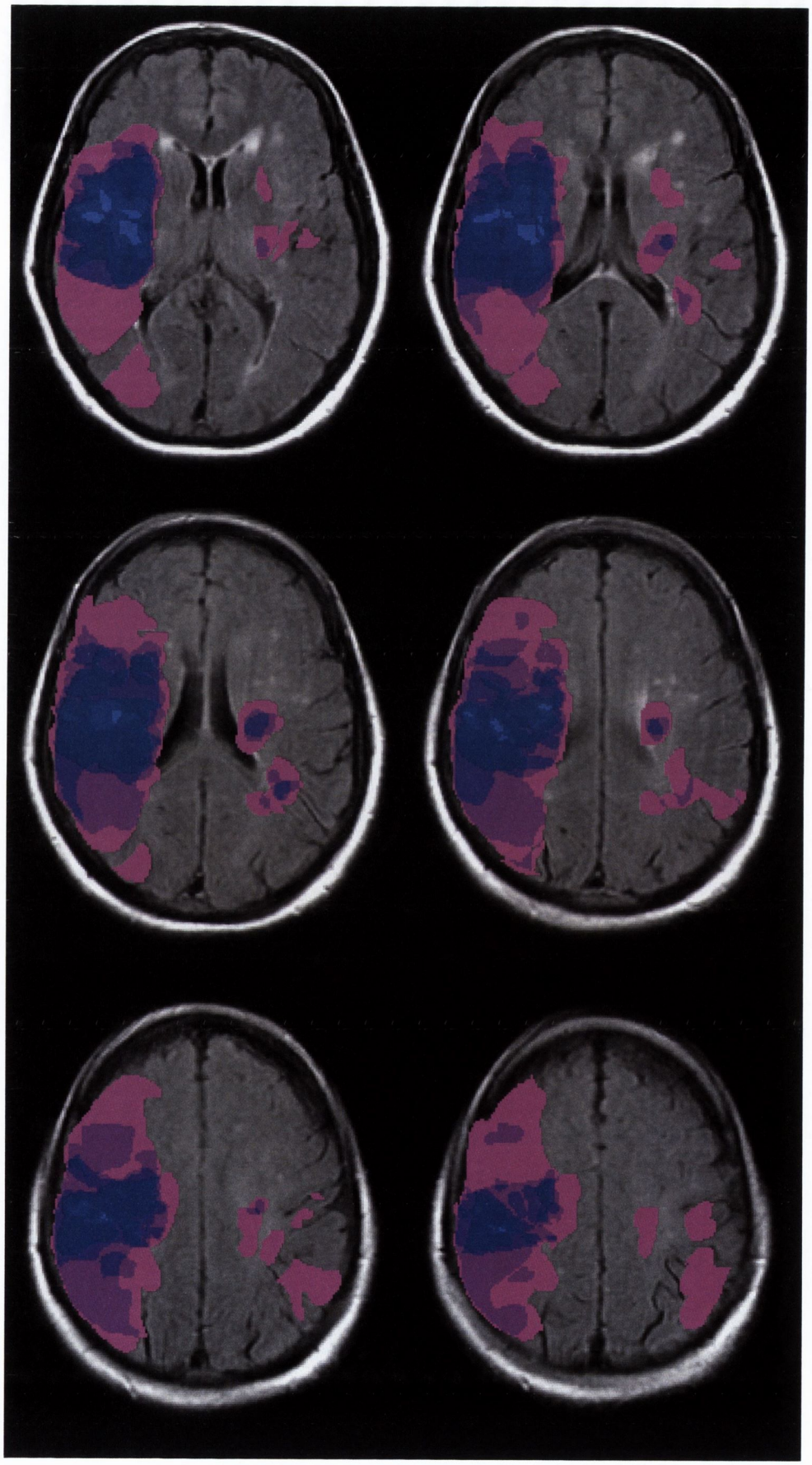


Figure 5.50: Overlay of ROIs of all patients with AOS. The colour bar underneath the first slice indicates the ROI density (dark violet for a single ROI, bright red for overlapping of all ROIs)

Lesion location in patients without AOS

Images of three patients without AOS (patient numbers 31, 43, 46) were not included in the overlap due to artifact precluding normalisation. One patient without AOS had only CT due to the presence of a pacemaker and thus is not included in the analysis (patient 34).





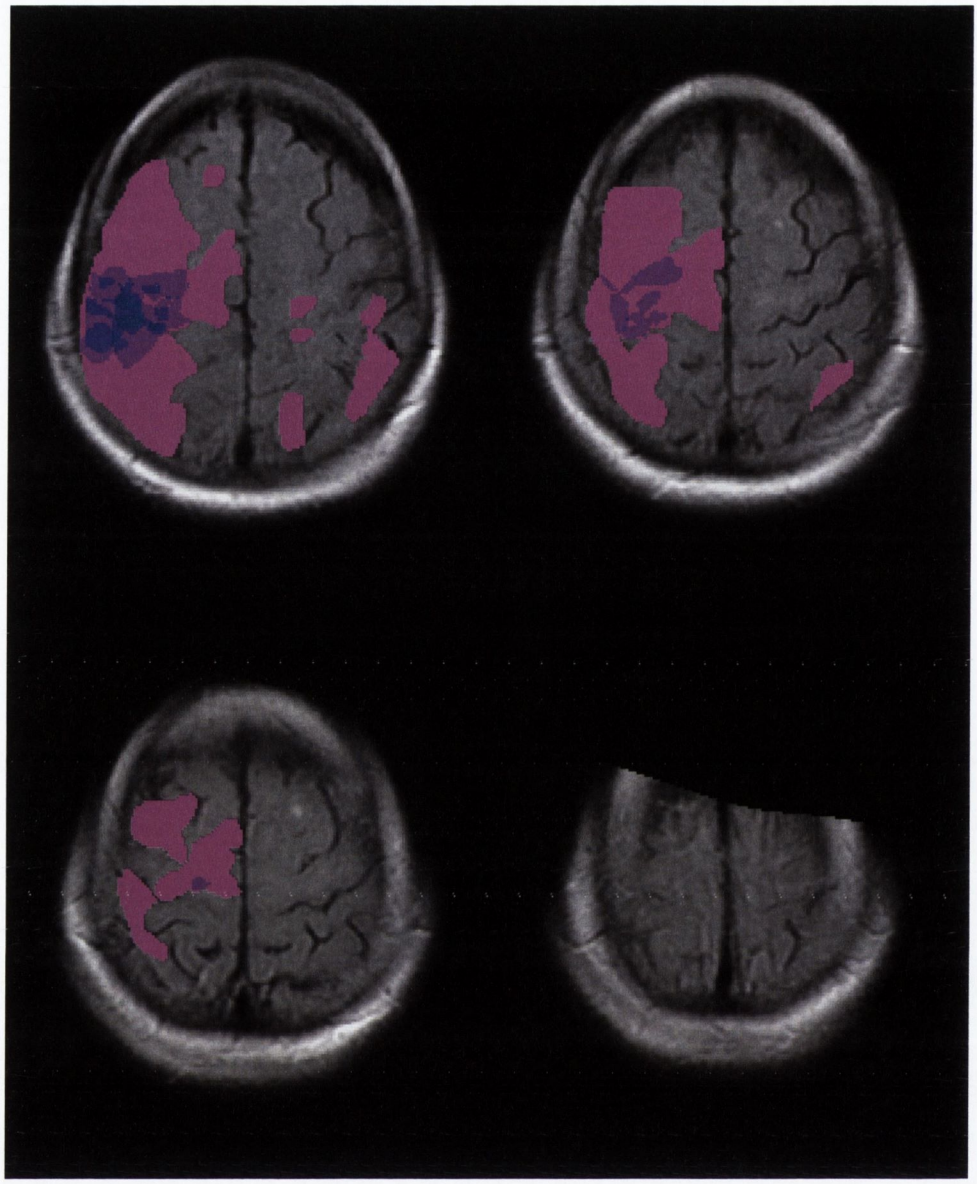


Figure 5.51: Overlap of ROIs of all patients without AOS. The colour bar underneath the first slice indicates the ROI density (dark violet for a single ROI, bright red for overlapping of all ROIs)

Lesion location in patients with AOS

All patients with AOS had left hemisphere lesions (Figures 5.1-5.18). When normalised ROI images of all patients with AOS were overlaid (Figure 5.50), there was no single area which was involved in every patient. However, the regions of

greatest overlap (represented in light green) included left-sided cortical structures in particular the insula, as well as subcortical structures: claustrum and putamen. Other regions of significant overlap (represented in pale blue) included left sided globus pallidus, posterior limb of internal capsule, optic radiation and centrum semiovale. In contrast, these areas were generally not involved in patients without AOS (Figures 5.19-5.44, and 5.51). When the MASK command was used to determine whether there was an area which was always involved in AOS and not involved when AOS was not present, no area was selected.

5.3.2 Reliability of lesion volume estimates

Inter-rater agreement

The results of volume measurements on a subset of 10 patients made by two raters is reported in table 5.1. Using paired *t*-tests, no significant differences were found between rater 1 and rater 2 measurements.

For this subsample, the SD of the mean difference between raters for a single measure of volume fell within the SD of the population mean (Table 5.3). Figures 5.52 and 5.53 demonstrate inter-rater agreement. The average difference between raters' measurements was near zero with a magnitude of $|0.36\ cm^3|$. The mean % difference in inter-rater measurements was 5.6 ± 9.2 %. The inter-rater ICC was excellent at 0.99 (Table 5.3).

Table 5.1: Results of stereological volume estimates on subset of 10 patients by two raters

Patient	Rater 1 (cm^3)	Rater 2 (cm^3)
1	3.823	2.979
2	26.419	25.523
3	71.666	71.218
4	41.554	38.074
5	68.001	73.090
6	15.847	14.634
7	8.728	8.780
8	16.348	14.027
9	36.387	37.046
10	3.056	2.906

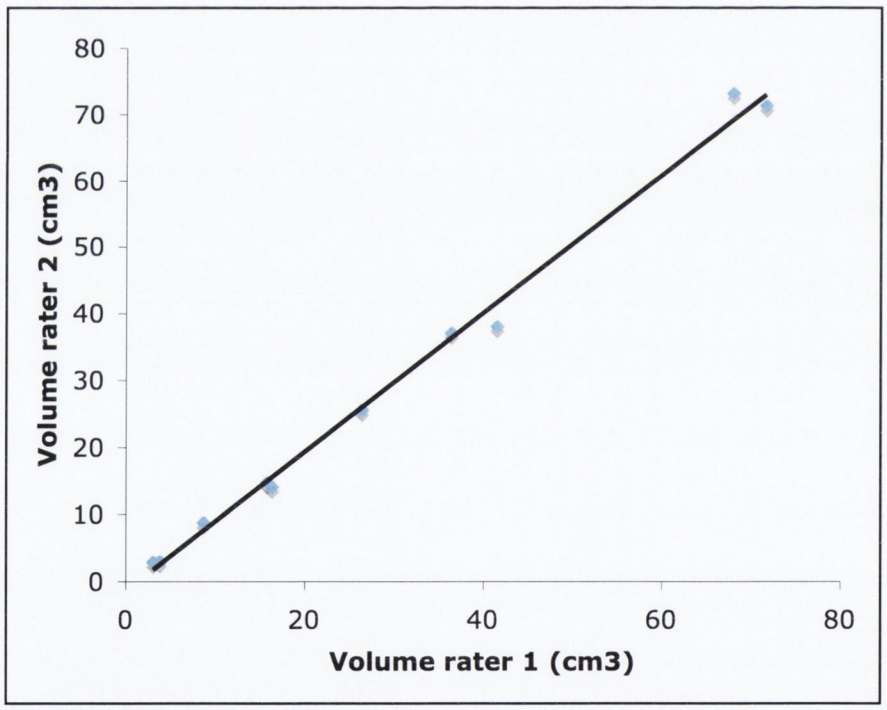


Figure 5.52: Scatter plot of measurements on a subset of 10 patients by two raters demonstrating good agreement of volume measurements

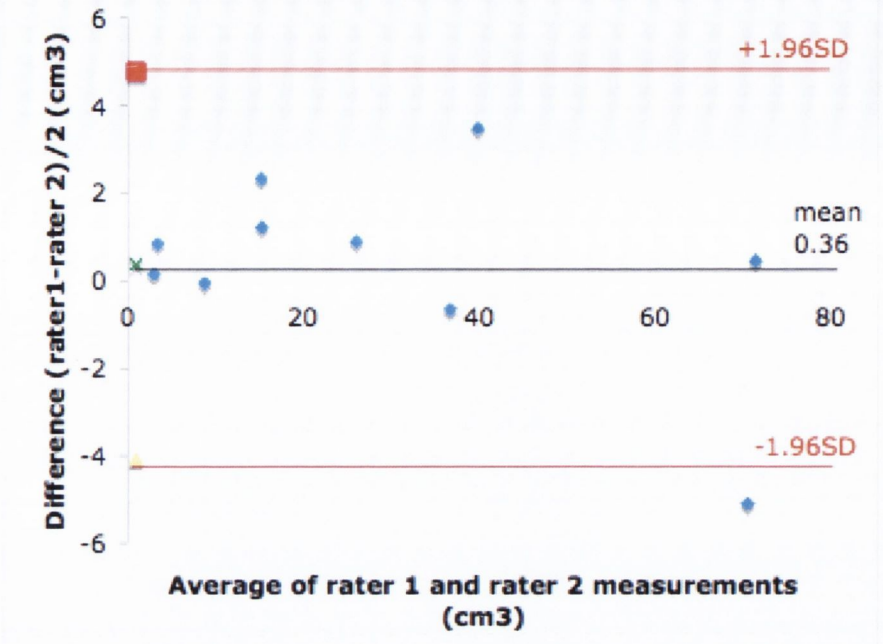


Figure 5.53: Bland-Altman plot of measurement difference over measurement average by two raters for inter-rater tests (n=10). For volume measurements, the majority of cases fall within the limits of agreement, which are determined as ±1.96 sd of the mean of repeated differences. The mean of each measure oscillates around zero, which demonstrates the lack of bias between one measurement and the next.

Intra-rater agreement

The results of two repeated volume measurements on a subset of 10 patients at least two weeks apart by the same rater is reported in Table 5.2. Using paired *t*-tests, no significant differences were found between repeated measures.

For this subsample, the limits of agreement for volume fell within ±1.96 sd of the population mean (Table 5.3). Figures 5.54 and 5.55 show the agreement between repeated measures. The average difference between repeated measurements is near

zero with a magnitude of |0.22 cm^3|. The mean % difference in intra-rater measurements was 1.5 ± 5.6 %. The intra-rater ICC was excellent at 0.99 (Table 5.3).

Table 5.2: Results of stereological volume estimates on subset of 10 patients by the same rater

Patient	Measurement 1 (cm3)	Measurement 2 (cm3)
1	13.526	12.524
2	2.755	2.655
3	1.239	1.213
4	32.168	32.563
5	24.073	22.148
6	8.780	8.622
7	58.931	62.780
8	32.669	31.878
9	11.470	12.551
10	69.662	66.155

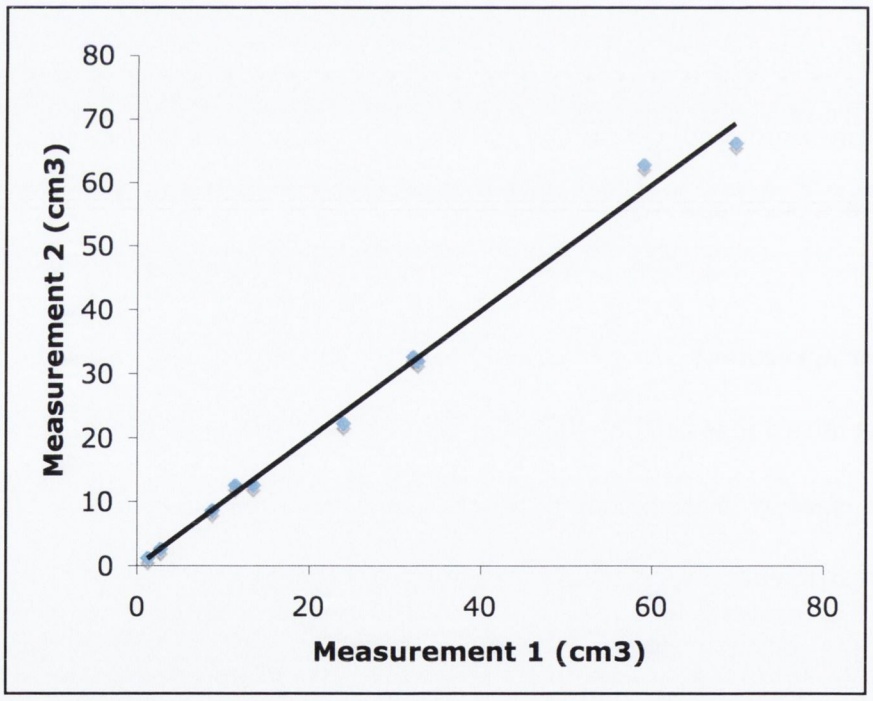


Figure 5.54: Scatter plot of volume measurements performed by the same rater on 10 patients demonstrating repeatability of volume measurements . All data points lie on or near the line of equality, demonstrating that measurements 1 and 2 are similar.

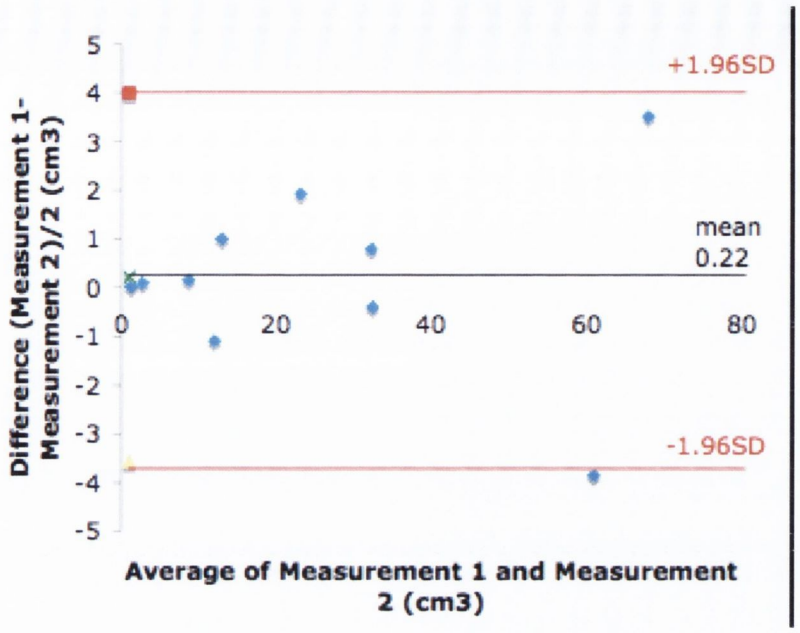


Figure 5.55: Bland-Altman plot of measurement difference against average measurement for intra-rater repeatability tests (n=10). For volume measurements, the majority of cases fall within the limits of agreement, which are determined as ±1.96 sd of the mean of repeated differences. The mean difference for each measure oscillates around zero, which demonstrates the lack of bias from one measurement to the next.

Table 5.3: Results of inter- and intra- rater repeatability tests

	sd (mean of repeated measures)	sd (mean of differences)	ICC
Inter-rater	25.46	2.26	0.996
Intra-rater	23.28	1.92	0.997

This table compares sd of the mean of two repeat estimates for the population (sd of average measure [(A+B)/2] with sd of difference between repeated population estimates (sd of average of [A-B]). ICC=intraclass correlation.

5.3.3 Lesion volume and presence of AOS

One patient could not have MRI due to the presence of a permanent pacemaker and thus had CT only. Volume estimates were not made for this patient as CT and MRI are not comparable.

Mean lesion volume in the 18 patients with AOS was 48.2 ± 48.8 cm^3 (range 0.55-162.8 cm^3) compared with 15.1 ± 25.8 cm^3 (range 0.2-71.4 cm^3) in the 27 patients without AOS. In the five patients with severe comprehension difficulty precluding assessment for AOS, mean volume was 94.0 ± 48.0 cm^3 (range 56.4-157.4 cm^3). ANOVA was used to compare means between groups; the difference in mean lesion volume between the three groups was statistically significant, p=0.0001 (Table 5.4).

Table 5.4: Mean lesion volume by patient group

	AOS n=18	**No AOS** n=27	**Unable to assess** n=5
Volume cm^3 (sd)	48.2 (48.8)	15.1 (25.8)	94.0 (48.0)

p=0.0001

5.3.4 Lesion volume and AOS severity

Increasing lesion volume correlated with increasing severity of AOS, with a Spearman correlation coefficient r of 0.53 ($p<0.0001$).

Multiple regression was performed to determine how much each variable contributed to AOS severity. When clinical stroke severity using NIHSS and lesion volume were used as variables to predict severity of AOS, r^2 was 0.42, both variables were

significant ($p=0.01$). When hemisphere, NIHSS and lesion volume were used as variables to predict severity of AOS, r^2 was 0.67. All three variables were significant ($p<0.0001$, 0.001 and 0.003 respectively).

5.4 Discussion

In this study, I documented lesion location and volume in patients with AOS following acute ischaemic hemispheral stroke. I investigated the association between AOS severity and lesion volume, as well as the association between AOS and clinical stroke severity as measured by the NIHSS.

5.4.1 Lesion location in patients with AOS

I demonstrated that the regions of greatest overlap in patients with AOS were the left insula, claustrum and putamen. Other regions of significant overlap included left sided globus pallidus, posterior limb of internal capsule, optic radiation and centrum semiovale. Thus, multiple different left-sided brain regions were involved in patients with AOS. In contrast to other studies which have invariably shown lesion overlap in a single brain region in a group of patients with AOS, we did not find that one single area was always involved.

Dronkers found that 25 patients with AOS all had lesions involving the superior precentral gyrus of the insula (SPGI) [4]. The majority of lesions were identified using CT rather than MRI and the patients were assessed a minimum of one year following stroke. Ogar et al overlapped reconstructed templates of CT/MRI images of 18 patients with AOS and found that all patients with AOS had lesions that involved the SPGI while eight patients without AOS had lesions involving much of the left hemisphere excluding the SPGI [32]. Both CT and MRI were used to localise the lesions, and patients were assessed several years following stroke. Over half of the patients in Ogar's study had also been in Dronker's original study, thus it is not

surprising that both reported similar results. Conversely, Hillis' study of 80 patients with acute left hemisphere stroke, 40 with and 40 without insula damage, did not find a significant association between lesions involving the left insula and AOS, but did find an association between lesions in Broca's area and AOS. However, there were five patients with AOS who did not have lesions in Broca's area as well as four patients with lesions in Broca's area without AOS. Thus, similarly to our results, there was no single area that was always involved in patients with AOS [33].

One of the reasons for the differing results of the above studies is likely to be related to the timing of assessment after stroke. Ogar [32] and Dronkers [4] both assessed patients several years after stroke; in addition, the CT or MRI images were often obtained a similarly long time after the stroke. This means that the speech deficit the patients had when assessed had probably changed significantly from the time of the acute event, as had the imaging findings. In addition, brain reorganisation may well have occurred during rehabilitation so the residual deficit may not reflect accurately an insult to the region identified [146].

Our study, and that of Hillis [33], assessed patients in the acute period after stroke. Thus it may be more likely that the clinical deficit more accurately reflects damage to the region identified, although it is possible that some of the clinical deficit may occur as a result of diaschisis rather than due to the area of infarction [63]. However, Hillis found an association between AOS and Broca's area, while we did not demonstrate significant lesion overlap in that area.

Single case reports and small series have also described patients with AOS and lesions in a variety of brain regions including the middle third of the left inferior frontal gyrus [147], the left face representation of the primary motor cortex at the depth of the central sulcus [136] and the precentral gyrus [9]. One familial left-handed patient with AOS had a lesion in the right precentral gyrus and the underlying deep white matter [44]. Ogar found that patients with moderate or severe AOS had lesions involving Broca's area, basal ganglia, external and internal capsules as well as the SPGI [32].

It is somewhat difficult to make comparisons between studies due to the variability in diagnostic criteria, timing of assessment, imaging parameters and methods of localisation used. In addition, most of the areas proposed to be responsible are within the arterial territory of the left middle cerebral artery which makes it difficult to separate the functions of the different areas. It is possible that hypoperfusion within this territory may result in transient dysfunction of one area while infarcting another, thus imaging will only show a lesion of the infarcted area even though the clinical deficit may have been caused by dysfunction of the other region. However, the brain regions we found to be involved in patients with AOS have all been described individually in other studies.

Several groups have studied normal controls rather than patients with stroke to attempt to determine the function of specific regions. Moser performed an fMRI study of normal controls and showed that an extensive network of brain regions including the left anterior insula and inferior frontal gyrus were activated when producing novel syllables, suggesting that these two areas are highly interactive, particularly when the

speech motor system is being taxed [148]. Wise used PET scanning in normal controls to demonstrate that the formulation of an articulatory plan was a function of the left anterior insula and that there was no activation of Broca's area during the speech task [135].

Conversely, Bonilha used fMRI to study 18 normal controls, comparing speech and non-speech oral movements, and found that speech movements did not recruit the insula but rather activated the left inferior frontal gyrus [60]. Similarly, patients with lesions in Broca's area have been shown to be impaired in sequencing pictures representing actions, suggesting that Broca's area has a specific role in sequencing [149].

Although most authors have focused their attention on cortical areas in their study of AOS, there is some evidence that basal ganglia and subcortical structures may also be involved in speech motor programming. Parallel pathways connecting frontal cortex with the striatum and elsewhere are concerned with planning and limb and eye movements. Much of the frontal cortex and thus the basal ganglia are concerned with organisation of movement. A review of basal ganglia lesions and apraxia found that isolated basal ganglia lesions including those of the putamen could cause apraxia (although most also involved peristriatal white matter), unfortunately in most cases the focus was on limb or orofacial apraxia and speech was often not mentioned [150].

In addition, the left caudate has been implicated in AOS in a study of a family with an inherited form of AOS. Volumetric and functional studies of affected family members demonstrated significantly less grey matter as well as overactivation in the left

caudate compared to unaffected family members and normal controls: these patients had orofacial as well as speech apraxia [142].

Subcortical aphasic syndromes, in contrast to the well known cortical syndromes, are described by the lesion location. Examples include thalamic aphasia and capsular-putaminal aphasia. Thalamic aphasia is fluent with relatively preserved repetition and semantic paraphrasias; associated memory deficits are common. Capsular-putaminal aphasia includes patients with good comprehension and slow but grammatical dysarthric speech, patients with poor comprehension and fluent Wernicke-type speech, and patients with global aphasia [151].

The mechanism of aphasia in subcortical stroke is controversial. There are several suggestions: that subcortical structures have a direct role in language [152]; that the deficit results from a diconnection of cortical areas important for language; that aphasia results from a diaschisis of remote cortical areas [153]; or that associated cortical hypoperfusion occurs during the vascular insult resulting in aphasia without infarction [154].

Some of the patients with subcortical aphasia reported in the literature could be interpreted to rather have AOS. Alexander et al examined 19 patients with subcortical aphasia. One patient had very abnormal speech with impairment of articulation, prosody and volume, but only rare paraphrasias. This individual had a lesion involving the putamen, anterior limb and genu of the internal capsule and periventricular white matter. Another patient with a lesion of the anterior superior periventricular white matter had a deficit of speech production with hesitation and

difficulty initiating speech. These two patients certainly have some of the features of AOS [155].

We found that the claustrum was often involved in patients with AOS. The claustrum is a very thin layer of grey matter lying below the insula and above the outer surface of the putamen with the extreme and external capsules on either side. Claustral neurons project to multiple areas of cortex on the same side, as well as some to contralateral cortex. In addition, most areas of cortex send projections to the claustrum. Established interconnections which may be of relevance to its association with AOS are with the motor cortex, prefrontal cortex, parietal cortex and caudate [156]. It is difficult to isolate the exact function of the claustrum as it is supplied by the middle cerebral artery, thus infarcts invariably involve more widespread associated areas. There are few reports in clinical literature of unilateral lesions within the claustrum; however, one study demonstrated absent somatosensory potentials contralateral to the lesioned side, suggesting that the claustrum influences the contralateral somatosensory cortex [157]. It has been postulated that the claustrum is important in the timing of cortical activity, and that it acts to coordinate various different cortical regions to integrate attributes both within and across modalities [156]. Thus it is feasible that this region could be implicated in programming of speech motor control.

The left putamen has been implicated in apraxia, though usually ideational/ideomotor/ orofacial apraxia rather than AOS and usually lesions involve periventricular white matter as well as the putamen [150]. A report of a patient with AOS documented subcortical haemorrhage involving left basal ganglia extending into the frontal white

matter [46]. The putamen has also been implicated in speech motor control, with one fMRI study of normal controls showing increased activation in bilateral putamina [158], another showing increased activation in the left putamen [159].

An fMRI study of normal controls producing paced syllables suggested that there were two separate networks involved in speech motor control: one for motor preparation including the supplementary motor area, dorsolateral frontal cortex including Broca's area, anterior insula and superior cerebellum, and one for motor execution including sensorimotor cortex, basal ganglia, thalamus and inferior cerebellum [158].

Given our findings and the results of prior studies all documenting multiple left-sided brain regions being implicated in AOS, it seems likely that there is no single brain region that contains a "motor speech programmer". Instead, AOS may occur as a result of disconnection of functionally related areas. Thus, damage anywhere within this network may result in AOS. This disconnection theory could explain why rapid recovery has been documented in patients with AOS; a disconnection may be more amenable to recovery/reorganisation than infarction of a vital "speech praxis" area.

5.4.2 Lesion volume in AOS

Patients with AOS had significantly larger lesion volumes than those without AOS. Lesion volume as well as hemisphere predicted the presence of AOS. In addition, increasing lesion volume was associated with increasing severity of AOS.

We demonstrated the reliability of the stereological methods using several intra- and inter- rater repeatability studies. These included the ICC which, at 0.99 for both intra- and inter- rater reliability, is considered excellent [113]. Percentage differences of 1.5% for intra-rater and 5.6% for inter-rater agreement are comparable to those demonstrated in published studies of MRI lesion volume estimation [160]. In addition, Bland and Altman plots showed a lack of significant bias between measurements for intra- and inter-rater measurements. Although some of the lesions were small (smallest lesion 0.55 cm^3) and thus may be expected to have a higher coefficient of error than larger lesions, previous studies have shown the technique used to be reliable for estimating volumes even of small lesions such as pituitary glands (mean 0.582 cm^3) [112]. Thus the results of volume measurements we obtained are considered reliable.

Only one study to date has investigated the association between AOS and lesion volume, examining 18 patients with AOS and eight without AOS at least one year after stroke [32]. The average time post onset was six years for those with AOS and two and a half years for those without AOS. In this study either CT or MRI was used and the lesions reconstructed onto templates. The reconstructions were then entered onto a computer for lesion overlapping. The manual transfer of lesions from a scan onto a template introduces the possibility of bias; in addition, CT and MRI are not comparable for detailed identification of brain areas. In particular, CT may not identify smaller areas of infarction which may be relevant to clinical deficits. This study did not describe the method by which lesion volume was estimated in their patients; it also did not document any reliability results for volume estimation.

Despite this, the authors found, similar to our results, that patients with AOS had larger lesions than those without (141.5cc, range 33-261cc versus 68.3cc, range 7.4-166.5cc). These volumes are larger than that documented in our patient group: this is likely to be due to the difference in timing of assessment. Our patients were assessed in the early post stroke period and patients with very large left hemisphere strokes were unable to be assessed due to significant impairment of comprehension.

Ogar demonstrated a significant correlation between lesion volume and AOS severity, r=0.61 [32]. We also found a correlation between lesion volume and AOS severity, with an r of 0.53 for all patients, i.e., right and left hemisphere. When hemisphere, NIHSS and lesion volume were used as variables to predict severity of AOS, r^2 was 0.67, all variables being significant. It is likely that the higher correlation achieved by Ogar is due at least partly to the fact that all patients in her study had left hemisphere stroke, whereas patients with both right and left hemisphere stroke were included in our study. Patients with large right hemisphere lesions (none of whom had AOS) would have reduced the correlation between lesion volume and the presence of AOS in our study. In keeping with this is the higher correlation achieved when lesion hemisphere was used as a variable. Thus our results are consistent with the only previous study of lesion volume in AOS.

It is possible that multiple different brain regions each play a specific role in motor speech programming, and the more regions are damaged (as with larger volume infarcts), the more severe the clinical deficit becomes. It is also possible that co-existing aphasic deficits (as may be seen with larger infarcts) modulate speech production in patients with AOS. Indeed, all patients with AOS had evidence of aphasia, similarly to previous reports [11, 21]. In Ogar's study of 18 patients with

AOS, only two did not have evidence of aphasia [32] and there was an association between the severity of aphasia and that of AOS. In Dronkers' study, only 8% of patients with AOS did not have aphasia compared to 37% of patients with left hemisphere lesions without AOS [4]. As discussed earlier, if AOS occurs as a result of disconnection of functionally related regions, larger infarcts may be more likely to result in AOS by interrupting a greater number of connections.

5.4.3 Strengths and limitations

There are several strengths to this study. Patients were assessed in the acute period, before significant functional adaptation could have occurred and before clinical deficits may have resolved, in contrast to other studies [4, 32]. This study included 18 patients with AOS which compares well with other studies [4, 32, 33]. Reliability measures for inter- and intra-rater variability for lesion volume measurements were very high. The computerised method of image normalisation and lesion overlap removes some of the bias which may occur using manual methods.

There are a number of limitations to this study. We used structural imaging with MRI to determine the lesion location. Thus we cannot outrule the possibility that AOS was due to diaschisis of remote regions rather than infarction of the area identified with MRI; however, this is a limitation common to many studies which have used structural imaging with CT or MRI [4, 32].

We used the ABAII to determine the presence and severity of AOS. To date there is no gold standard diagnostic battery for AOS, and much debate over diagnostic

criteria. However, the ABAII is a standardised tool which has undergone reliability and validity testing and which is often used in practice [131, 132, 161]. Hill demonstrated adequate inter- and intra-rater reliability measures when using the ABAII [131], and several studies have found agreement between experts in classifying patients as having AOS, whether they used a diagnostic battery or not [132, 162]. In these papers, therapists' judgements were based on a checklist of behaviours which are included in the ABAII.

It is worth noting that MRI in some patients demonstrated residual cortical oedema. It is possible that recovery of oedema may be one reason for early improvement in AOS following stroke (although we did not document any patient with marked early improvement in AOS in this study). As imaging was only performed once in most cases, we are unable to say what the effect of resolution of oedema has on AOS recovery.

5.5 Conclusions

In conclusion, we found that AOS only occurred in patients with left hemisphere lesions, the regions of greatest overlap included the left insula, claustrum and putamen; multiple other left-sided regions were involved in individual patients. However, there was not one single brain region that was involved in all patients with AOS. We demonstrated an association between lesion volume and the presence of AOS. In addition, there was an association between AOS severity and lesion volume, as well as with clinical stroke severity. These findings, and in particular the heterogeneity of lesions associated with AOS, give support to the hypothesis that there is a functional network of brain regions involved in motor speech programming. This network is based in the left hemisphere and involves both cortical and subcortical structures. As a result, AOS may occur as a result of damage to many different areas.

Further work is required to establish the precise details of this functional network. However, given the complexity of the integrated networks underlying speech and language, one wonders whether this will ever be possible.

Chapter 6: Linguistic dysprosody following acute ischaemic hemispheral stroke

6.1 Introduction

6.1.1 Hemispheric lateralisation of linguistic prosody

There has been an emphasis on emotional (affective) dysprosody in the literature, most of which implicates damage to the right hemisphere as the cause. Patients have been described with right hemisphere damage (RHD) who developed affective dysprosody in spoken language [64, 75, 77]. In addition, RHD patients have been described with "receptive" or "sensory" affective dysprosody (difficulty comprehending spoken emotional tone in others) [75, 77, 78].

As discussed in more detail in Chapter 1, hemispheric lateralisation of linguistic prosody remains unclear. It is clear when reviewing the prosody literature that most research has focused on the right hemisphere. However, impaired perception of linguistic prosody has been documented in patients with RHD [72, 73], in patients with left hemisphere damage (LHD) [74], and in patients with either left or right hemisphere damage [78, 79]. In addition, studies of normal control individuals have also demonstrated a role for the right hemisphere [71], the left hemisphere [76] and both hemispheres [80-82].

6.1.2 Prosody in AOS

Speech is clearly dysprosodic in patients with AOS. Features include a tendency toward equal stress on each syllable with inappropriate inter-syllabic pauses. Intonational and loudness contours are altered with a restricted range of fundamental frequency (*f*o). Patients exhibit effortful, groping, repetitive attempts to produce sounds correctly; this is most obvious at the initiation of an utterance, being displayed as false starts. Rate of speech is slowed overall, due to articulatory prolongation and syllable segregation [6, 7, 11, 24]. In AOS, the rate of speech is slower than normal, even when production is free of errors. Microsegmental rate is also reduced (transition from one movement to the next, interword intervals) and errors increase when syllables are stressed or strung together in a word or sentence [163].

A study of one patient with mild and one patient with moderate AOS found that both subjects were unable to produce significant differences in acoustic cues corresponding to differing emotional intentions. The authors attributed this deficit as being due to the groping, inter-syllable pauses and word inititation difficulties (all intrinsic features of AOS) which disrupted the subjects' ability to produce variations in *f*o, duration and amplitude. The severity of AOS did not appear to impact on the ability to produce emotional prosody [89].

A study comparing prosody production in patients with AOS compared to conduction aphasic, ataxic dysarthric and normal controls found that those with AOS had the highest rate of errors of syllabic stress, spoke at a slower rate, had a larger number of prolonged consonants and vowels, demonstrated difficulty with smooth sound-to-

sound movements, misarticulated vowels especially when associated with a consonant and exhibited inaccurate vowel production more often in the initial position [93]. Another study of patients with either AOS or conduction aphasia demonstrated that the group with AOS had significantly greater dysprosody despite both groups struggling to correct their errors [164].

The facts that patients with conduction aphasia and dysarthria do attempt to correct their speech errors [93, 164], and that patients with severe AOS can still produce emotional prosody [89], suggest that it is not simply the effort put into attempting correct speech that causes dysprosody in AOS.

As, traditionally, prosody had been thought of as a right hemisphere function and AOS due to left hemisphere dysfunction, it had been proposed that dysprosody occurred in AOS due to compensatory mechanisms employed by patients with AOS [11]. In fact, Darley's original definition implied this [19]. Wertz, Rosenbek and LaPointe suggested that dysprosody in AOS may be due to compensatory mechanisms as well as from the motor deficit itself [24].

Boutsen and Christmas, in their review of prosody in AOS, separate prosody into intrinsic and extrinsic forms. They include within intrinsic prosody timing, pauses, voice onset time and production of transients and suggest that the left hemisphere-basal ganglia-cerebellum complex is involved in this area of speech programming. Extrinsic prosody, on the other hand, refers to conscious expression of mood and communicative intent and is driven by the right hemisphere [163].

However, most of the literature regarding prosody in AOS has focused on production rather than comprehension of prosody. The literature on perception of linguistic prosody is unclear with regard to lateralisation. Many authors suggest that the right hemisphere mediates comprehension of linguistic prosody [71-73]. If, then, linguistic dysprosody in AOS occurs as a result of compensatory mechanisms and is mediated by the right hemisphere, one would expect that receptive prosody should be unaffected in patients with AOS. However, some authors have demonstrated impaired comprehension of linguistic prosody in patients with left hemisphere lesions [74], and others have demonstrated impaired comprehension of linguistic prosody in patients with either right or left hemisphere lesions [78, 79].

The uncertainty in the literature may be due to methodological differences between studies. For example, subjects have not always been examined using the same tasks. In addition, the nature of stimuli presented has often differed, and the extent to which linguistic processing is required varied. Some investigators have used natural, well-formed, semantically correct utterances; others have attempted to remove the semantic content and isolate the intonational contour by digitally altering utterances or by using nonsense utterances.

In order to further understand how linguistic prosody is processed in patients with hemispheral damage due to stroke, we used some of the tasks used previously in patients with both right and left hemisphere lesions as well as normal controls. We focused only on comprehension of linguistic prosody as abnormal expression of prosody would have been more difficult to distinguish from difficulties due to dysarthria, aphasia and apraxia. We separated assessment of linguistic prosody into

discrimination (same or different) and identification (question or statement) as some studies have used only one or the other method and there may be differences between the two.

6.2 Specific aims

The specific aims for this study were to determine the frequency of receptive linguistic dysprosody and its natural history following acute ischaemic hemispheral stroke; to determine the association between AOS and impaired perception of linguistic prosody; and to determine the neuroanatomic substrate for receptive linguistic dysprosody (for identification and discrimination) in patients following acute ischaemic hemispheral stroke.

6.3 Results

6.3.1 Linguistic prosody scores in normal controls

Nine controls were recruited. They scored mean 9.6 ± 1.7 for identification and 10.3 ± 0.9 for discrimination (out of a total score of 12) (Table 6.1). Thus, lower limit of normal for identification was 6.2/12 and 8.5/12 for discrimination (using 2 standard deviations below the control mean as the lower limit of normal).

6.3.2 Linguistic prosody scores in patients following acute ischaemic hemispheral stroke

In total, during the course of the study, 26 patients showed evidence of linguistic dysprosody for either identification or discrimination or both (26/45, 57.8%, Table 6.2). Five patients (all with left hemisphere stroke) were unable to be assessed due to significant comprehension difficulties.

Seven patients had linguistic dysprosody only for identification, all had left hemisphere stroke. Eight patients had linguistic dysprosody only for discrimination, all had right hemisphere stroke. Ten patients had linguistic dysprosody for both identification and discrimination, all had left hemisphere stroke. Twenty had no evidence of linguistic dysprosody, seven with right and 13 with left hemisphere stroke (Figure 6.1 and Table 6.2).

Accuracy scores for assessment at the three different time points, both raw data and percentage correct, are presented in tables 6.1, 6.3, 6.4.

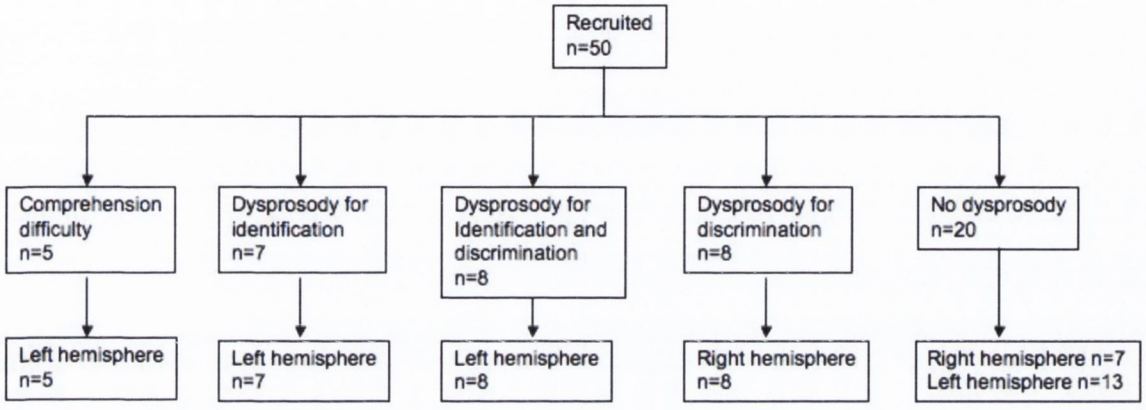


Figure 6.1: Flow chart demonstrating patients with linguistic dysprosody

Tables 6.1A and B: Mean accuracy and percentage correct by group on linguistic identification and discrimination tasks at first assessment

	n	Identification correct/12 ± sd	Identification % correct	Discrimination correct/12 ± sd	Discrimination % correct
Controls	9	9.6 ± 1.7	80.0	10.3 ±0.9	85.8
All patients	39	8.3 ± 2.7 p=0.2	69.2	8.4 ± 2.9 p=0.6	70.0
AOS	13	6.7 ±3.4 p=0.03	55.8	7.2 ± 3.6 p=0.02	60.0
No AOS	26	9.1 ± 1.8 p=0.5	75.8	9.0 ± 2.4 p=0.1	75.0

	n	Identification correct/12 ± sd	Identification % correct	Discrimination correct/12 ± sd	Discrimination % correct
Controls	9	9.6 ± 1.7	80.0	10.3 ±0.9	85.8
RHD	14	9.6 ± 1.1 p=1	80.0	8.4 ± 2.5 p=0.04	70.0
LHD	25	7.6 ± 3.1 p=0.07	63.3	8.4 ±3.2 p=0.09	70.0

sd=standard deviation; RHD=right hemisphere damaged; LHD=left hemisphere damaged; AOS=apraxia of speech; p=difference from controls

Table 6.2: Linguistic dysprosody: number of patients affected by hemisphere

	Unable to be assessed n=5	Dysprosody for Identification n=7	Dysprosody for Discrimination n=8	Dysprosody for Identification and Discrimination n=10	No Linguisti Dysprosod n=20
Right hemisphere n=15	0	0	8	0	7
Left hemisphere n=35	5	7	0	10	13

Tables 6.3 A and B: Mean accuracy and percentage correct by group on linguistic identification and discrimination tasks at second assessment

	n	Identification correct/12 ± sd	Identification % correct	Discrimination correct/12 ± sd	Discrimination % correct
Controls	9	9.6 ± 1.7	80.0	10.3 ±0.9	85.8
All patients	37	8.5 ± 2.4 p=0.2	70.8	9.1 ± 2.9 p=0.2	75.8
AOS	12	6.5 ± 3.3 p=0.02	54.2	7.3 ± 3.7 p=0.03	60.8
No AOS	24	9.4 ± 1.0 p=0.7	78.3	9.7 ± 2.1 p=0.4	80.8

	n	Identification correct/12 ± sd	Identification % correct	Discrimination correct/12 ± sd	Discrimination % correct
Controls	9	9.6 ± 1.7	80.0	10.3 ±0.9	85.8
RHD	13	9.6 ± 1.0 p=1	80.0	9.0 ± 2.1 p=0.1	75.0
LHD	25	7.9 ± 2.7 p=0.09	65.8	8.8 ± 3.3 p=0.2	73.3

sd=standard deviation; RHD=right hemisphere damaged; LHD=left hemisphere damaged; AOS=apraxia of speech; p=difference from controls

Tables 6.4 A and B: Mean accuracy and percentage correct by group on linguistic identification and discrimination tasks at final assessment

	n	Identification correct/12 ± sd	Identification % correct	Discrimination correct/12 ± sd	Discrimination % correct
Controls	9	9.6 ± 1.7	80.0	10.3 ±0.9	85.8
All patients	38	9.0 ± 1.6 p=0.3	75.0	8.9 ± 2.7 p=0.1	74.2
AOS	13	8.8 ± 2.0 p=0.3	73.3	7.9 ± 2.8 p=0.02	65.8
No AOS	20	9.1 ± 1.4 p=0.4	75.8	9.5 ± 2.5 p=0.4	79.2

	n	Identification correct/12 ± sd	Identification % correct	Discrimination correct/12 ± sd	Discrimination % correct
Controls	9	9.6 ± 1.7	80.0	10.3 ±0.9	85.8
RHD	11	9.2 ± 0.4 p=0.5	76.7	9.2 ± 2.4 p=0.2	76.7
LHD	25	8.9 ± 1.8 p=0.3	74.2	9.1 ± 2.8 p=0.2	75.8

sd=standard deviation; RHD=right hemisphere damaged; LHD=left hemisphere damaged; AOS=apraxia of speech; p=difference from controls

6.3.3 Linguistic dysprosody for identification: change over time

There was a significant difference between linguistic prosodic identification in patients with AOS, who scored 55.8% and 54.2% at the first and second assessments respectively, compared to controls who scored 80% (Table 6.1A, $p \leq 0.03$). By the time of the final assessment, scores for this group of patients had improved and there was no significant difference between patients and controls.

There was a significant difference between linguistic prosodic identification in patients with left hemisphere stroke, who scored 63.3% and 65.8% at the first and second assessments respectively compared to 80% in controls (Table 6.1B, $p=0.02$). By the final assessment, scores for this group of patients had improved and there was no significant difference between patients and controls.

Although mean scores in patient subgroups improved over time, the number of individuals with linguistic dysprosody for identification did not change significantly over time. Ten patients at the first, 9 patients at the second and 9 patients at the third assessments had linguistic dysprosody for identification.

6.3.4 Linguistic dysprosody for discrimination: change over time

There was a significant difference between linguistic prosodic discrimination in patients with AOS and in patients with right hemisphere stroke compared to controls at the first assessment (Table 6.1, $p \leq 0.04$). By the second assessment, mean scores had improved in patients with right hemisphere stroke. At the final assessment, there

remained a significant difference between patients with AOS compared to controls (p=0.02).

Although mean scores in patient subgroups improved over time, the number of individuals with linguistic dysprosody for discrimination did not change significantly over time. Eleven patients at the first, 9 patients at the second and seven patients at the third assessments had linguistic dysprosody for discrimination.

6.3.5 Association between linguistic dysprosody and AOS

Identification

There was a significant difference in the number of patients with AOS who had evidence of linguistic dysprosody for identification compared to patients who did not have AOS (12/18 versus 5/27; χ^2=10.7, p=0.001) (Table 6.5).

Discrimination

There was no significant difference in the number of patients with AOS who had evidence of linguistic dysprosody for discrimination compared to patients who did not have AOS (9/18 versus 9/27; χ^2=1.3, p=0.3)(Table 6.6).

Table 6.5: Association between linguistic dysprosody for identification and AOS

	Linguistic dysprosody for identification	No Linguistic dysprosody for identification
AOS n=18	12	6
No AOS n=27	5	22

χ^2=10.7, p=0.001

Table 6.6: Association between linguistic dysprosody for discrimination and AOS

	Dysprosody for Discrimination	No Dysprosody for Discrimination
AOS n=18	9	9
No AOS n=27	9	18

χ^2=1.3, p=0.3

6.3.6 Association between linguistic dysprosody and hemisphere

Identification

Overall, seven patients had evidence of linguistic dysprosody for identification alone and 10 had evidence of linguistic dysprosody for both identification and discrimination (Table 6.2). All these 17 patients had left hemisphere stroke (Figure 6.1,).

There was a significant difference in linguistic dysprosody for identification between patients with right versus left hemisphere stroke (Fisher's exact test, p=0.0002). No patients with RHD had linguistic dysprosody for identification, whereas a large proportion of patients (17/30, 56.7%) with LHD did (Table 6.7).

Table 6.7: Association between linguistic dysprosody for identification and hemisphere

	Linguistic dysprosody for identification	No linguistic dysprosody for identification
LHD n=30	17	13
RHD n=15	0	15

Fisher's exact test, p=0.0002

Discrimination

Overall, eight patients had evidence of linguistic dysprosody for discrimination alone and 10 had evidence of linguistic dysprosody for both identification and discrimination (Table 6.2). The eight patients with linguistic dysprosody for discrimination alone all had right hemisphere stroke while the 10 patients with linguistic dysprosody for both discrimination and identification had left hemisphere stroke (Figure 6.1).

There was no significant difference in the frequency of linguistic dysprosody for discrimination between patients with RHD versus those with LHD (χ^2=1.7, p=0.2; Table 6.8).

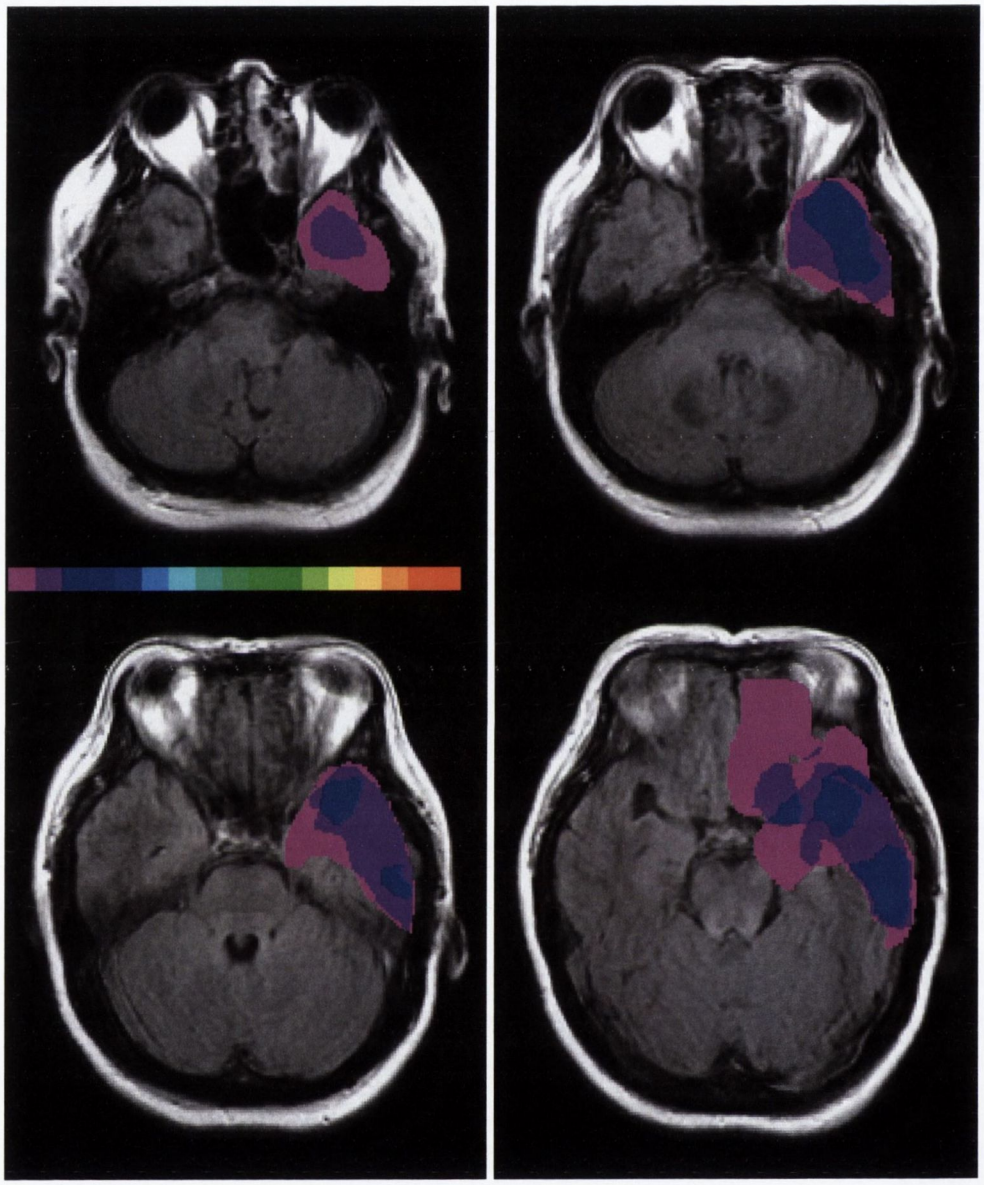
Table 6.8: Association between linguistic dysprosody for discrimination and hemisphere

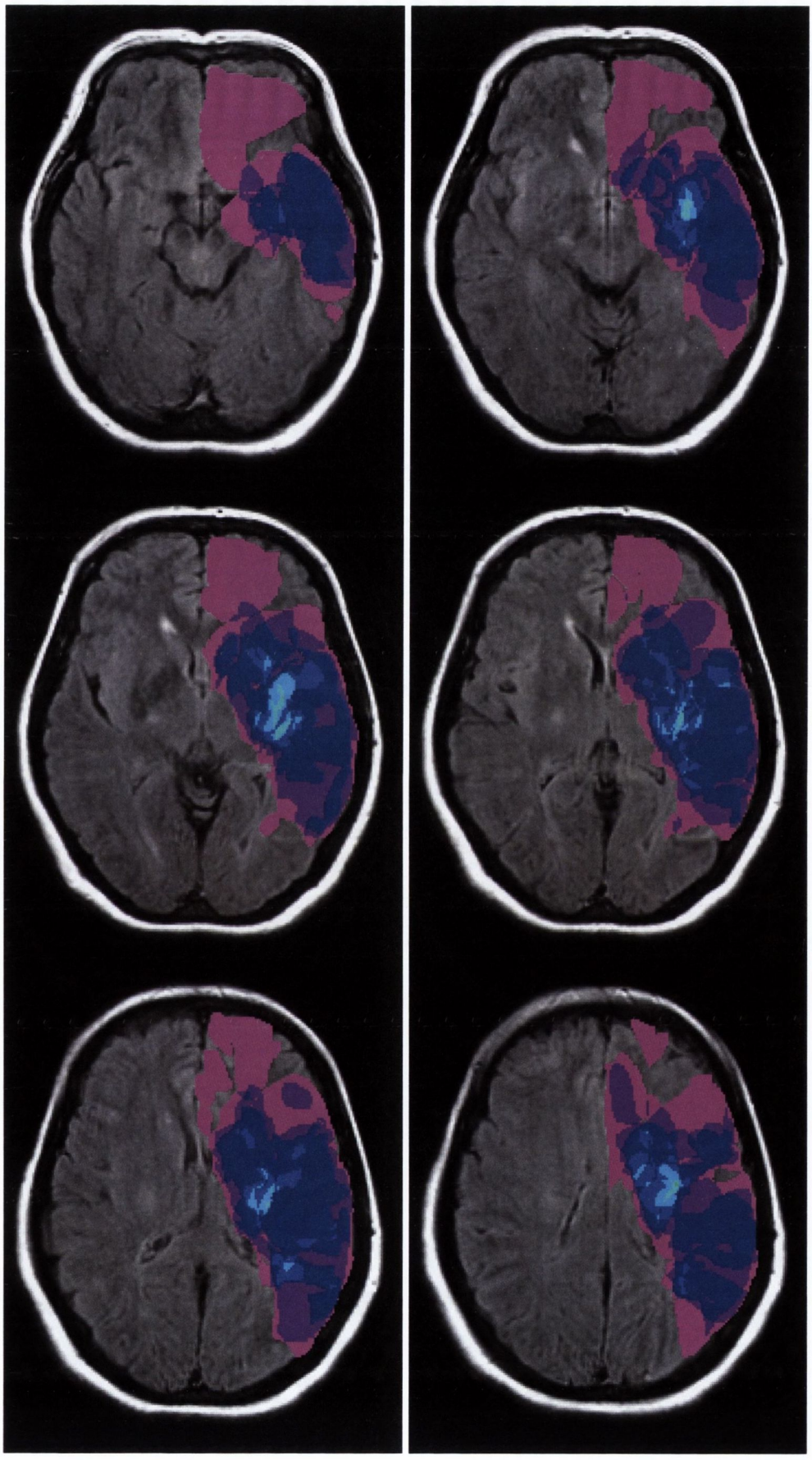
	Linguistic dysprosody for discrimination	**No linguistic dysprosody for discrimination**
LHD n=30	10	20
RHD n=15	8	7

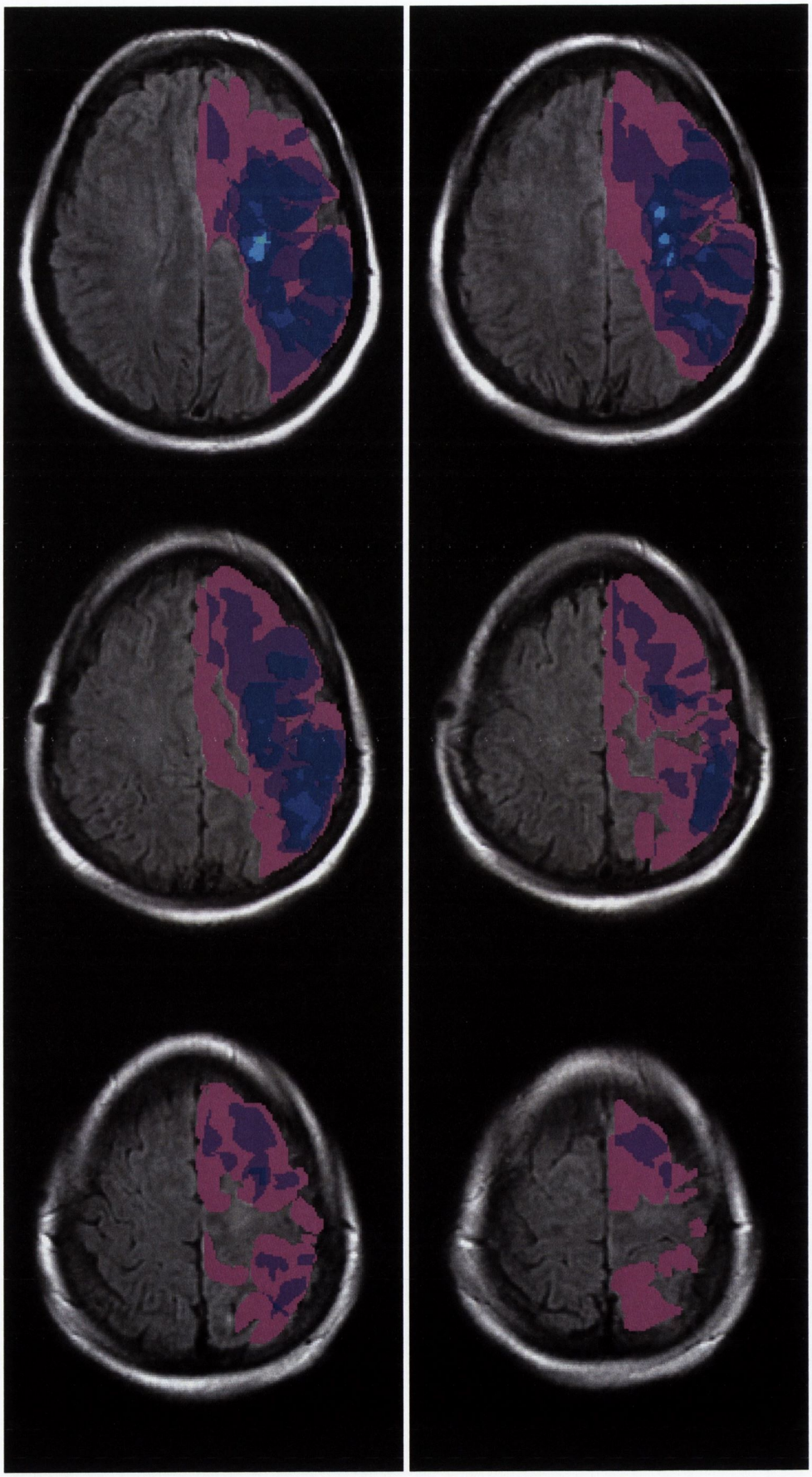
RHD=right hemisphere damage; LHD=left hemisphere damage

χ^2=1.7, p=0.2

6.3.7 Lesion location in patients with linguistic dysprosody for identification







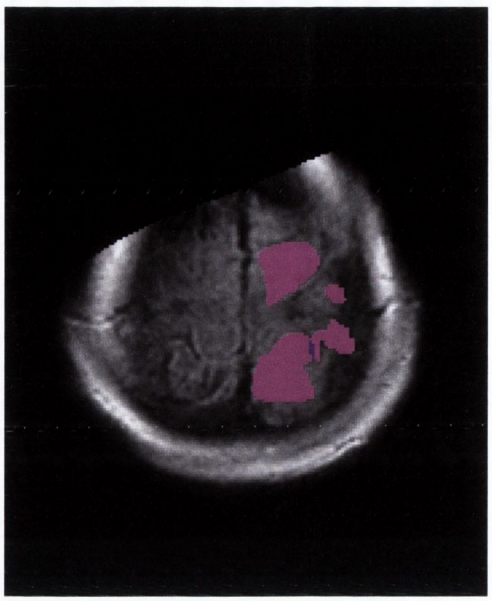
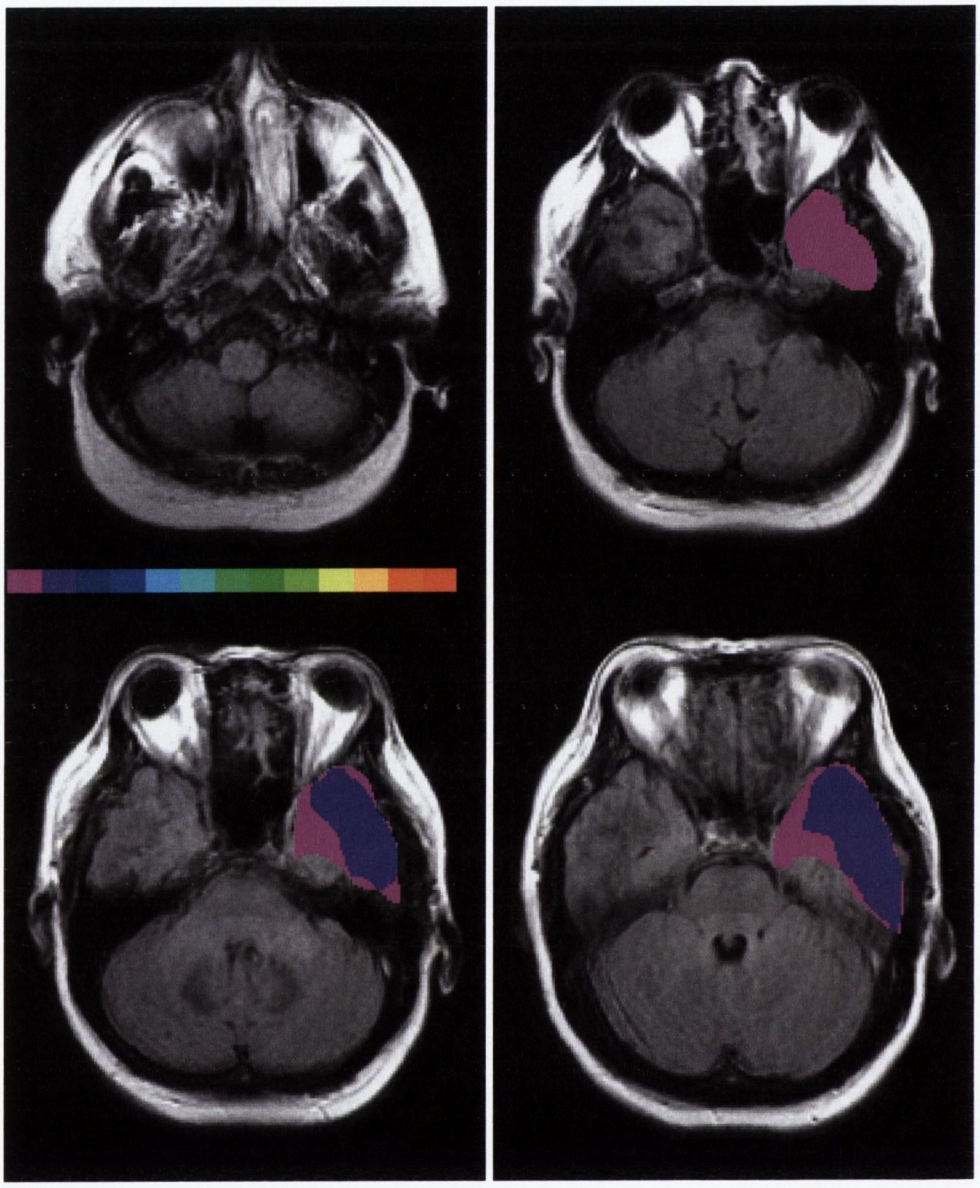
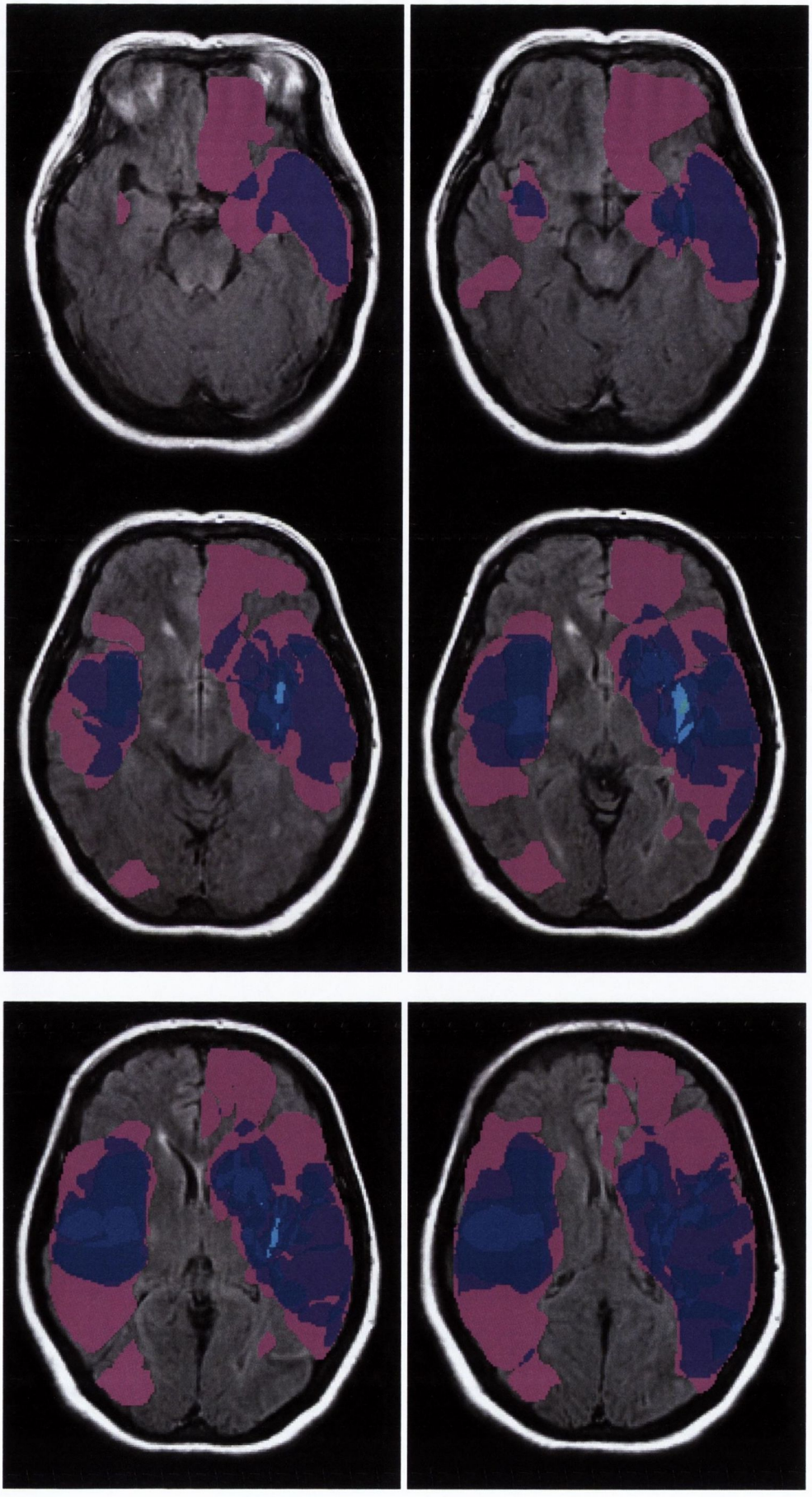


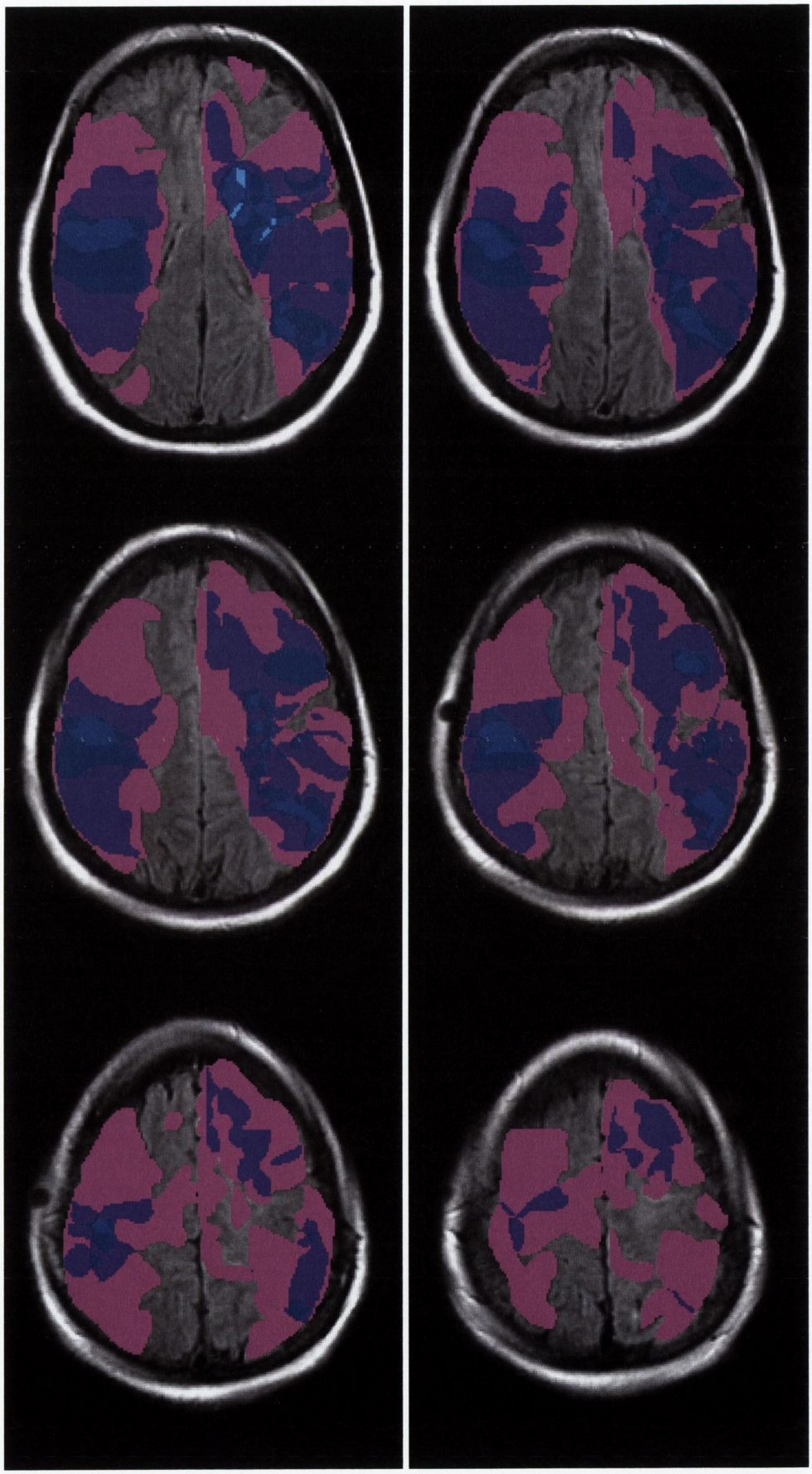
Figure 6.2: Overlay of ROIs of all patients with linguistic dysprosody for identification. The colour bar underneath the first slice indicates the ROI density (dark violet for a single ROI, bright red for overlapping of all ROIs)

Lesion overlap demonstrates that only patients with left hemisphere stroke showed evidence of linguistic dysprosody for identification. As demonstrated in figure 6.1 above, almost every region within the left hemisphere was involved; however, there was no single region which was involved in every patient.

6.3.8 Lesion location in patients with linguistic dysprosody for discrimination







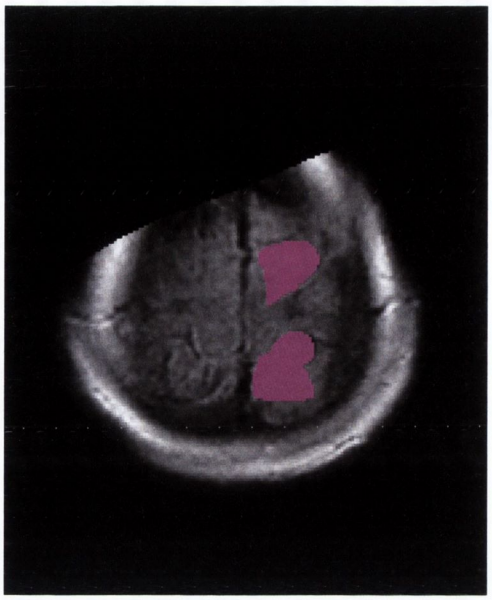


Figure 6.3: Overlay of ROIs of all patients with linguistic dysprosody for discrimination. The colour bar underneath the first slice indicates the ROI density (dark violet for a single ROI, bright red for overlapping of all ROIs)

Lesion overlap demonstrates that patients with evidence of linguistic dysprosody for discrimination had stroke in either right or left hemisphere, and most areas of both hemispheres were involved. There was no single brain region which was involved in every patient.

When the MASK command was used to determine whether there was any brain region that was always involved in linguistic dysprosody (either for identification or discrimination) and never in patients without linguistic dysprosody, no region was identified.

6.4 Discussion

This study investigated the frequency and natural history of linguistic dysprosody following acute ischaemic hemispheral stroke; how unilateral brain damage affected linguistic prosodic comprehension; and whether there was an association between AOS and linguistic dysprosody. It also investigated lesion location in patients with receptive linguistic dysprosody.

6.4.1 Frequency and natural history

Linguistic dysprosody occurred frequently following acute ischaemic hemispheral stroke, affecting 57.8% of patients overall. Although patient subgroups mean prosody scores improved over time, relatively few individuals with linguistic dysprosody recovered over a six-month follow-up period. This incidence seems high, but no other studies have systematically examined the frequency or natural history of dysprosody (linguistic or otherwise) following stroke. In addition, the total number of patients assessed was relatively modest, therefore this frequency may over- or under-estimate the actual rate.

A possible confounding factor is that people become more familiar with an accent over time, however, there was very little change in mean scores between the first and second assessments (Tables 6.1, 6.3) so it seems unlikely that gaining familiarity with the accent made a significant difference in this study. In addition, we used a speaker from Dublin to create the prosodic tests. Since most patients recruited were from the

catchment area of the hospital, which is within Dublin, one would not expect them to have any difficulty understanding a Dublin accent.

6.4.2 Linguistic Dysprosody for Identification

On identification tasks, when compared to normal subjects, the subgroups of patients with AOS and those with left hemisphere strokes were significantly impaired in their ability to recognise intonational meanings in the early post-stroke period.

When comparing the absolute number of patients with linguistic dysprosody, we demonstrated that patients with left hemisphere stroke were significantly more likely to have evidence of linguistic dysprosody for identification compared with those with right hemisphere stroke. Similarly, patients with AOS were significantly more likely to have evidence of linguistic dysprosody for identification compared to those without AOS.

It is perhaps not surprising that the results between the group with left hemisphere stroke and the group with AOS are similar, given that all patients with AOS had left hemisphere strokes. Nevertheless, there remained a significant association between AOS and linguistic dysprosody when the groups were controlled for hemisphere.

Our findings that patients with left hemisphere stroke performed significantly worse than those with right hemisphere stroke on tests of linguistic prosody for identification are in keeping with some reports in the literature [79]. It is notable that the patients with right hemisphere stroke performed as well as controls in this task.

Similarly, Hughes found no significant difference between patients with right hemisphere damage and normal controls in the identification of linguistic prosody; however, patients with left hemisphere damage were not assessed [77].

Our results are in contrast to Heilman's paper; however, the methodology is likely to account for the difference in outcome. Heilman found that patients with right hemisphere damage had impaired comprehension of linguistic prosody compared to controls and found no difference between patients with left and right hemisphere lesions, i.e., both hemisphere damaged groups were similarly impaired in comprehending linguistic prosody [78]. However, the test stimuli in this study were digitally altered sentences so that the words were unintelligible, thus the test could be considered to be assessing comprehension of tonal changes rather than true linguistic prosody.

The fact that patients with left hemisphere stroke performed worse than those with right hemisphere stroke on tests of comprehension of linguistic identification (indeed, no patient with right hemisphere stroke had significant difficulty with this task) suggests that this aspect of prosodic processing is lateralised to the left hemisphere.

A study by Wood using auditory evoked potentials in normal subjects found that neural responses occurred in the left hemisphere during analysis of linguistic versus non-linguistic parameters of the same acoustic signal [68]. Although the methods used differ to those in the current study, the results again support left hemisphere lateralisation of linguistic prosodic processing.

6.4.3 Linguistic Dysprosody for Discrimination

There was a significant difference in mean scores between controls and patients with AOS and those with right hemisphere stroke on discrimination tasks in the early post-stroke stage.

However, it appears when comparing patients with left and right hemisphere strokes that there was no significant difference between the groups in terms of the number of patients who demonstrated linguistic dysprosody for discrimination. Thus, lesions in either hemisphere may adversely affect linguistic prosodic discrimination. This implies that cooperation between the hemispheres is required for intact linguistic prosodic processing for discrimination tasks.

It is interesting, however, that the eight patients with linguistic dysprosody for *discrimination only* all had right hemisphere stroke. Although 10 patients with left hemisphere stroke had evidence of linguistic dysprosody for discrimination as well, these patients also had evidence of linguistic dysprosody for identification (i.e., had a more diffuse linguistic prosody impairment).

Again, the literature is sparse with regard to linguistic discrimination tasks. Pell and Baum found that patients with both right or left hemisphere damage performed more slowly than controls in discrimination tasks but that accuracy was not affected. The methods used were similar to those in the current study, using semantically well-formed stimuli [79]. Two further studies investigated linguistic discrimination tasks, one in a single patient, the other in 9 patients all with right hemisphere stroke. Both

found that patients with right hemisphere lesions were impaired compared to normal controls; however, no patients with left hemisphere damage were studied [72, 73].

6.4.4 Lesion location in patients with linguistic dysprosody

We demonstrated that all patients with linguistic dysprosody for identification had left hemisphere strokes, whereas patients with linguistic dysprosody for discrimination had either right or left hemisphere strokes. Lesions ranged from small subcortical infarcts to large infarcts involving cortex and subcortex. There was no single brain region which was always involved for either type of linguistic dysprosody.

These results support the literature suggesting a role for the left hemisphere in identification [76, 79] as well as that suggesting a role for both hemispheres in discrimination tasks [72]. Other studies have not always distinguished between identification and discrimination tasks thus direct comparison between different studies is not always possible.

Since we did not specifically assess patients' production of linguistic prosody we cannot determine whether perception and production of linguistic prosody are associated. It is possible, for example, that production of linguistic prosody may become impaired as a result of an inability to perceive linguistic prosody. Alternatively perception and production of linguistic prosody may be independent and thus a patient with difficulty perceiving linguistic prosody may still be able to produce prosodic speech and *vice versa*. Aziz-Zadeh *et al* demonstrated that similar brain regions were activated during production and perception of linguistic prosody in

normal controls (left inferior frontal gyrus) [165]. Another study, however, demonstrated that patients with both right and left hemisphere lesions produced linguistically dysprosodic speech but listeners had the most difficulty interpreting the productions of the right hemisphere group [166].

6.5 Conclusion

In conclusion, the results of this study suggest that receptive linguistic dysprosody occurs frequently following acute ischaemic hemispheral stroke and often persists at six-month follow-up. Contrary to some reports, linguistic prosodic (suprasegmental) information is not processed by the right hemisphere in isolation. In fact, linguistic identification tasks appear to be predominantly mediated by the left hemisphere while linguistic discrimination tasks require both hemispheres to work in cooperation. Identification tasks may require more complex linguistic processing than discrimination tasks which may be a possible explanation for the left lateralisation of these processes.

The heterogeneity of lesions resulting in receptive linguistic dysprosody in this study suggests that there is not a single brain region, or even a single hemisphere, responsible for linguistic prosodic processing. It is more likely that a complex network involving both hemispheres exists and, depending on lesion site, processing of linguistic prosody for either identification, discrimination or both may be affected.

These results suggest that a dynamic interaction must occur between the two hemispheres for the correct processing of linguistic prosody in spoken language.

Chapter 7: Conclusions and suggestions for future work

The main hypothesis underlying this thesis was that AOS is more common following stroke than previously thought; that as an apraxia it is largely due to disrupted functional anatomic connections and thus is amenable to rapid recovery; that such recovery is also common; and in part this may be the explanation for rapid recovery of speech in the early stages of stroke in some cases.

In order to test this hypothesis, I documented the prevalence and natural history of AOS by assessing 50 patients using the ABA II at three time points following acute ischaemic hemispheral stroke; I determined whether the PAL word/non-word repetition test was useful in the assessment of patients with AOS; and determined the neuroanatomic substrate of AOS using MRI and lesion overlap techniques. In addition, I documented the prevalence and natural history of receptive linguistic dysprosody following acute ischaemic hemispheral stroke, its association with AOS and its neuroanatomic substrate.

7.1 Frequency and natural history of AOS following acute ischaemic hemispheral stroke, its association with OFA and use of the PAL subtest 7 in AOS

In Chapter 4, I demonstrated that AOS occurred frequently following acute ischaemic hemispheral stroke: 40% of patients who could be tested had evidence of AOS. This prevalence is much higher than has been suggested by prior studies; however, there have been very few studies of speech and language deficits in acute stroke. Those that exist have focused on aphasia rather than AOS [123], or have selected patients with stroke in specific locations [33]. Similarly, series of patients attending speech and language rehabilitation have documented a low proportion of patients having AOS compared to aphasia [11, 48]. Thus, this study is the first to determine the frequency of AOS in a group of patients at an early time point following acute ischaemic hemispheral stroke, and supports the hypothesis that AOS occurs frequently following ischaemic stroke.

Although there was improvement in the severity of AOS with time in the majority of cases, there was no evidence of rapid early recovery. Several authors have documented rapid early recovery of AOS in the days following acute stroke. Patients have been described who were almost mute at symptom onset and who recovered normal speech within hours to days [45, 51]. We witnessed an improvement in AOS severity in three patients in the first week following stroke; however, the improvement was only modest. Initial AOS severity predicted the final outcome with regard to AOS. Only three of 15 patients with AOS following stroke had normal

speech at six months. Thus, the results of this study do not support the hypothesis that AOS recovers rapidly following stroke.

There was a significant association between AOS and OFA, all patients with OFA showing evidence of AOS, but five patients with AOS had no evidence of OFA. Thus, these results suggest that AOS does not occur as the result of disruption of a "common praxis centre".

When using the PAL subtest 7, patients with AOS scored significantly worse than those without AOS in repetition of words and non-words. However, so too did patients with left hemisphere stroke. In addition, standard deviations in the AOS group were large, suggesting a wide range of scores within this group. Thus, impaired word/non-word repetition may simply reflect left hemisphere damage rather than being specific for AOS. Accordingly, the results of this test should be viewed with caution as it does not appear to be sensitive enough to reliably distinguish patients with AOS from those without.

The results of this study provide important information regarding AOS. The paucity of literature on AOS in comparison to aphasia reflects the popular opinion that it is an uncommon condition. In addition, there is a misconception that, when it occurs, AOS often recovers rapidly following stroke. As a result, there are no randomised controlled trials of treatment for AOS following stroke [50]. The high prevalence and persistent nature of AOS documented following acute ischaemic hemispheral stroke in this study demonstrates that AOS is much more common than previously thought,

and warrants further study. These results should also prompt neurologists and speech and language therapists to assess all patients carefully for AOS following stroke.

7.2 AOS: association with lesion location and volume

In Chapter 5 I demonstrated that all patients with AOS had left hemisphere lesions. When normalised images of patients with AOS were overlaid, the regions of greatest overlap were left-sided structures including the insula, claustrum, putamen, globus pallidus, posterior limb of internal capsule, optic radiation and centrum semiovale. Many of these regions have been implicated in AOS previously [4, 46, 90]. These areas were generally not involved in patients without AOS. However, there was no single area which was involved in every patient, in contrast to previous studies [4, 32].

This study also demonstrated an association between AOS severity and lesion volume; as lesion volume increased so too did the severity of AOS. These results are similar to those found in a previous study [32]. In addition, initial severity of AOS determined final outcome at six months; thus, larger lesions are associated with more severe AOS at onset and, consequently, a more persistent speech deficit at six months.

These results add to the understanding of the neuroanatomic basis of AOS and support the hypothesis of a functional network as the basis for speech praxis. Given our findings documenting multiple left-sided brain regions being implicated in AOS, it seems likely that there is no single brain region that contains a "motor speech programmer". Instead, AOS may occur as a result of disconnection of functionally related areas. Thus, damage anywhere within this network may result in AOS. This disconnection hypothesis may explain why rapid recovery has been documented in some patients with AOS (although we did not witness this); disconnection may be

more amenable to recovery/reorganisation than infarction of a vital "speech praxis" area. The larger the brain lesion, the more likely it may be that functional networks are disrupted and thus result in AOS. It may also be that larger lesions may result in more persistent speech deficits due to less potential for functional reorganisation within that region.

7.3 Linguistic dysprosody in acute ischaemic hemispheral stroke

In Chapter 6 I demonstrated that linguistic dysprosody occurred frequently following acute ischaemic hemispheral stroke, affecting almost 60% of patients overall. Although mean prosody scores improved over time, relatively few individuals with linguistic dysprosody recovered over a six-month follow-up period. This incidence seems high, but no other studies have systematically examined the frequency or natural history of dysprosody (linguistic or otherwise) following stroke.

Seven patients had linguistic dysprosody only for identification, all had left hemisphere stroke, in keeping with some reports in the literature [79, 80]. The fact that patients with left hemisphere stroke performed worse than those with right hemisphere stroke on tests of comprehension of linguistic identification (indeed, no patient with right hemisphere stroke had significant difficulty with this task) suggests that this aspect of prosodic processing is lateralised to the left hemisphere. Identification tasks may require more complex linguistic processing than discrimination tasks which may be a possible explanation for the left lateralisation of these processes.

Eight patients had linguistic dysprosody only for discrimination, all had right hemisphere stroke. Ten patients had linguistic dysprosody for both identification and discrimination, all had left hemisphere stroke. It is interesting, however, that the eight patients with linguistic dysprosody for *discrimination only* all had right hemisphere stroke. Although 10 patients with left hemisphere stroke had evidence of linguistic

dysprosody for discrimination as well, these patients also had evidence of linguistic dysprosody for identification (i.e., had a more diffuse linguistic prosody impairment). Overall, there was no significant difference in the number of patients with right or left hemisphere stroke who had linguistic dysprosody for discrimination. Thus, lesions in either hemisphere may adversely affect linguistic prosodic discrimination. This implies that cooperation between the hemispheres is required for intact linguistic prosodic processing for discrimination tasks.

Lesions ranged from small subcortical infarcts to large infarcts involving cortex and subcortex. There was no single brain region which was always involved for either type of linguistic dysprosody.

The results of this study provide important information regarding linguistic dysprosody. An interaction must occur between the right and left hemispheres for effective processing of linguistic prosody; this is in contrast to suggestions that prosody is mediated by the right hemisphere [71-73]. The high frequency and persistent nature of linguistic dysprosody following acute ischaemic hemispheral stroke should prompt neurologists and speech and language therapists to assess all patients carefully for linguistic dysprosody following stroke.

7.4 Strengths and weaknesses

One of the major difficulties in the AOS literature is that differing definitions of AOS have been applied and various methods of ascertaining the presence of AOS utilised. This means that an individual study using one method may diagnose patients with AOS whereas another study using a different method may exclude the same patients. Thus, it is difficult to apply the results of such studies more generally as they relate only to the patient group studied. For this reason it is important that there is more widespread agreement about the methods of assessment or batteries used for diagnosis. In aphasia studies, there is widespread use of a number of batteries, such as the Boston Diagnostic Aphasia Examination (BDAE) [35] and the Porch Index of Communicative Ability (PICA) [34]. However, many studies of AOS have not used standardised batteries; instead the authors have used their own individual method of diagnosing AOS, which makes comparison between studies almost impossible.

In this study the ABA II was used [22]. This is a standardised battery which has been shown to have good inter- and intra- rater reliability [131] and is in widespread clinical use. The use of the ABA II in this study means that these results can be used by speech and language therapists, as most use this battery frequently in clinical practice.

Another issue in the AOS literature is the timing of assessment. Most studies to date have assessed patients some time, often many years, after stroke [4, 32]. It is difficult to know how a persistent structural lesion from a stroke which occurred some years previously correlates with the speech deficit at this later time point. PET and fMRI

data have demonstrated that many changes occur during recovery from aphasia after stroke; there is no reason to think that the same changes do not occur during recovery from AOS. In particular, there is some recovery/reactivation in the damaged region [167-169]; peri-lesional reorganisation in the left hemisphere [170]; and shift of activation to homologous areas in the right hemisphere [129, 171-173]. Thus, any study of AOS carried out some years after stroke is subject to limitations in the conclusions that can be drawn.

In this study, patients were assessed twice in the first week following acute ischaemic hemispheral stroke and again at six months. Thus, patients were assessed initially before significant functional adaptation could have occurred and before clinical deficits may have resolved. Consequently, the results of lesion analysis are likely to be more applicable than studies which have examined patients months or years after stroke. In addition, no other study to date has performed longitudinal follow-up of patients with AOS following stroke; thus, our study is unique in this regard, and provides useful information on the natural history of AOS.

One limitation of this study is that we did not perform exhaustive aphasia testing on recruited patients. This is mainly because aphasia batteries are time consuming and impractical in the acute stroke period. Our test battery did, however, include assessment of comprehension, naming, reading and repetition. In addition, we documented speech and language therapists' assessment of the presence or absence of associated aphasia.

Another limitation of this study is that the mean time between onset of stroke and initial assessment was four days. Some of the rapid recovery described previously [45] [51] could have occurred within this time and therefore earlier assessments might have given an even higher rate of AOS. I think it is unlikely, however, that we missed significant early recovery as none of the patients recruited gave a history of any dramatic improvement prior to recruitment.

Perhaps the main limitation of this study is that a second rater did not examine patients for AOS using the ABA II. Although this would have been ideal, personnel and time restrictions did not allow this. However, as discussed previously, the ABA II has been shown to have good inter- and intra- rater reliability [131]. In addition, other studies have demonstrated high levels of inter-rater agreement of the diagnosis of AOS, even without the use of any diagnostic battery [132]. Thus, it is unlikely that a second rater would have documented significantly different results.

7.5 Future directions

It goes without saying that this work represents only a small step in the understanding of the brain networks underlying speech programming and prosody. However, it opens several avenues for future work in this area.

As this is the first longitudinal study of AOS and linguistic dysprosody following acute ischaemic hemispheral stroke, further study is required to confirm that these findings are reproducible and applicable to patients with stroke. Ideally, a larger patient cohort should be examined.

Imaging techniques are being developed and updated at a rapid pace, thus more advanced and more detailed imaging techniques could be used (eg. fMRI, DTI, high resolution perfusion MRI etc.) to further delineate the neuroanatomic network underlying motor speech programming and prosody.

It would be interesting, and relevant, to examine production as well as comprehension of linguistic prosody. In aphasia, production and comprehension are distinct processes and are located separately. For linguistic prosody it is unclear whether one can have impaired comprehension but intact production or *vice versa*. This would add further to the literature on the neuroanatomic substrate of prosody.

7.6 Summary

This thesis adds to the literature in documenting the high prevalence of AOS and linguistic dysprosody following acute ischaemic hemispheral stroke; it adds to the understanding of the neuroanatomic basis of AOS and linguistic dysprosody; it also highlights the difficulty interpreting the current literature due to methodological differences. It is important for the future that there is more widespread agreement of a definition of AOS and use of a standardised battery when assessing patients with AOS. Only then can we know that published results are applicable to the same group of patients. This would also mean that it would be easier to collect large numbers of patients to undertake trials of specific therapies.

Appendix 1

Patient information sheet

Study Title:

Investigation of apraxia of speech and linguistic dysprosody following acute hemispheral ischaemic stroke.

Dear _____

You have been admitted to hospital with a stroke. Speech difficulties are common after stroke. We are currently doing a study looking at the course and recovery of speech problems following stroke.

Taking part in this study will not lengthen your stay in hospital and will not change treatment of your condition.

If you agree to participate in our study you will undergo the usual tests for patients with stroke, i.e., blood testing for cholesterol and diabetes, an ultrasound of your neck and heart, a heart monitor and a brain scan.
In addition, we will carry out some tests of your speech. These will involve listening to an audio recording of words and sentences and naming pictures. You will also be asked to perform some simple gestures. These tests will be performed twice while in hospital.
All your details and the results of these tests will remain confidential.
You will be required to visit the stroke out patient clinic 6 months after your discharge from hospital when we will repeat the tests.

You are at no obligation to participate in this study and can withdraw at any time.
Dr Sinead Murphy, Dr Colin Doherty and Dr Joan Moroney are conducting the study and you may contact us to answer any questions you have about the study.

Yours sincerely,

Dr Sinead Murphy
Stroke Research Registrar
Beaumont Hospital
01 8093000
bleep 823

Dr Joan Moroney
Consultant Neurologist
Beaumont Hospital
01 8092258

Dr Colin Doherty
Senior Lecturer
Beaumont Hospital
01 8092116

Appendix 2

Patient consent form

Study Title

Investigation of apraxia of speech and linguistic dysprosody following acute hemispheral ischaemic stroke.

Names of investigators directing research:

- Dr. J Moroney, Consultant Neurologist, Neurology Department, Beaumont Hospital.
  Telephone: 8092258
- Dr. S Murphy, Stroke Registrar, Neurology Department, Beaumont Hospital.
  Telephone: 8093000 bleep 823.
- Dr. C Doherty, Senior Lecturer, Neurology Department, Beaumont Hospital
  Telephone 8092116

I have read the patient information sheet and kept a copy.

I have discussed this study with Dr. _____ and all my questions have received satisfactory answers.

I have understood the purpose of the study and know what my involvement will be.

I do not need any further information now, but am free to request it at any time.

I understand that I can refuse to take part in this study or withdraw at any time without giving a reason and without affecting my medical care.

I understand if I have any questions concerning this study I can contact the Doctors listed above.

I agree to take part in this study:

Signed: _____ Date:
Patient / Next of kin

Doctor's Signature: _____ Date:

Appendix 3

General Practitioner information sheet

Study Title

Investigation of apraxia of speech and linguistic dysprosody following acute hemispheral ischaemic stroke.

Investigators:

Dr Joan Moroney, Consultant Neurologist, Beaumont Hospital
Telephone 01 809 2258
Dr Sinead Murphy, Stroke Research Registrar, Beaumont Hospital
Telephone: 01 8093000 bleep 823
Dr Colin Doherty, Senior Lecturer, Beaumont Hospital
Telephone 01 8092116

Dear Dr _____,

Your patient, _____ , has consented to be involved in the above study.

The study is recruiting patients admitted to Beaumont Hospital following acute ischaemic stroke. We aim to assess the evolution of speech apraxia and prosody following acute ischaemic stroke.

Inpatient interview to collect data with regard to demographics, medical history and vascular risk factors will be conducted. During the inpatient stay we will administer a speech apraxia and prosody battery within 48 hours of admission and at 72-96 hours. Follow-up at the stroke speciality clinic will be at 6 months when we will repeat the test battery.

_____ has given informed consent (a copy is attached).

This study will not change the medical management of your patient's care.
The patient is free at any time to withdraw from the study.
If you have any questions regarding the study please contact the doctors listed above.

Yours sincerely,

Dr Sinead Murphy
Stroke Research Registrar

Appendix 4

Comprehension Yes/No task Adapted from LaPointe L [98]

Is your name (correct name)?
Is your name (incorrect name)?
Do you live in (incorrect)?
Do you live in (correct)?
Are you a (incorrect occupation)?
Are you a (correct occupation)?
Are you wearing a (incorrect)?
Are you wearing a (correct)?
Do you have (correct) eyes?
Do you have (incorrect) eyes?

Are you in the hospital?
Are you in the cinema?
Is the light on?
Is the light off?
Do you live in (correct)?
Do you live in (incorrect)?
Is there a car in this room?
Is there a bed in this room?
Is the door closed?
Is the door open?

Is Bertie Aherne the Taoiseach?
Is Scotland part of Ireland?
Is a window made of glass?
Do you light a cigarette with a chair?
Is 5 more than 2?
Do people sleep on a table?
Does milk come from a cow?
Does coke come from a cow?
Do you catch fish with a bus?
Do you tell time with a watch?

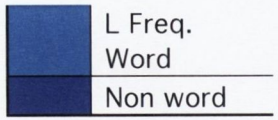
Appendix 5a

Word / non-word repetition [99]

	Words/ Non Words	Code				Types of Errors				
			Word			WORDS			NON WORDS	
			Freq.	W	N W	Semantic	Phonemic	Other	Lexicalization	Other
1	SLINED									
2	BROCCOLI									
3	GROUND									
4	BINE									
5	NID									
6	BRANCH									
7	HEEN									
8	DITE									
9	WEED									
10	PENSAFON									
11	HUB									
12	BALL									
13	BIP									
14	PRECIPICE									
15	SLAZENY									
16	TUD									
17	FRIEND									
18	DROCCOFY									
19	DRINT									
20	GULL									

21	PRINT								
22	TEMESONE								
23	STETHOSCOPE								
24	CLARINET								
25	SMURT								
26	ROAD								
27	DAT								
28	JOB								
29	WIG								
30	STIBUNATION								
31	DIPE								
32	BOAT								
33	PLANT								
34	FAR								
35	BROSK								
36	TAIN								
37	CROCODILE								
38	ROKE								
39	PLART								
40	GAUZE								
	TOTAL								

Key	
	CCVCC
	CVC
	Complex
	H Freq. Word



Key		#Correct
	CCVCC	/10
	CVC	/20
	Complex	/10
	H Freq. Word	/10
	L Freq. Word	/10
	Non word	/20

Appendix 5b
Word / non-word repetition table of norms [99]

Table of norms using 97 control patients

Mean Percent Correct (SD)

	Words			Non-Words		
	CVC	CCVCC	Complex	CVC	CCVCC	Complex
Control	98.5 (5.3)	99.2 (4.0)	97.1 (7.1)	91.3 (16.4)	88.5 (15.0)	87.6 (17.9)
LCVA	83.6 (27.0)	78.7 (31.0)	67.7 (32.2)	62.8 (31.1)	58.3 (33.3)	52.8 (38.3)
RCVA	97.4 (7.5)	96.5 (9.8)	91.3 (11.8)	81.3 (17.7)	82.6 (19.4)	72.2 (22.4)
CHI	100.0 (0.0)	98.6 (5.3)	97.1 (7.3)	89.3 (10.0)	92.9 (12.7)	88.6 (12.9)

Appendix 6

NIH Stroke Scale [96]

1.a. Level of Consciousness:

0	Alert
1	Not alert, but arousable with minimal stimulation
2	Not alert, requires repeated stimulation to attend
3	Coma

1.b. Ask patient the month and their age:

0	Answers both correctly
1	Answers one correctly
2	Both incorrect

1.c. Ask patient to open and close eyes:

0	Obeys both correctly
1	Obeys one correctly
2	Both incorrect

2. Best Gaze (only horizontal eye movement):

0	Normal
1	Partial gaze palsy
2	Forced deviation

3. Visual Field Testing:

0	No visual field loss
1	Partial hemianopia
2	Complete hemianopia
3	Bilateral hemianopia (blind including cortical blindness)

4. Facial Paresis (Ask patient to show symmetrical movement of teeth or raise eyebrows and close eyes tightly):

0	Normal
1	Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
2	Partial paralysis (total or near total paralysis of lower face)
3	Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)

5. Motor Function - Arm (right and left): (extends arms 90 (or 45) degrees for 10 seconds without drift)

0	Normal
1	Drift
2	Some effort against gravity
3	No effort against gravity
4	No movement
9	Untestable (Joint fused or limb amputated)

6. Motor Function - Leg (right and left): (hold leg 30 degrees position for 5 seconds)

0	Normal

1 Drift
2 Some effort against gravity
3 No effort against gravity
4 No movement
9 Untestable (Joint fused or limb amputated)

7. Limb Ataxia:

0 No ataxia
1 Present in one limb
2 Present in two limbs

8. Sensory (Use pinprick to test arms, legs, trunk and face -- compare side to side)

0 Normal
1 Mild to moderate decrease in sensation
2 Severe to total sensory loss

9. Best Language (describe picture, name items, read sentences)

0 No aphasia
1 Mild to moderate aphasia
2 Severe aphasia
3 Mute

10. Dysarthria (read several words):

0 Normal articulation
1 Mild to moderate slurring of words
2 Near unintelligible or unable to speak
9 Intubated or other physical barrier

11. Extinction and Inattention:

0 Normal
1 Inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities
2 Severe hemi-inattention or hemi-inattention to more than one modality

Appendix 7

THE BARTHEL INDEX [102]

Activity	Score
FEEDING	
0 = unable	
5 = needs help cutting, spreading butter, etc., or requires modified diet	
10 = independent	_____
BATHING	
0 = dependent	
5 = independent (or in shower)	_____
GROOMING	
0 = needs to help with personal care	
5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING	
0 = dependent	
5 = needs help but can do about half unaided	
10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS	
0 = incontinent (or needs to be given enemas)	
5 = occasional accident	
10 = continent	_____
BLADDER	
0 = incontinent, or catheterized and unable to manage alone	
5 = occasional accident	
10 = continent	_____
TOILET USE	
0 = dependent	
5 = needs some help, but can do something alone	
10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK)	
0 = unable, no sitting balance	
5 = major help (one or two people, physical), can sit	
10 = minor help (verbal or physical)	
15 = independent	_____
MOBILITY (ON LEVEL SURFACES)	
0 = immobile or < 50 yards	
5 = wheelchair independent, including corners, > 50 yards	
10 = walks with help of one person (verbal or physical) > 50 yards	
15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS	
0 = unable	
5 = needs help (verbal, physical, carrying aid)	
10 = independent	_____
TOTAL (0–100):	_____

Provided by the Internet Stroke Center — www.strokecenter.org

Appendix 8

Modified Rankin Scale (mRS) [101, 104, 174]

SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): ____

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Appendix 9

Apraxia Battery for Adults II (ABA II) [22]

ABA–2 Profile/Examiner Record Form

Apraxia Battery for Adults–Second Edition

Section I. Identifying Information

Name _____ Female ☐ Male ☐ Address _____

Date Tested _____ Examiner's Name _____

Date of Birth _____ Examiner's Title _____

Age _____ Referral Source _____

Section II. History

Date of Onset _____ Handedness: Original_____ Current_____

Primary Medical Diagnosis _____ Primary Language: Spoken_____ Written_____

Secondary Medical Diagnosis _____ Educational History _____

Facility _____ Hobbies/Interests _____

Insurance _____ Occupational History and Vocational Interests _____

Physical Deficits: Motor _____ Sensory_____

Section III. Raw Scores and Levels of Impairment

A. Subtest Raw Scores

	Subtest	Raw Score	Level of Impairment		Subtest	Raw Score	Level of Impairment
1	Diadochokinetic Rate	____	____	3B	Oral Apraxia	____	____
2A	Increasing Word Length	____	____	4	Utterance Time for Polysyllabic Words	____	____
2B	Increasing Word Length	____	____	5	Repeated Trials	____	____
3A	Limb Apraxia	____	____	6	Inventory of Articulation Characteristics of Apraxia	____	
Characteristics of Apraxia		____	____				

B. Cutoff Scores for Determining the Level of Impairment

	Subtests						
Level	1	2A	2B	3A	3B	4	5
None (N)	26+	0–1	0–1	44–50	44–50	0–15	28–30
Mild (Mi)	7–25	2–4	2	37–43	35–43	16–55	16–27
Moderate (Mo)	2–6	5–7	3–5	25–36	21–34	56–80	5–15
Severe (S)	0–1	8+	6+	0–24	0–20	81–100	0–4

C. Level of Impairment Profile

	Subtest	None (N)	Mild (Mi)	Moderate (Mo)	Severe (S)
1	Diadochokinetic Rate	.	.	.	.
2A	Increasing Word Length	.	.	.	.
2B	Increasing Word Length	.	.	.	.
3A	Limb Apraxia	.	.	.	.
3B	Oral Apraxia	.	.	.	.
4	Utterance Time for Polysyllabic Words	.	.	.	.
5	Repeated Trials	.	.	.	.

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Section IV. Administration Conditions/Patient Response Pattern

A. Date(s) administered:

_____

_____

_____

_____

B. Place Tested _____

	Interfering	Noninterfering
C. Noise Level	_____	_____
D. Interruptions	_____	_____
E. Distractions	_____	_____
F. Lighting	_____	_____
G. Temperature	_____	_____

	Interfering	Noninterfering
H. Energy Level	_____	_____
I. Attitude	_____	_____
J. Rapport	_____	_____
K. Perseverance	_____	_____
L. Others (specify)	_____	

Other Comments _____

Section V. Interpretation and Recommendations

Section VI. Record of Items and Subtest Performance

Subtest 1: Diadochokinetic Rate

Materials: Stopwatch

Instructions: Say, "I want you to say some sounds. Say as many as you can, as fast as you can. Say /pʌ/." If the examinee responds with a single combination and does not continue, demonstrate by saying "/pʌpʌpʌpʌ. . ./." Present the three single-syllable practice items, /pʌ/, /tʌ/, and /kʌ/, but do not score. Give three 1-second trials for each of these syllables. After these practice trials, begin administering the subtest with the combination /pʌtʌ/. Present each item three times. Allow 3 seconds for each two-syllable trial and 5 seconds for each three-syllable trial.

Scoring: Write the number of correct repetitions in the corresponding column for each trial. Enter the score of the highest of the three trials in the Best Trial column. Then add the scores from the Best Trial columns and enter the sum in the Total box.

Syllables	Seconds	Trial 1	Trial 2	Trial 3	Best Trial
/pʌ/	1				
/tʌ/	1				
/kʌ/	1				
/pʌtʌ/	3				
/tʌkʌ/	3				
/pʌtʌkʌ/	5				
/plʌkrʌtʌ/	5				
				Best Trial Total (Raw Score)	

Subtest 2: Increasing Word Length

Materials: None

Instructions: Say, "Now I'm going to say some words. You repeat what I say." Give each word only once, making sure you have the examinee's attention before proceeding. Provide the opportunity for the examinee to look at your face as you say each word. Present words from left to right as follows: "thick" (pause, examinee repeats); "thicken" (pause, examinee repeats); and "thickening" (pause, examinee repeats).

Scoring: 2—The examinee's response is correct, without hesitation, without struggle, and without articulatory error.

1—The examinee self-corrects, delays significantly, displays visible or audible searching, commits one or more articulatory errors, but maintains the correct number of syllables and general conformation of the word.

0—The examinee gives no response, attempts but does not produce a word, says the wrong number of syllables, or misarticulates to the extent that the word is no longer recognizable.

For example, suppose the examinee is attempting the word *thicken*. If the examinee says, "thick," score 0. Even though an accurately articulated word was produced, it contained the wrong number of syllables and was a different word from the one intended. If the examinee says, "thicklen," score 1. An articulatory error (addition) occurred, but the examinee was able to maintain the proper number of syllables and general conformation of the word.

A. Increasing Word Length

Administer the words in Columns 1, 2, and 3. Total each column and subtract the Column 3 total from the Column 1 total to obtain the Deterioration in Performance Score for Part A.

Column 1 Words	Score
thick	
zip	
jab	
please	
love	
hard	
jig	
strength	
hope	
soft	
Total	

Column 2 Words	Score
thicken	
zipper	
jabber	
pleasing	
loving	
harden	
jiggle	
strengthen	
hopeful	
soften	
Total	

Column 3 Words	Score
thickening	
zippering	
jabbering	
pleasingly	
lovingly	
hardening	
jiggling	
strengthening	
hopefully	
softening	
Total	

Column 1 Total		Column 3 Total		Deterioration in Performance Score (Raw Score)
	–		=	

B. Increasing Word Length

Administer the words and sentences in Columns 1, 2, and 3. Total each column and subtract the Column 3 total from the Column 1 total to obtain the Deterioration in Performance Score for Part B. DO NOT score the Deterioration in Performance Score for individuals who scored in the moderate or severe impairment levels for Part A.

Column 1 Words	Score
instruct	
attract	
city	
beauty	
response	
dispose	
democrat	
emotion	
character	
national	
The man at the computer was typing.	
Total	

Column 2 Words	Score
instructive	
attractive	
citizen	
beautiful	
responsible	
disposable	
democratic	
emotional	
characteristic	
nationalistic	
They said the man at the computer was typing quickly.	
Total	

Column 3 Words	Score
instructively	
attractively	
citizenship	
beautifully	
responsibility	
disposability	
democratically	
emotionally	
characteristically	
nationalistically	
I'm not sure if they said that the man at the computer was typing quickly or slowly.	
Total	

Column 1 Total		**Column 3 Total**		**Deterioration in Performance Score (Raw Score)**
	–		=	

Subtest 3: Limb Apraxia and Oral Apraxia

Materials: None

Instructions: Say, "I'd like you to show me how you do some things. Listen carefully. Show me how you (insert appropriate stimulus)." After you give the initial stimulus item on Part A or Part B, drop the carrier phrase "Show me how you. . . ."

Scoring: 5—The examinee gives an accurate, prompt, complete, and readable gesture.

4—The examinee gives an ambiguous or incorrect gesture, but self-corrects to an accurate response.

3—The examinee's gesture is basically correct, but crude and defective in amplitude, speed, or accuracy.

If the examinee makes no response for 10 seconds or attempts a response but is unsuccessful, you should demonstrate the gesture and then score as follows:

2—The examinee performs correctly after demonstration.

1—The examinee's gesture is basically correct, but crude and defective in amplitude, speed, or accuracy.

0—The examinee is unable to perform the correct gesture even after the demonstration.

After scoring each section, place a check in the Searching Behavior column when searching behavior was an observed part of a response.

A. Limb Apraxia

Stimulus	Score	Searching Behavior?
make a fist		
wave good-bye		
snap your fingers		
throw a ball		
hide your eyes		
make a hitchhiking sign		
make a pointing sign		
salute		
play the piano		
scratch		
Total (Raw Score)		

B. Oral Apraxia

Stimulus	Score	Searching Behavior?
stick out your tongue		
whistle		
puff out your cheeks		
kiss a baby		
clear your throat		
bite your lower lip		
show me your teeth		
take a deep breath and hold it		
lick your lips		
open your mouth		
Total (Raw Score)		

Subtest 4: Latency Time and Utterance Time for Polysyllabic Words

Materials: Stopwatch, Plates 1 through 10 in Picture Book

Instructions: Say, "I'm going to show you some pictures and I'd like you to tell me the names of the things you see. Say the name as soon as you see the picture." Present the example Plate A (telephone). Once the examinee understands that he or she is supposed to name the picture, proceed to Plate 1 (flashlight). As soon as the picture is presented, begin to measure latency time—that is, the time between presentation of the picture and initiation of an attempt to produce the target word. Then measure utterance time—that is, the time from initiation of an attempt at the target word to its successful completion. Record the number of seconds it takes in the proper columns. Both visible (i.e., articulatory posturing) and audible (i.e., speech sound) behaviors should be observed in determining initiation of attempts at the target word. The limit for both latency and utterance times is 10 seconds. If the examinee is not successful in producing the word within the time limit, record both the latency and utterance times as 10 seconds and place a check in the Unable To Utter Word column. If the examinee calls the picture by a name other than that on the list (such as "paper" for "newspaper"), prompt the examinee by saying, "Another word for it is . . ." and keep timing until the desired word is given or until the 10-second limit is reached.

Scoring: Record the number of seconds (0 through 10) in each of the first two columns, rounding to the nearest whole second. Transfer *only* the Utterance Time score to Section III on page 1 of the Profile/Examiner Record Form.

Plate	Latency Time (seconds)	Utterance Time (seconds)	Unable To Utter Word
A. telephone			
1. flashlight			
2. umbrella			
3. newspaper			
4. banana			
5. elephant			
6. potatoes			
7. butterfly			
8. motorcycle			
9. computer			
10. refrigerator			
Total (Raw Score)			

Subtest 5: Repeated Trials

Materials: Tape recorder

Instructions: Say, "I'm going to say some words. I'll say each word one time and then I want you to say it three times." Say the sample word, "telephone." If the examinee responds correctly, initiate testing with the first word (*flashlight*). If the examinee does not respond correctly, model the correct response, using the trial word *telephone* until the examinee demonstrates an understanding of the task.

Scoring: This task is designed to determine whether the examinee's production improves, deteriorates, or remains unchanged over successive repetitions of the same word. In order to make this determination, tape record and/or phonetically transcribe each of the three productions of the word. Count the number of errors in each production and record that number in the appropriate Trial column. Compare Trial 1 and Trial 3 and write a "–" (minus sign) in the Trials 1 and 3 Compared column if Trial 1 contained fewer errors than Trial 3, a "+" (plus sign) if Trial 3 contained fewer errors than Trial 1, or a "0" if there was no change. For example, if the examinee makes 2 errors in Trial 1 and 3 errors in Trial 3, there are fewer errors in Trial 1 and the change is recorded as a –. After these marks are recorded, total the number of + marks and enter that number into the Number of +'s box, total the number of – marks and enter that number into the Number of –'s box, and then subtract the latter from the former to get the Total Amount of Change score. Next, count the number of + and – marks recorded to arrive at the Variability score. For example, if you recorded 2 +'s and 3 –'s, then the Variability would be 5. Finally, count the number of words that contained errors—not the number of errors. For example, if an examinee made 2 errors while pronouncing *flashlight,* 3 errors while pronouncing *potatoes,* and 1 error while pronouncing *motorcycle,* the number of words with errors would be 3 (whereas the number of errors would be 6). To compute the Raw Score for this subtest, subtract the number of words with errors from 30 and record this score in the box.

Word	Trial 1	Trial 2	Trial 3	Trials 1 and 3 Compared
Example: telephone				
flashlight				
umbrella				
newspaper				
banana				
elephant				
potatoes				
butterfly				
motorcycle				
computer				
refrigerator				

Number of +'s		Number of –'s		Total Amount of Change
	–		=	

		Variability	=	

		Number of Words with Errors		Raw Score
30	–		=	

Subtest 6: Inventory of Articulation Characteristics of Apraxia

Materials: Tape recorder, the action picture (Plate 11) and the "My Grandfather" passage (Plate 12) in the Picture Book

Instructions: Engage the subject in the three following types of tasks to provide opportunities to observe the 15 speech behaviors listed below:

1. *Spontaneous Speech.* Show the action picture (Plate 11) and say, "Tell me what's happening in this picture."
2. *Reading.* Show the "My Grandfather" passage (Plate 12) and say, "Read this story aloud."
3. *Automatic Speech.* Say, "Count to 30," and then, "Now, count backwards from 30."

Scoring: For each speech behavior you observe, place a check in the appropriate task column. Use the Observed/Noted Elsewhere? column to check any of the behaviors exhibited by the examinee during spontaneous off-task conversation in the test session or while performing the tasks on the earlier five subtests. In the Overall column, record a 1 if the speech behavior was noted in any of the four columns; otherwise record a 0. After all tasks have been completed, total the score. The presence of 5 or more of these speech behaviors is highly indicative of apraxia. The more checks that are recorded in the grid overall, the more certain you can be that the examinee is apraxic.

Speech Behavior	Tasks			Behavior Observed/Noted Elsewhere?	Overall (mark 1 if present, 0 if not)
	Spontaneous Speech	Reading	Automatic Speech		
1. Exhibits phonemic anticipatory errors (gleen glass for green glass)					
2. Exhibits phonemic perseverative errors (pep for pet)					
3. Exhibits phonemic transposition errors (Arifca for Africa)					
4. Exhibits phonemic voicing errors (ben for pen)					
5. Exhibits phonemic vowel errors (moan for man)					
6. Exhibits visible/audible searching					
7. Exhibits numerous and varied off-target attempts at the word					
8. Errors are highly inconsistent					
9. Errors increase as phonemic sequence increases					
10. Exhibits fewer errors in automatic speech than in volitional speech					
11. Exhibits marked difficulty initiating speech					
12. Intrudes a schwa sound /ə/ between syllables or in consonant clusters					
13. Exhibits abnormal prosodic features					
14. Exhibits awareness of errors and inability to correct them					
15. Exhibits a receptive–expressive gap					
				Total (Raw Score)	

The Grandfather Passage

You wished to know all about my grandfather. Well, he is nearly ninety-three years old; he dresses himself in an ancient black frock coat, usually minus several buttons; yet he still thinks as swiftly as ever. A long, flowing beard clings to his chin, giving those who observe him a pronounced feeling of the utmost respect. When he speaks, his voice is just a bit cracked and quivers a trifle. Twice each day he plays skilfully and with zest upon our small organ. Except in the winter when the ooze or snow or ice prevents, he slowly takes a short walk in the open air each day. We have often urged him to walk more and smoke less, but he always answers, "Banana oil!" Grandfather likes to be modern in his language.

Appendix 10

Prosodic stimuli

QQ "Was she washing clothes all day?" (rising boundary tone)

SQ "Was she washing clothes all day?" (falling boundary tone)

Q "She was washing clothes all day?" (rising boundary tone)

S "She was washing clothes all day." (falling boundary tone)

QQ "Was she writing with a pen?"

SQ "Was she writing with a pen?"

Q "She was writing with a pen?"

S "She was writing with a pen."

QQ "Was she riding her new bike?"

SQ "Was she riding her new bike?"

Q "She was riding her new bike?"

S "She was riding her new bike."

Appendix 11

Results of ABA II subtest scores at each assessment for patients with AOS

Table 11.1: ABA II subset scores at first assessment: patients with AOS

	ABA II SUBTEST							
PATIENT	**1**	**2a**	**2b**	**3a**	**3b**	**4**	**5**	**6**
1	10	0	1	29	43	79	30	8
5	16	0	0	50	50	18	28	4
7	0	6	*	27	35	100	3	11
10	0	U/A	U/A	17	10	100	0	6
13	0	2	*	48	35	100	0	10
15	9	7	*	37	40	100	21	7
16	3	6	*	29	20	95	12	10
20	15	15	*	47	49	28	27	7
25	21	2	7	49	50	18	26	9
26	0	U/A	U/A	23	15	100	0	8
30	2	U/A	U/A	50	43	47	8	12
37	0	U/A	U/A	30	21	49	4	8
39	15	0	3	45	50	28	30	6
44	17	0	6	50	50	13	22	10

U/A=unable to perform; *=if patient scored ≥2 in subset 2a they do not need to perform subset 2b

Table 11.2: ABA II subset scores at second assessment: patients with AOS

	ABA II SUBTEST							
PATIENT	**1**	**2a**	**2b**	**3a**	**3b**	**4**	**5**	**6**
1	16	0	2	38	43	79	30	8
5	14	0	2	50	50	13	30	4
4	5	U/A	U/A	28	32	70	0	10
7	#							
10	0	U/A	U/A	25	16	100	0	5
13	0	2	*	47	44	100	5	12
15	7	3	*	42	38	95	27	9
16	4	8	*	18	18	69	7	9
20	8	7	*	49	49	13	27	3
23	0	U/A	U/A	42	42	100	0	8
25	31	2	5	50	50	17	28	9
26	0	U/A	U/A	34	23	100	0	8
30	3	6		50	41	53	8	10
37	0	U/A	U/A	6	9	83	0	8
39	24	0	2	45	50	13	30	5
44	19	0	5	50	50	13	29	7

U/A=unable to make any sounds; *=patients who score in the moderate or severe range in subtest 2a are not assessed on subtest 2b; #=too unwell to assess

Table 11.3: ABA II subtest scores at final assessment: patients with AOS

	ABA II SUBTEST							
PATIENT	**1**	**2a**	**2b**	**3a**	**3b**	**4**	**5**	**6**
1	30	0	0	50	50	10	30	4
4	14	1	6	48	50	14	24	3
5	28	0	0	50	50	13	30	4
7	RIP							
10	10	6	N/A	32	36	91	5	10
13	32	0	0	50	50	10	27	3
15	21	2	N/A	46	50	64	25	8
16	3	4	N/A	38	34	19	30	8
20	21	1	12	49	49	13	29	4
22	22	8	N/A	30	41	100	20	7
23	6	10	N/A	50	46	22	20	7
25	RIP							
26	2	14	N/A	49	43	30	14	8
30	^							
37	10	3	N/A	46	41	12	25	9
39	36	0	1	45	50	13	30	5
44	^							
50	20	0	12	50	50	27	24	7

RIP = deceased; ^ = lost to follow-up

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