Hangul Dysgraphia in Patients with Alzheimer′s Disease

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ABSTRACT

Background: Dysgraphia is the collective term used for various acquired disorders of spelling and writing caused by diverse neurological diseases or brain damages. Dysgraphia may take various forms depending on the specific graphemic system of a given language. The Korean alphabet, Hangul (or Hangeul), is unique in its written application. Linguistically, each of the 24 Hangul characters corresponds to one phoneme. Unlike the alphabetic written language system (e.g., English and Italian), Hangul has nonlinguistic characteristics, such as physical forms of graphemes and visuospatial/constructional arrangement of graphemes within a syllable. Especially, Hangul syllables differ from those in alphabetical systems which are written horizontally. Due to these visuospatial/constructional features, the configuration of Hangul syllables invokes visuospatial/constructional functions that other writing systems use less extensively. Traditionally, the left hemisphere might control a linguistic component in writing, while the right hemisphere might control a nonlinguistic component. Hangul has both linguistic and nonlinguistic value. Therefore, interactivity between the left and right hemispheres may be essential to ensure Hangul writing processing. Alzheimer's disease (AD) is characterized by the deposition of beta-amyloid plaques and neurofibrillary tangles in the brain. Due to the bilateral involvement of the tempoparietal-frontal areas, the disease can result in both visuoconstructional and language dysfunction in some stage of their disease process. Because of the specialized characteristics of Hangul, the nonlinguistic errors, as well as the linguistic ones may be easily observed in the Korean patients with AD. ***Objectives*****:** The purpose of this study is to delineate 1) the characteristics of writing in Korean patients with AD, 2) the feature of visuospatial representation of Hangul syllable, 3) the relationship between Hangul task and other related cognitive functions, and 4) associated neural correlates of Hangul writing. ***Methods*****:** A study sample of 75 patients with AD and 20 healthy controls (HC) performed a Hangul writing task. We analyzed the erroneous responses of the subjects according to linguistic and nonlinguistic characteristics. A Hangul representation task was used to assess the knowledge of the general shape of a Hangul syllable. In addition, we evaluated the relationship between Hangul writing and the neuropsychological variables. [F]fluoro-2-deoxy-D-glucose(^{18}FDG)-positron emission tomography **(**PET) was utilized to measure the resting state regional brain glucose metabolism. ***Results*****:** The number of total erroneous responses significantly differed according to disease severity. In addition, the patients demonstrated nonlinguistic errors even in the early stages of the disease. The performance of Hangul representation might be relatively preserved in the later stage of AD patients even though these patients showed low performance in the writing to dictation task. Multiple cognitive domains such as attention, language, immediate memory, visuospatial and frontal executive functions significantly correlated with the performance of Hangul writing. Glucose metabolism correlated with the number of correct responses was located in the right occipitotemporal lobe and the left temporoparietal lobe. ***Conclusions*****:** Language-specific features our patients showed may represent the unique arrangement of graphemes within the square form of a Hangul syllable. The PET findings objectively support the notions that Hangul has both linguistic and nonlinguistic (visuoconstructional) characteristics, and the impairment of Hangul writing performance in Korean AD patients might be closely related to a functional decline in both the right and left hemispheres. The results provide clinical implications in that the writing impairment would be one of the possible clues of diffuse brain changes, and thus, writing ability should be monitored from an early stage of the disease.

Key words: Hangul, Hangeul, writing, dysgraphia, linguistic, nonlinguistic, Alzheimer’s disease, PET

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Ⅰ. INTRODUCTION

Writing is not a unitary process, but requires coordination of linguistic and motor aspects.[1,2] The terms, ‘central’ and ‘peripheral’ with reference to writing were coined by Ellis.[1] Central processes are involved in generation of spelling that applies to all possible modalities of output (e.g., handwriting, oral spelling, writing with block letters, typing). Peripheral processes, on the other hand, are restricted to converting orthographic information into motor commands for writing movements.

1. Spelling and writing processes

The central processes are linguistic in nature and they include more than one potentially independent spelling routes. For investigating the spelling routes, researchers have employed word-level analyses to identify patterns of spelling deterioration. Stimuli used in studies have been commonly categorized in the following ways: (a) regular, irregular, and nonwords; (b) predictable and unpredictable words; (c) familiar and unfamiliar or novel words; and (d) ambiguous and unambiguous words. Orthographically regular words have predictable phoneme–grapheme correspondence (e.g., bat), whereas irregular words have atypical phoneme–grapheme correspondences (e.g., laugh). Nonwords or pseudowords are nonmeaningful, pronounceable letter strings that conform to phoneme–grapheme conversion rules, and are often used to assess phonological spelling. Predictable words are those with regular spellings and entirely unambiguous sound–letter correspondences; unpredictable words are those with more than one common spelling pattern of the word's phonological rime (e.g., claim and flame).[3] In addition to categorizing stimuli, errors are also categorized. Phonologically plausible spellings or misspellings occur when the orthographic form corresponds to the pronunciation of the word (e.g., circut for circuit), whereas implausible spellings include errors of letter transpositions, omissions, and substitutions.[4]

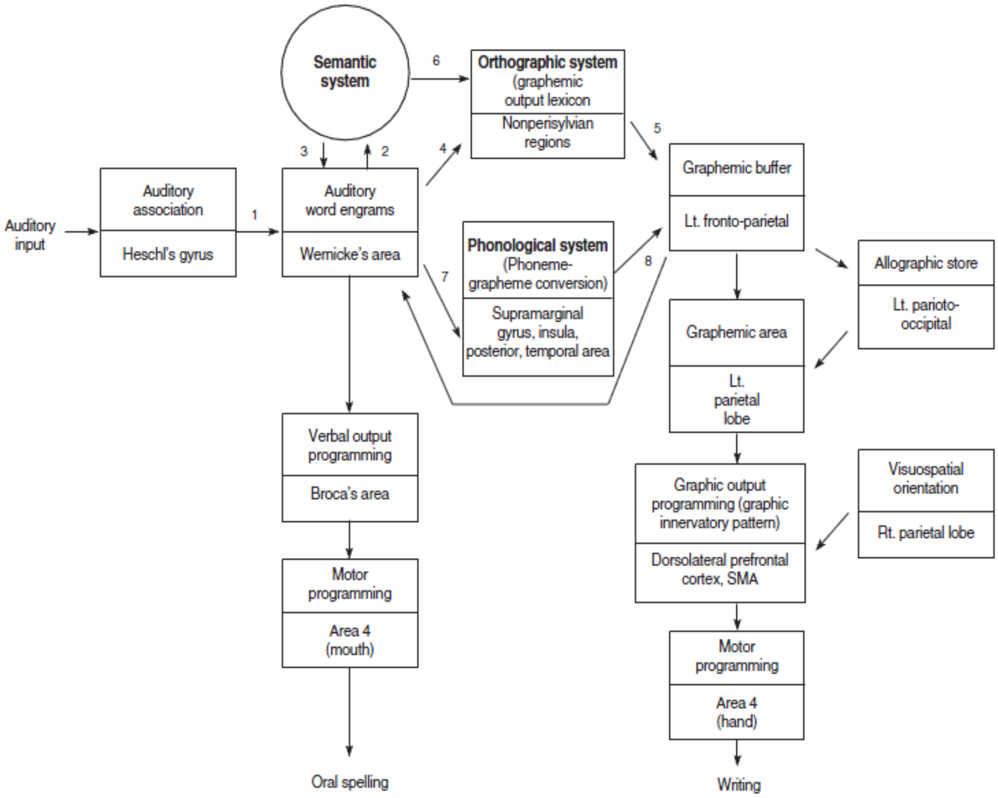
According to the revised information processing and neuropsychological model of spelling and writing based on Roeltgen & Heilman(Figure 1),[5,6] the central spelling processes are thought to generate orthographic representations of words via lexical routes (whole words from an internal dictionary) or phonological routes (sounding out a logical but possibly incorrect spelling). A further division of the lexical route has been suggested; that is, lexical with semantic input or lexical without sufficient semantic input. In the case that semantic input is insufficient, a task such as spelling homophones to dictation may elicit a correctly spelled word, but the incorrect homophone. For example, the patient may spell seen in response to "spell scene as in, it was a beautiful scene." Normal spellers are presumed to have access to a lexical spelling system. This systemutilizes a whole-word retrieval process in producing letter sequences for words, and requires access to and integrity of an internal memory store of learned spellings that has been referred to as the graphemic output lexicon.[7.8] In other words, spellers rely on orthographic representations of individual words stored in an orthographic lexicon. This lexical system is believed to mediate spelling of orthographically regular words, and is relied on exclusively in the spelling of orthographically irregular words or those that cannot be interpreted based upon phoneme–grapheme conversion rules alone, such as choir.[9] Furthermore, in ambiguous spellings, the graphemic output lexicon may be accessed to select the correct spelling from among possible spelling choices. Recent investigators suggest that the left posterior inferior temporal cortex is critical in the production of irregular spellings that rely on the lexical system.[10]

In addition to a lexical spelling system, it is theorized that normal spellers may also access a phonological route. In the phonological route, orthographic representations are accessed directly from phonological input representations without the involvement of the semantic system. The phonological system relies on sound–letter correspondences, or phoneme–grapheme conversion rules, to convert auditory phoneme strings to written lexical representations. These rules convert phonemes into the graphemes with which they most frequently correspond. This system can be relied on during spelling of orthographically regular words and during spelling of nonwords that conform to the rules of English phonotactics (e.g., wap). Furthermore, phoneme–grapheme conversion can also be used to access phonologically plausible, although not always correct, spellings of unpredictable or ambiguous words (e.g., proud). The phonemic sequences of these unpredictable words can correspond with more than one common orthographic pattern. For example, the phonological rime of proud and crowd are the same. This sound pattern is commonly represented by either of the two spellings: -oud and -owd. Phonological spelling is believed to be supported by the left hemisphere perisylvian regions.[6]

Lexical and phonological systems are believed to be involved in the mediation of normal spelling processes. Spellers are thought to rely on the lexical system for rapid online access to representations of regular, unpredictable, and irregular words, as long as the words are familiar and have a stored representation in the graphemic output lexicon. However, when an unfamiliar word without a stored representation is encountered, spellers must rely on the alternate phonological spelling system to generate a novel orthographic representation of the word's sound pattern. This is also the case for nonwords that have not been previously encountered and therefore lack a stored orthographic representation.

The central processes are hypothesized to converge at the level of the "graphemic buffer," a working memory system that temporarily stores orthographic representations of words while motor processes are activated for output production via peripheral motor processes of oral or written spelling.[7] Working memory is considered a short-lasting, online manipulation of information; the hypothetical graphemic buffer may be considered a component or type of working memory. It is generally accepted that spellings share the same graphemic buffer regardless of whether the output is written or oral spelling.[8,11]

Following the completion of central processes involved in spelling, peripheral processes necessary for the generation of motor output are thought to become activated. The first of these, known as the allographic system, involves the selection of appropriate letter shapes or physical forms of graphemes for the string of graphemes held in the graphemic buffer. This allographic representation does not contain information about the sequence of strokes necessary to create a desired letter form, or the specific muscles that are to be used for movement execution. The remaing processing components in the model are directly concerned with the graphic motor programming and execution of writing movements required to produce the letter shapes designated by the allographic representation. The graphic motor programming specifies the direction, relative size, position, and order of strokes. The execution system involves the controlling of neuromuscular commands.



Subtypes	Pathway
Lexical-semantic route	1→2→3→4→5
	1→2→6→5
Lexical-nonsemantic route	1→4→5
Phonological route	1→7→8

Figure 1. Revised neuropsychological model of spelling and writing based on Roeltgen & Heilman[5,6]

Dysgraphia is the collective term used for various acquired disorders of spelling and writing caused by diverse neurological diseases or brain damages. However, studies on dysgraphia usually have focused on the alphabetic writing system and patients with focal brain lesions to this date.[10,12-15] From the previous studies, linguistic errors such as substitution, addition, and omission of letters were reported. In addition, evidence consistently shows that the left hemisphere processes written language, as well as oral language systems. Recent investigators suggested that damage to the left non-perisylvian lesions results in lexical dysgraphia, whereas phonological dysgraphia for perisylvian lesions.[6,16] However, these findings might not apply to all written language systems because dysgraphia may take various forms depending on the specific graphemic system of a given language. In order to look into the different aspects in detail, we will first review the Korean writing system and compare the alphabetic writing system with it.

2. Korean alphabet and hemispheric processing

The Korean alphabet, Hangul (or Hangeul), is unique in its written application. In 1443, King Sejong published his dissertation entitled 'Hoon-min-jeong-um', which is the primal name of Hangul. Although originally composed of 28 characters, the modern Hangul alphabet consists of 24 characters, split between 10 vowel-graphemes (known as 'mo-eum'; ㅏ, ㅑ, ㅓ, ㅕ, ㅗ, ㅛ, ㅜ, ㅠ, ㅡ, ㅣ) and 14 consonant-graphemes (known as ‘ja-eum’; ㄱ,ㄴ,ㄷ,ㄹ,ㅁ,ㅂ,ㅅ,ㅇ,ㅈ,ㅊ, ㅋ,ㅌ,ㅍ,ㅎ). Double consonants (e.g., ‘ㄲ’) and vowels (e.g., ‘ㅙ’) consist of two of the characters.

Linguistically, each of the 24 Hangul characters corresponds to one phoneme and that is the reason why we call Hangul a phonogram. In this point of view, Hangul is analogous to English, and thus, most of the previous studies on Korean dysgraphia have shown the linguistic errors in the left hemispheric stroke patients.[17-20] Most of them reported that linguistic errors such as substitution were significantly dominant in patients with left hemispheric lesion.[17-19] In another study,[20] the researchers reported a Korean-English bilingual patient with the left hemispheric lesion, who demonstrated transposition errors only in English and not in Korean writings.

However, unlike the alphabetic written language system (e.g., English and Italian), Hangul has nonlinguistic characteristics such as physical forms of graphemes and visuospatial/constructional arrangement of graphemes within a syllable. In the physical forms of graphemes, the ten basic vowels are derived from three basic geometric shapes, which represent the three fundamental elements in Eastern cosmology (heaven, earth, and humanity). The consonants modeled after pictorial vocal representations. For example, ‘ㄱ/g/’ depicts the root of the tongue blocking the throat (Figure 2). In the visuospatial/constructional arrangement of graphemes, Hangul syllables differ from those in alphabetical systems which are written horizontally. Each grapheme (consonant, vowel, or double consonant or vowel) must be placed within a square space to form a syllable and a combination of these syllables form a word (호텔) (Figure 3).

Korean syllables typically include an onset, which is a consonant (/cho-seong/), followed by a vowel (/jung-seong/). This may be followed by another consonant (/jong-seong/). That is, each syllable contains at least one consonant-grapheme and one vowel, and a final optional consonant (Figure 4). Using this combinatorial rule, one may generate 11,172 Korean syllables. These are further classified into three subtypes, according to their visuospatial construction: (a) vertical (drawn from top-to-bottom), (b) horizontal (drawn from left-to-right), and (c) mixed-orientation (a combination of the horizontal and vertical orientations) syllables (Figure 5). Due to these visuospatial/constructional features, the configuration of Hangul syllables invokes visuospatial/constructional functions that other writing systems use less extensively.

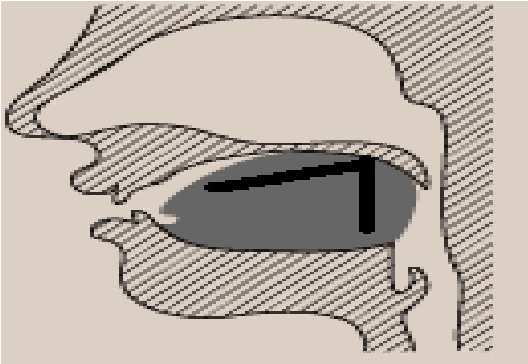


Figure 2. An example of ‘ㄱ/g/’

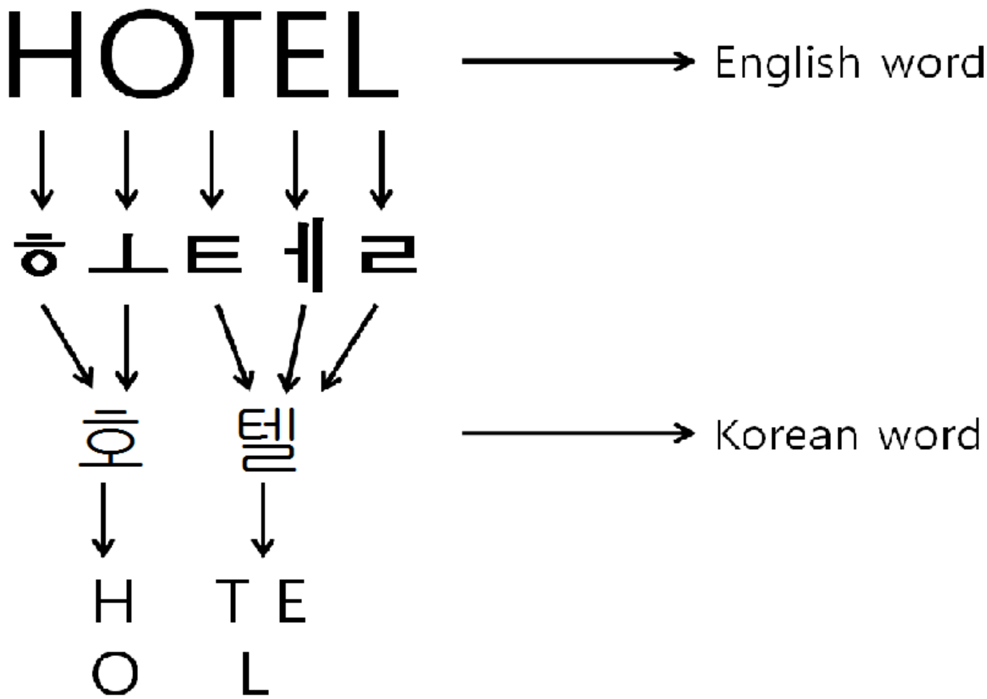


Figure 3. Letters in English words are written in a linear fashion, while graphemes in Korean words are arranged in a square pattern

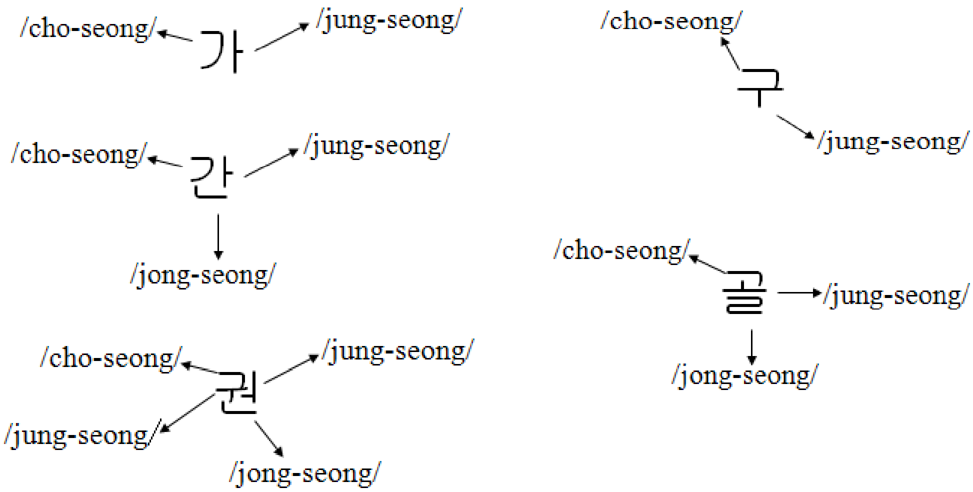


Figure 4. Combination of Hangul syllable

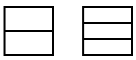
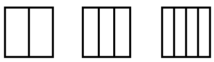
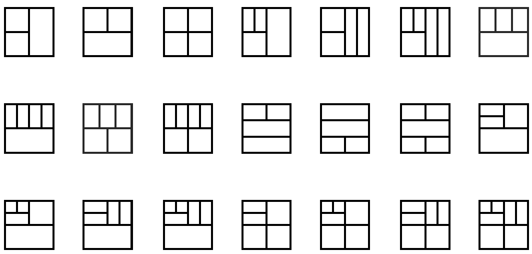
Subtypes	Configuration
(1) Vertical writing	
(2) Horizontal writing	
(3) Mixed-orientation writing	

Figure 5. Subtypes of Hangul configuration (direction of writing)

Traditionally, functions of visuospatial construction and drawing are processed by the right hemisphere. In writing, the right hemisphere might govern the ability to arrange strokes and to draw a character.[21] From this point of view, the right hemisphere might involve the nonlinguistic features of Hangul writing. As a matter of fact, the Korean patients with right hemispheric stroke displayed prominent errors relevant to the physical form, such as stroke omission and addition, and visuoconstructional error, such as graphemic shifting.[22,23]

In summary, the left hemisphere might control a linguistic component in writing, while the right hemisphere might control a nonlinguistic component. Hangul has both linguistic and nonlinguistic value. Therefore, interactivity between the left and right hemispheres may be needed to ensure Hangul writing processing. As shown above, however, all of these previous studies on Korean dysgraphia have been designed to focus on a certain unilateral hemispheric lesion and such studies would emphasize the left hemispheric lesion rather than right.

3. Alzheimer's disease (AD)

Alzheimer's disease (AD) is characterized by the deposition of beta-amyloid plaques and neurofibrillary tangles in the brain.[24] Neuritic plaques are bits and pieces of degenerating neurons that clump together and have a beta-amyloid core. Beta-amyloid is a protein fragment that has been separated from a larger protein called amyloid precursor protein. The disjoined beta-amyloid fragments aggregate and mix with other molecules and neurons. Neurofibrillary tangles are disintegrating microtubules. They break down because of chages in the protein, tau. As they disintegrate, they become tangled and are a signature morphologic change. In addition to these, atrophy or the shirinking of tissue, is common in AD.

AD begins in the perirhinal cortex, the hippocampal complex in the temporal lobes, and the basal forebrain, areas important to episodic memory.[24] When neuropathology extends to temporal and parietal cortices, semantic memory is affected. In addition to the semantic memory loss, patients with AD manifest language impairments, including deficits of naming, verbal fluency, comprehension, and writing due to the lesions of the left temporal lobe.[25]

Among these language disorders, numerous studies on AD have focused on anomia and shows that the naming ability deteriorates even at an early stage of the AD process.[26-29] However, patients with AD may show deficits not only in naming, but also in their written language abilities.[30] Some studies have reported that writing impairments, in other words, dysgraphia is also manifested at a fairly early stage of the disease.[8,31,32] Moreover, the authors[8,31,32] suggest that dysgraphia is a more sensitive indicator of language deficits in AD than anomia.

4. Dysgraphia in AD

Alöis Alzheimer reported the writing impairment of his patient Auguste D.: “She repeats separate syllables many times, omits others, and quickly breaks down completely."[33,34] Although Alzheimer's initial report of the patient was published in 1907, the disease did not become the focus of extensive study until the 1980s. Indeed, until the 70s and 80s, studies were very wide-ranging and based on the analysis of a small corpus of dictated sentences or written descriptions of stories in picture form. These laid stress on the early appearance of the deficits, on their severity compared with the deterioration of oral language, and on their relationship with the severity of dementia.[26,31,32,35] The late 80s proved to be more prolific and coincided with an upsurge in multidisciplinary research and the contribution of cognitive psychology. In fact, it was in the field of written language that cognitive neuropsychology first came to the fore. Rapcsak et al[9] was thus the first to apply the theoretical frameworks and experimental paradigms used in research into dysgraphia by focal lesion to the study of central writing disorders in AD.

After that, there have been many systematic studies[36-40] on dysgraphia of AD. Most studies on dysgraphia in AD that have been performed in countries using the Roman-alphabetic system, focused on the central processes of writing, and have analyzed dysgraphia from a linguistic perspective.[3,36-42] In these studies, researchers used word-level stimuli (e.g., regular, irregular, and nonwords) and attempted to explain error patterns by identifying components that may have been disrupted in the underlying central process of writing and the function of the left hemisphere. Especially regarding central processes, studies of AD patients have often highlighted a pattern of lexical dysgraphia, characterized by a regularity effect and the production of phonologically plausible errors. In other words, compared with controls, patients make more errors on irregular words or orthographically ambiguous words than on regular words or nonwords. This deficit of lexical orthographic processing, first described by Rapcsak et al,[9] has since been reported in several papers.[3,25,42-47]

Compared to the central processes, the nonlinguistic or peripheral aspects of writing in AD had received less attention even though they were mentioned in early reports. Several studies have noted that the spatial aspect of handwriting starts to deteriorate at an advanced stage of dementia.[35,37,48] Research is often restricted to the observation of one particular component of apraxic dysgraphia, characterized by stroke errors in the formation of letters. The authors had to assess the spelling abilities through oral spelling, as they claimed that the latter "suffered from apraxic dysgraphia". In terms of the allographic level, there were few studies on this aspect of writing which described errors, such as upper and lower case substitution of a letter, letter formation, and stroke placement.[3,41,42,46,49] However, these findings were not based on the results of the systematic studies (Table 1).

Table 1. Summary of demographic characteristics of subjects, stimuli, and error types in studies on agraphia in Alzheimer's disease

No. of Ref.	Authors	No. of AD subjects (M:F)	MMSE* score(SD)/ severity	Stimuli	Spelling errors	Motoric-writing errors
50	Glosser & Kaplan, 1989	12 (6:6)	16.55(4.79)*/ mild to moderate	16 regular, 16 irregular words	phonologically accurate regulation error, phonologically inaccurate spelling errors	nonlinguistic errors
9	Rapcsak et al, 1989	11	12.9*	regular, irregular, nonwords	PPE, PIE	X
45	Platel et al, 1993	22	10-26*	10 regular, 10 irregular, 10 nonwords	PPE, PIE(Substitution, omission, insertion)	graphomotor errors(reliance on capital letter, separated & shaky letter)
40	Neils et al, 1995	23	22.6(2.45)* / mild	Copying 62 words, writing to dictation 70 real words, 20 regular, 20 irregular, 20 nonwords	PPE, letter errors(PIE)	X
51	Penniello et al, 1995	11	10-26* / mild to moderate	10 regular, 10irregular, 10 nonword	PPE, non-phonological spelling errors	allographic errors
52	Neils et al, 1995	20 (11:9)	22.70(2.72)*	25 pair of homophone words, 20 nonwords, copying62(41 words, 21 nonwords) words	PPE(homophone confusion), PIE	construction dysgraphia(difficulty forming letters, slow rate and laborious writing

25	Lambert et al, 1996	12 (9:3)	11 to 25* / mild to moderate	10 regular, 10 irregular, 10 nonwords	PPE, PIE(substitution, transposition, deletion, additions), graphomotor error(letter malformation)	graphemic buffer, allographic errors
8	Croisile et al, 1996	33 (14:19)	mild 20.6(2.2)*, moderate 12.6(2.9)*	writing to dictation and spelled orally (18 regular, 18 ambiguous, 18 irregular, 18 nonwords, 12 function words)	phonologically accurate errors, phonologicalyl inaccurate errors, substitutions	X
53	Aarsland et al, 1996	16 (11:5) (4 mild, 12 moderate)	21.1*	20 regular, 30, irregular, 36 nonwords	lexical accuracy, nonlexical accuracy	X
3	Hughes et al, 1997	31 (4:27) (11 minimal, 20 mild)	minimal 24-28*, mild 16-23*	72 single syllable word(24 predictable, 24 unpredictable, 24 irregular), 26 letter copying, cross-case transcription	Phonologically acceptable errors, PIE	allographic errors
49	Neils-strunjas et al, 1998	1 (male)	22* / moderate	36 words	Letter omission, addition, substitution, transposition,	poorly formed letter, stroke omission, superimposed letters. perseveration
43	Glosser et al, 1999	23 (15:8)	97.4† / Mild to moderately severe	24 regular, 24 ambiguous, 24 irregular, 54 nonwords	regularization, orthographic related, unrelated errors, lexicalization	X

54	Slavin et al, 1999	16 (4:12)	12.88* / mild to severe	writing cursive letter 'l' (four times)with varying levels of visual feedback	X	perseveration of stroke
44	Pestell et al, 2000	24	mild 21.2(3.0)*, moderate 14.2(2.0)*	12 regular, 12 irregular, 8 nonwords	PPE, PIE	X
55	Karvie & Neils-Strunjas, 2002	14 (8:6)	22.14(2.25)* / mild	20 regular/irregular words, 24 pairs of homophone words	-	-
42	Luzzatti et al, 2003	23 (11:12)	19.73(3.48)* / mild to moderate	80 regular, 55irregular, 25non words	PPE, PIE, semantic and morphological substitution	X
56	Ardila et al, 2003	1 (female)	91 ∮	8 words, 10 nonwords, copying 44 words	PPE, omission, addition	X
57	Cortese et al, 2003	61	very mild(CDR 0.5)‡, mild AD(CDR 1)‡	20 real word, 20 regular words, 20 irregular words	-	-
39	Groves-Wright et al, 2004	mild 14 (7:7) moderate 14 (9:5)	mild AD(19≤)*, moderate AD(13-18)*	35 real words, 5 nonwords	-	-
36	Carthery et al, 2005	mild 15 (9:6), moderate 13 (7:6)	mild 21.73(2.63)* moderate 16.69(2.39)*	40 nonwords, 40 irregular words	Regularization, (substitution, omission, addition, transposition)	graphomotor errors(persevera tion)
58	Werner et al, 2006	22 (11:11)	AD: 23.7(2.8)*	copying words and paragraph	X	slow rate, lower pressure
59	Silveri et al,	22 mild, 14 severe	mild 21.50(3.19)*,	46 words, 12 nonwords	PPE, PIE, lexicalization	omission, repetition of

	2007		severe 12.86(2.73)*			stroke, allographic errors
41	Lambert et al, 2007	59 (18:41)	21.8(3.3)*	24 regular, 24 irregular, 24 nonword	PPE, PIE	graphomotor, allographic errors

* : Mini-Mental State Exam (Forstein & Forstein & McHugh, 1975) for classifying severity of dementia.
† : Mattis Dementia Rating Sclae(MDRS)(Mattis, 1988) for classifying severity of dementia.
‡ : Clinical Dementia Rating(CDR, Hughes et al., 1982) for classifying severity of dementia
∮ : Neuropsi-Brief Neuropsychological Test Battery for Spanish Speakers(Ostrosky, Ardila, & Rosselli, 1999) for classifying severity of dementia.
- : Data were not presented.
X : not reported
PPE: phonologically plausible errors
PIE: phonologically implausible errors

5. Purpose of the study

AD results in neuropathological changes in diffuse brain regions, including the hippocampus and entorhinal cortex, and the association cortices of the frontal, temporal, and parietal lobes.[24] Given that AD generates widespread cortical atrophy, it is unlikely that written language deficits in AD result solely from selective damage to brain regions that govern linguistic aspects of writing. In addition, AD is a disease that can result in both visuoconstructional and language dysfunction in some stage of their disease process, due to the bilateral involvement of the tempoparietal-frontal areas.[60] Thus, this population may be suitable to explore the nonlinguistic (visuoconstructional) aspects, as well as the linguistic aspects. Besides that, because of the specialized characteristics of Hangul, the nonlinguistic errors, as well as the linguistic ones may be easily observed in the Korean patients with AD. In terms of the justifiability on the study, the largest increase in the prevalence of AD occurs in Korea, so language-specific analysis was necessitated to investigate the characteristics of Korean dysgraphia.

This study aims to investigate the characteristics of writing in Korean patients with AD, and the relationship between Hangul task and other related cognitive functions. Four research questions were as follows:

First, if there were errors in the aspects of linguistic and nonlinguistic domains in AD patients. For this, an examiner instructed patients to write from dictation 60 monosyllabic stimuli. This task allows us to evlauate the effects of particular components in writing, such as linguistic and nonlinguistic aspects. Other than that, if there were specific error patterns dependent of disease severity, disease progression might induce the change of the patients' performance. Here, the Clinical Dementia Rating (CDR) scale was used to quantify the severity of symptoms of dementia. This scale assesses general cognitive and social function of patients, and is broadly accepted by clinicians as a staging measure for dementia.[61-63] The typical distribution and progression of AD has been described by Braak and Braak,[24] with neurofibrillary tangles starting in the medial temporal lobes and spreading to involve the temporoparietal and frontal neocortex. The temporal lobe involves the linguistic function, while the parietal and frontal lobes control the nonlinguistic function, such as the visuospatial construction.[64]

Therefore, according to the disease progression, the first step of error pattern in AD might be linguistic errors, followed by the nonlinguistic errors, such as stroke deletion, addition, and distortion.

Second, if the visuospatial representation of Hangul syllable and letter shapes could be resistant to the disease. In the previous study,[23] the authors proposed that the syllabic shape of Hangul is sufficiently robust and the representation remained intact despite of the cerebrovascular disease. In order to identify the knowledge of a letter shape, the author used a Hangul representation task. Due to the characteristics of Hangul, the performance of the Hangul representation task might be preserved in the later stage of AD patients.

Third, I evaluated the relationships between the performance of Hangul writing and that of neuropsychological variables. Writing is a complex task involving multiple cognitive processes, and previous researchers have demonstrated that writing requires integration of multiple cognitive domains, including frontal executive function, attention, and memory, as well as language, and visuoconstructional abilities.[21] It is vulnerable to disruption by many types of neuropsychological deficits.

Last, I also used positron emission tomography (PET) data to investigate the neural correlates of Hangul writing in AD. In the MR diffusion and perfusion imaging study,[64] impaired spelling ability have been attributed to damage to the left temporal and parietal lobes. Hangul has linguistic and nonlinguistic value. The linguistic component of writing might be related to the temporoparietal lobe in the left hemisphere, while the nonlinguistic component might be related with the bilateral temporoparietal lobe. Thus, the nature of Hangul writing might be vulnerable to dysfunction of both the left and right hemispheres.

II. MATERIALS AND METHODS

1. Participants

Initially, I recruited 80 consecutive patients diagnosed with AD at the Memory Disorder Clinic at Samsung Medical Center in Seoul, Korea between September 2009 and August 2011. AD patients fulfilled the criteria for probable Alzheimer's disease proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA).[65]

The exclusion criteria were as follows: 1) those with less than “6 years of education”, for they might have had difficulty writing Hangul in the premorbid state; 2) those who showed abnormal findings on laboratory tests, which included a complete blood count, blood chemistry, vitamin B_{12}/folate, syphilis serology, and thyroid-function tests; 3) those with showing territorial cerebral infarctions, brain tumors, and other structural lesions on MRI; 4) those with mild bradykinesia and rigidity that can affect writing ability; 5) those who refused to complete the experimental testing.

Four patients refused to complete the experimental testing. One patient with mixed dementia was ultimately excluded. Finally, 75 patients were included in this study; 27 were males and 48 were females. The range of age of the patients was 46 to 92 years old. A panel consisting of 2 neurologists (D.L.N. and S.W.S.) and 1 neuropsychologist (J.C.) with expertise in dementia research made the clinical decisions including diagnosis and clinical dementia rating (CDR) after reviewing the patients' clinical data. The patient group included 16 very mild (CDR 0.5), 37 mild (CDR 1), 19 moderate (CDR 2) and 3 severe (CDR 3) patients.

In order to assess performances on the writing tests, I recruited 20 age-and education-matched healthy controls (HC) from among caregivers from the same memory disorder clinics of the hospital. These subjects had no history of neurological or psychiatric illnesses. The demographic features of the 75 AD patients and 20 HC's are presented in Table 2. All subjects were right-handed, spoke standard Korean, and reported no history of writing disturbances before diagnosis.

Table 2. Demographic variables for the HC and AD groups

	HC (N=20)	AD (N=75)
Age (years)	71.5±7.1	73.1±9.5
Sex: female, *N* (%)	12(60%)	48(64%)
Education (years)	10.9±3.7	11.1±3.7
MMSE	29.0±1.0	17.5±5.8*
CDR	N/A	1.2±0.6

Mean±SD, HC: healthy control, AD: early onset Alzheimer's disease, MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating; N/A; Not applicable
*p<.05

Table 3. Demographic variables according to the disease severities

	HC (N=20)	CDR 0.5 (N=16)	CDR 1 (N=37)	CDR 2 (N=19)	CDR 3 (N=3)
Age (years)	71.5±7.1	71.1±11.3	73.5±8.6	74.3±9.5	68.7±11.4
Sex: female, *N*(%)	12(60%)	12(75.0%)	28(75.6%)	13(68.4%)	2(66.7)
Education (years)	10.9±3.7	11.4±4.1	10.8±3.9	11.1±3.1	12.3±3.5
MMSE	29.0±1.0	21.6±3.7*	18.2±4.3*	13.8±6.6*†‡	8.3±4.0*†‡

Mean±SD, HC: healthy control, AD: early onset Alzheimer's disease,
MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating,
* p<0.05 between HC and CDR 0.5, HC and CDR 1, HC and CDR 2, and between HC and CDR 3
† p<0.05 between CDR 0.5 and CDR 2, and between CDR 0.5 and CDR 3
‡ p<0.05 between CDR 1 and CDR 2, and between CDR 1 and CDR 3

2. Materials

A. Hangul writing to dictation task

The main focus of the study was to analyze the peripheral aspect, especially the visuoconstructional aspect of the errors. Thus, I preferred analyzing only single syllable characters instead of complete words, because the single syllables are simple and more suitable in investigating the visuoconstructional aspect of writing errors. Furthermore, another purpose of using syllable targets was to exclude the central processes in the error analyses. So, in order to prevent the effects of the central processes in writing the target syllables, in addition to the fact that these syllables are in one-to-one grapheme to phoneme correspondence, all of the syllables were selected from parts of words (e.g., ‘가’ (/ka/) of ‘가위’ (/ka-wi/) (scissors)); so the patient could use either the phonological route or the lexical route.

The writing task consisted of sixty single syllable characters. The basic construction of the Hangul script is the ‘syllable’ consisting of three parts: ‘cho-seong’, ‘jung-seong’, and ‘jong-seong’ (Figure 4), as mentioned in the introduction. A combination of the syllables consist a word, (e.g., ‘컴퓨터’) consists of three syllables.

The selection of these stimuli was based on configuration, frequency, and imageability. In terms of configuration, characters with 4 graphemes or less were selected to make the task less complicated. In the vocabulary frequency, words were selected from among the frequently used words in the Learner’s dictionary of Korean.[66] In terms of imageability, all words were concrete words. The stimuli are provided in the Appendix.

B. Hangul representation task

Hangul representation task was aimed to assess the knowledge of the shape of a correct Hangul syllable. In this scenario, I created the wrong-shaped syllables as distracters which were not included in the Korean syllable inventory. This task was divided into two subcategories; the first subtask included ten yes-no questions; while, the second subtask included ten multiple choice exercises. Correct and wrong-shaped syllables belonged to the stimuli. The stimuli are provided in the Appendix.

C. Language test

All patients completed the Korean version of the Western Aphasia Battery (WAB)[67] composed of subtests, such as spontaneous speech, auditory comprehension, repetition, naming, reading, and writing. Among these, the oral language subtests, spontaneous speech, auditory comprehension, repetition, and naming, are used to assess the severity and the type of aphasia. The summary of their scaled scores provide an Aphasia Quotient (AQ). The last two, reading and writing, are used to assess written language ability. When the reading and writing scores are added, the Language Quotient (LQ) is obtained. The Patients with AD exhibited a mean AQ of 82.1 and a LQ of 76.5 (maximum score=100). Table 4 shows the results of the language test according to the dementia disease severities. HCs were not underwent WAB.

Table 4. The results of the language test according to the dementia disease severities

	HC (N=20)	CDR 0.5 (N=16)	CDR 1 (N=37)	CDR 2 (N=19)	CDR 3 (N=3)
Spontaneous speech	-	17.9±1.5	17.3±1.5	15.9±2.7*	13.0±2.8*†
Auditory comprehension	-	9.3±0.3	8.9±1.2	7.8±1.7*†	6.2±2.8*†
Repetition	-	9.1±0.6	8.4±1.5	6.6±2.6*†	5.8±3.4*
Naming	-	8.6±0.6	7.9±1.4	5.7±2.4*†	4.7±3.1*†
Reading	-	8.1±1.3	7.4±2.4	4.9±2.8*†	3.0±3.5*†
Writing	-	8.0±2.0	7.3±2.1	4.6±3.3*†	2.6±3.6*†
AQ	-	90.2±4.5	85.2±9.8	72.6±17.4*†	59.7±22.5*†
LQ	-	87.0±8.1	81.1±13.8	63.5±21.3*†	47.7±28.1*†

HC: healthy control, CDR: Clinical Dementia Rating, -: was not done
AQ: Aphasia Quotient, LQ: Language Quotient
*p<0.05 between CDR 0.5 and CDR 2, and between CDR 0.5 and CDR 3
†p<0.05 between CDR 1 and CDR 2, and between CDR 1 and CDR 3

D. Neuropsychological tests

Only 68 patients underwent neuropsychological testing using a standardized neuropsychological battery, the Seoul Neuropsychological Screening Battery (SNSB).[68] 7 patients either refused to undergo the test, or the duration of time between the date of the test and the Hangul writing test was over 6 months. The battery contains tests for attention, praxis, four elements of Gerstmann syndrome, visuospatial function, verbal and visual memory, frontal/executive function, and the Clinical Dementia Rating (CDR). Among these, the scorable tests contained digit span (forward and backward), the Rey-Osterrieth Complex Figure Test (RCFT; copying, immediate and 20-min delayed recall, and recognition), the Seoul Verbal Learning Test (SVLT; three learning-free recall trials of 12 words, 20-min delayed recall trial for these 12 items, and recognition), the phonemic and semantic Controlled Oral Word Association Test (COWAT), and the Stroop Test (color reading of 112 items during a 2-min period). Age-, sex-, and education-specific norms for each test based on 447 normal subjects are available.[68] According to the normative data and criteria, the scores of these scorable cognitive tests were classified as abnormal when they were below the 16th percentile of the norms for the age-, sex-, and education-matched normal subjects.

3. Procedure

The test was performed in a carpeted room with an ambient noise level. Firstly, all patients performed the Korean version of the Western Aphasia Battery (WAB)[67] in order to investigate the oral language ability. Additionally, Hangul writing to dictation, representation tasks, and SNSB were performed. For the Hangul writing to dictation task, I requested the subjects to write on an A4 sheet of paper. Each of the Hangul stimuli was verbally presented to the patient with a word cue and the subject was asked to verbally repeat the target stimuli before writing to ensure that the patient had no deficits in the auditory input ability. Each Hangul stimulus was verbally presented to the patient with a word cue; for example, “please write the syllable ‘가’ (/ka/) of ‘가위’ (/ka-wi/).” The subject was asked to verbally repeat the target stimulus before writing to ensure that the stimuli were correctly understood.

The Hangul representation task was used to assess the knowledge of the general shape of a Hangul syllable. It did not require either the written production of the syllable or the verbal description. As mentioned earlier, this task was divided into two subcategories. The first subtask was a yes-no questionnaire task. Here, the subjects were shown one stimulus printed in the sheet. The instruction was “Try to judge if the shapes of the written Hangul syllables are correct or not.” The second subtask was a multiple choice questionnaire. The general principle of this subtask involved pointing to a correct shaped syllable in a four-optioned multiple choice exercise. The instruction was “Point the correct shaped Hangul syllable.” The subjects performed a preliminary exercise (‘가’) before starting 20 target items to ensure that the stimuli and instruction were correctly understood. All HCs underwent MMSE and Hangul writing to dictation task. No time limit was imposed.

4. Writing error analysis

A. Hangul writing to dictation task

In terms of accurate responses, the number of the correctly produced Hangul syllables was counted. At this part, I assigned a score of “1”, if the patient showed correct responses of all grapheme in a syllable, and a score of “0”, if the subject displayed incorrect responses, linguistically, or visuospatially. If the subject responded, “I don’t know”, or showed no response, it was considered incorrect. The maximum possible score was 60 and the minimum was 0.

In terms of analyzing errors, I proposed a new set of analysis criteria based on the previous studies.[18,22,23,69,70] As mentioned above (in the writing task section), the central processes involved in the linguistic errors were the main consideration in this paper; thus, for the linguistic errors, the graphemic errors (e.g., spelling errors) within the target syllable were counted. More specifically, the linguistic errors consisted of graphemic omission, substitution, and addition, which changed the target syllable to a different syllable. The nonlinguistic errors consisted of awkward shaping and impossible configurations of Korean graphemes or syllables, such as stroke omission, stroke addition, and graphemic misposition. Stroke omission errors were defined as deleting one part of the grapheme. Stroke addition errors were defined as errors that added redundant strokes to an original grapheme. Errors of graphemic misposition, which is a slight shift of a grapheme, create a nonexistent form within the boundaries of the Korean syllable.

For example, there is the Korean syllable '다'. If the upper horizontal stroke is deleted on the consonant 'ㄷ' the remaining syllable would look like '나', which is one of the existing Korean characters. However, if the lower stroke of '다' is deleted resulting in '┌ㅏ', this would be one of the non-existing Korean grapheme. Errors similar to the former example were analyzed as linguistic errors, where omission, substitution, and addition changed a target syllable to a different syllable. In cases similar to the latter example, I analyzed them as nonlinguistic errors, where omission and addition within a stroke level or graphemic misposition may render a syllable meaningless.

Overall, the writing errors could be considered either linguistic, nonlinguistic errors, mixed (linguistic plus nonlinguistic), or miscellaneous, which included unintelligible responses, picture drawing, or no response. Hence, more than one error could be documented per syllable because the errors were counted per grapheme.

Table 5. Criteria of error analysis

category	subtypes	examples
Linguistic Errors	Graphemic omission	석 → 서
	Graphemic substitution	지 → 비
	Graphemic addition	우 → 운
Nonlinguistic Errors	Stroke addition	깨 → 
	Stroke omission	뭐 → 
	Graphemic misposition	원 → 
Miscellaneous	No response Picture drawing Unintelligible	

B. Hangul representation task

I assigned a score of “1”, if the patient showed correct responses, and a score of “0”, if the subject displayed incorrect responses. The maximum possible numbers of points were 20.

5. Statistics

A T-test was conducted to confirm the differences in the total numbers of correct or error responses between the AD and HC groups. One-way analysis of variance and *post hoc* Bonferroni correction were conducted to identify differences according to disease severity within the AD group regarding the number of correct or erroneous responses. To evaluate the relationship between neuropsychological or language results and Hangul writing in the AD group, partial correlation analysis was conducted after adjusting for age, sex, and duration of education.

6. Positron emission tomography (PET) imaging analysis

The resting state regional brain glucose metabolism was measured, using [1F]fluoro-2-deoxy-D-glucose(18FDG). Thirty-minute positron emission tomography **(**PET) scans were acquired 40 minutes after the intravenous injection of 4.8 MBq/kg FDG using a GE Advance PET scanner. Protocol for obtaining PET scan had been published elsewhere.[71] Of 75 patients, 22 underwent FDG-PET; the rest of the patients either did not take the PET imaging within the period of six months of performing the Hangul writing test, or had refused to take the imaging because of their personal reasons. The mean age (73.4±8.8 years), sex ratio (8 males), and education (11.9±3.4 years) of patients with FDG-PET did not differ from those without FDG-PET. The PET study was approved by the Institutional Review Board (IRB; no. 2006-03-011) of the Samsung Medical Center.

The PET images were analyzed using SPM5 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK) and implemented using Matlab 7.0 (MathWorks Inc.,Sherborn, MA). Prior to the statistical analysis, all of the images were spatially normalized into the MNI standard template (Montreal Neurological Institute, McGill University, Montreal, Canada) in order to remove intersubject anatomical variability. Spatially normalized images were smoothed with 16 mm FWHM isotropic Gaussian kernel. The count of each voxel was normalized to the average count of the cerebellum with proportional scaling in SPM5. After the spatial and count normalization, In order to investigate hypometabolic brain areas that were associated with the performance, we performed multiple linear regression analysis within the patient group (corrected $p<.05$, FDR: false discovery rate) after adjusting for the age and education factors as a covariate of no interest. For the visualization of the *t* score statistics (SPM1 map), the significant voxels were projected onto the 3-D rendered brain or a standard high-resolution MRI template provided by SPM5.

III. RESULTS

1. Overall number of accurate response

Comparing the mean total number of correct responses in the two groups, the performance of the HC group (M=58.6; SD=1.3) was significantly better ($p < .001$) than that of the AD group (M=41.1; SD=18.3). Within the AD group, the number of correct responses significantly differed according to CDR ($p < .001$) (Table 6). By comparing the mean number of correct responses among the patient groups, there were significant differences between CDR 0.5 and CDR 2, CDR 0.5 and CDR 3, CDR 1 and CDR 2, and between CDR 1 and CDR 3. No differences were observed between CDR 0.5 and CDR 1, and between CDR 2 and CDR 3($p < .05$).

Table 6. The number of correct responses according to CDR

	HC (N=20)	CDR 0.5 (N=16)	CDR 1 (N=37)	CDR 2 (N=19)	CDR3 (N=3)	Total AD (N=75)
N	58.6±1.3	49.1± 10.2*	46.1±15.2*	29.0±20.5*†‡	3.6±6.3*†‡	41.4±18.3*

Mean±SD, HC: healthy control, AD: early onset Alzheimer's disease,
N: number of correct responses
* p<0.05 between HC and CDR 0.5, HC and CDR 1, HC and CDR 2, HC and CDR 3, and between HC and AD group
† p<0.05 between CDR 0.5 and CDR 2, and between CDR 0.5 and CDR 3
‡ p<0.05 between CDR 1 and CDR 2, and between CDR 1 and CDR 3

2. Number of writing errors according to CDR

In terms of the analysis of the erroneous response, more than one error could be documented per syllable. When the total erroneous responses between the AD and HC groups were compared, the performance of the AD group (M: 32.5, SD: 44.5) was significantly worse than that of the HC group (M: 1.3, SD: 1.4) ($p<.001$).

Within the AD group, the number of total erroneous responses significantly differed according to CDR ($p<.001$) (Table 7). By comparing the mean number of erroneous responses among the patient groups, there were significant differences between CDR 0.5 and CDR 1, CDR 0.5 and CDR 2, CDR 0.5 and CDR 3, CDR 1 and CDR 2, and between CDR 1 and CDR 3. No differences were observed between CDR 2 and CDR 3.

In error subtypes, HC group showed only linguistic errors. Within the AD group, the number of nonlinguistic and miscellaneous errors were significantly different among CDR groups ($p<.05$). In nonlinguistic errors, there were significant differences between CDR 0.5 and CDR 2, CDR 0.5 and CDR 3, CDR 1 and CDR 2, and between CDR 1 and CDR 3. In the miscellaneous errors, there were significant differences between CDR 0.5 and CDR 3, and between CDR 1 and CDR 3. With respect to the error patterns, CDRs of 0.5 and 1 yielded more linguistic errors, while CDRs of 2 and 3 demonstrated more miscellaneous errors. The maximum score of erroneous responses was 170.

Table 7. The number of erroneous responses according to CDR

	HC (*N*=20)	CDR 0.5 (N=16)	CDR 1 (N=37)	CDR 2 (N=19)	CDR3 (N=3)	Total AD (N=75)
Linguistic	1.3±1.4	9.6±11.5*	10.8±12.9*	20.0±19.4*	22.0±33.0*	13.2±15.8*
Nonlinguistic	0.0±0.0	2.1±2.9	2.3±3.1	7.8±12.7*†‡	8.0±13.0*†‡	3.8±7.5
Mixed	0.0±0.0	0.5±0.9	2.8±11.0	5.9±17.0	0.0±0.0	2.9±11.5
Miscellaneous	0.0±0.0	2.4±4.1	4.0±15.3	28.9±55.5*	60.6±94.8*†‡	12.2±36.5*
N	1.3±1.4	14.8± 15.9*	20.0±28.6*	62.6±58.4*†‡	90.6±81.5*†‡	32.5±44.5*

Mean±SD, HC: healthy control, AD: early onset Alzheimer's disease,
N: number of erroneous responses
* p<0.05 between HC and CDR 0.5, HC and CDR 1, HC and CDR 2, HC and CDR 3, and between HC and AD group
† p<0.05 between CDR 0.5 and CDR 1, CDR 0.5 and CDR 2, and between CDR 0.5 and CDR 3
‡ p<0.05 between CDR 1 and CDR 2, and between CDR 1 and CDR 3

3. The performance of the representation task and the Hangul writing to dictation task

In the early stage of disease (CDR 0.5 and 1), the patients showed correct responses above 75% in both writing to dictation and Hangul representation tasks. CDR 2 showed correct responses below 50% in Hangul writing to dictation task, but the Hangul representation was preserved with 60% of accuracy. In CDR 3, although the patients showed correct responses below 10% in Hangul writing to dictation task, they could manifest 41.5% of accuracy in Hangul representations.

Table 8. The number of correct responses and frequency of writing to dictation task and Hangul representation task

	CDR 0.5 (N=16)	CDR 1 (N=37)	CDR 2 (N=19)	CDR3 (N=3)	Total AD (N=75)
Writing to dictation(60)*	49.1± 10.2 (81.6%)	46.1±15.2 (76.6%)	29.0±20.5 (48.3%)	3.6± 6.3 (6.0%)	41.4± 18.3 (69.0%)
Representation(20)*	18.2± 1.4 (90%)	16.6± 3.0 (80%)	12.3± 6.4 (60%)	8.3± 5.7 (41.5%)	15.5± 4.7 (77.5%)

*The number of maximum correct response

4. The relationship between the performance of other neuropsychological or language testing and the performance of the writing task

The number of correct responses in the writing task was correlated with the scores for forward and backward digit span, SVLT (immediate recall), RCFT (copy and immediate recall), COWAT (animal, supermarket, and phonemic), Stroop Test, MMSE, and CDR. In addition, the number of correct responses in the writing task was correlated with all sub scores of the WAB. The results are provided in Table 9.

Table 9. Partial correlations between the sub-scores of neuropsychological and language testing and the number of correct responses in Hangul writing

	Correlation coefficient
Attention	
Digit span forward/backward(***N***=67/64)	.433**/.465*
Visuospatial function RCFT: copy(***N***=66)	.608**
Memory	
SVLT: sum of three recall trials(***N***=68)	.564**
SVLT: delayed recall(***N***=67)	.126
SVLT: recognition score (true positives/false positives)(***N***=67/67)	.143/-.160
RCFT: immediate recall(***N***=66)	.416**
RCFT: delayed recall(***N***=63)	.190
RCFT: recognition score (true positives/false positives)(***N***=64/64)	-.055/-.123
Frontal/executive function	
COWAT: animal(***N***=67)	.558**
COWAT: supermarket(***N***=68)	.572**
COWAT: phonemic fluency(***N***=60)	.507**

Stroop test: color reading(***N***=59)	.460**
MMSE score(N=75)	.712**
CDR(N=75)	-.471**
Western Aphasia Battery (N=75)	
Spontaneous speech	.534**
Auditory comprehension	.779**
Repetition	.654**
Naming	.724**
Reading	.856**
Writing	.914**
Aphasia quotient	.735**
Language quotient	.876**

RCFT: Rey-Osterrieth Complex Figure Test, SVLT: the Seoul Verbal Learning Test, COWAT: Controlled Oral Word Association Test, MMSE: Mini-Mental State Examination, CDR: clinical dementia rating, N: the number of patients who performed the subtests

*significant at $p<.05$

**significant at $p<.01$

5. SPM analysis of FDG-PET

The voxels, for which glucose metabolism positively correlated with the number of correct responses were located in the right occipitotemporal lobe and left temporoparietal lobe (Table 10, Figure 6).

Table 10. Regions of hypometabolism related to the correct response within the AD group (corrected *p*<.05, FDR, k=200), k: cluster size, FDR: false discovery rate

Regions	MNI coordinates			Brodmann area	t-value
	X	Y	Z		
Rt. inferior temporal gyrus	52	-62	-8	37	6.06
Rt. middle occipital lobe	40	-72	16	19	4.65
Lt. inferior parietal lobule	-56	-54	34	39	5.35
Lt. inferior temporal gyrus	-56	-60	6	37	5.30
Lt. superior temporal pole	-46	6	-20	38	5.34
Lt. middle temporal gyrus	-58	2	-16	21	4.86
Rt. posterior cingulate gyrus	2	-24	40	23	4.83

Lt: left, Rt: right

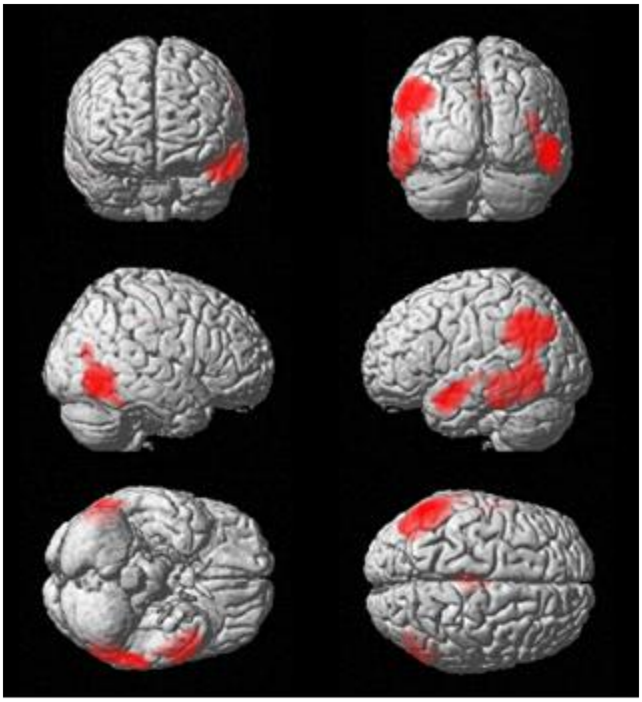


Figure 6. Regions of glucose metabolism (red color) related to the correct response within the AD group

The voxels for which glucose metabolism positively correlated with AQ were located in the left temporal, parietal, and frontal lobe (Table 11, Figure 7).

Table 11. Regions of hypometabolism related to the AQ scores within the AD group (corrected $p<.05$, FDR, k=200), k: cluster size, FDR: false discovery rate

Regions	MNI coordinates			Brodmann area	t-value
	X	Y	Z		
Lt. inferior parietal lobule	-56	-54	34	39	8.21
Lt. middle temporal gyrus	-50	6	-20	21	5.25
Rt. middle temporal gyrus	42	-68	14	21	7.73
Lt. posterior cingulate gyrus	-4	-32	38	23	5.35
Lt. precentral gyrus	-32	10	44	6	3.60
Lt. middle frontal cortex	-34	8	36	44	3.40

Lt: left, Rt: right, AQ: aphasia quotient

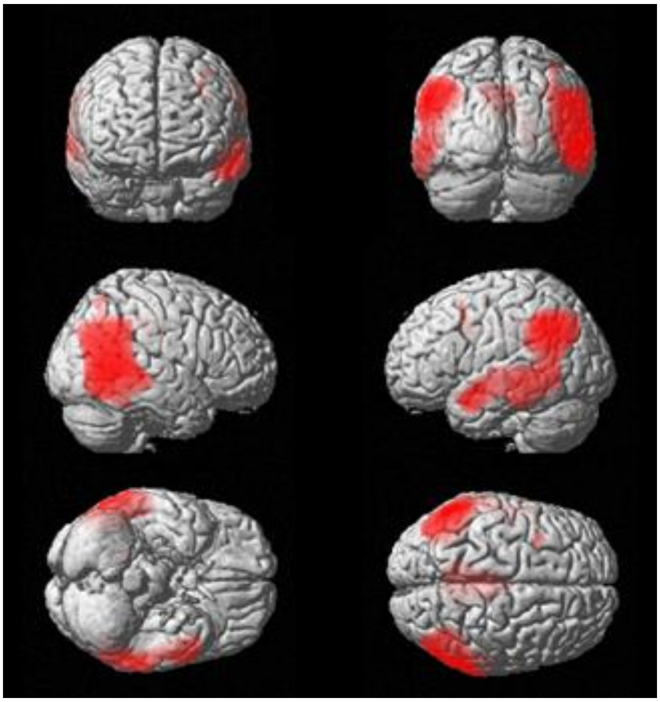


Figure 7. Regions of glucose metabolism (red color) related to the AQ scores within the AD group

The voxels for which glucose metabolism positively correlated with RCFT performance were located in the right occipitotemporal lobe (Table 12, Figure 8).

Table 12. Regions of hypometabolism related to RCFT performance within the AD group (uncorrected *p*<.001, k=200), k: cluster size

Regions	MNI coordinates			Brodmann area	t-value
	X	Y	Z		
Rt. inferior temporal gyrus	50	-58	-4	37	5.65
Rt. middle occipital lobe	42	-76	18	19	4.20

Rt: right

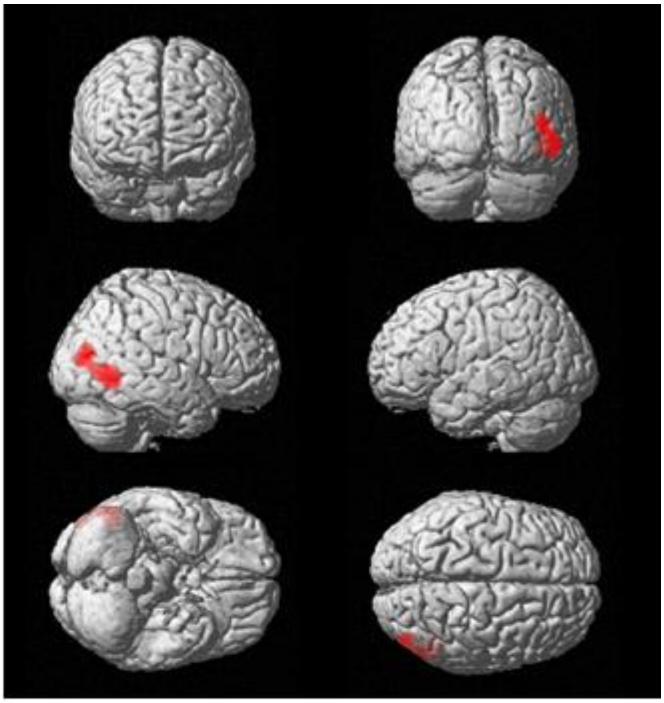


Figure 8. Regions of glucose metabolism (red color) related to RCFT scores within the AD group

IV. DISCUSSION

1. Language-universal writing error patterns in Korean AD patients

The AD patients demonstrated more errors than the normal control. This is hardly surprising, as the patients had cognitive dysfunctions. Within the AD group, as CDR stage increased, the total number of errors also increased. The CDR scale may not reflect language ability per se. However, many studies reported that the deficits of central writing processes gets worsen with the progression of disease,[3,25] supporting the findings of this study. With respect to error patterns according to CDR, the CDR 0.5 and 1 groups showed more linguistic errors, while the CDR 2 and 3 groups produced mostly miscellaneous errors (Figure 9). These results might reflect the fact that trends in error patterns differ according to disease severity. In the initial stages of the disease course, patients can write plausible syllables even if they demonstrate linguistic errors. However, since the ability of writing plausible syllables was impaired in the patients with CDR of 2 and 3, later-stage patients might produce illegible errors instead of writing the syllable legibly. Forbes et al.[46] demonstrated that patients with severe disease tend to rely upon more simplistic writing forms of print. As such, the CDR 3 patients might be expected to produce simplistic picture-like form errors (e.g., circles and loops) of Hangul syllables.

The patient group showed the linguistic errors included graphemic omission, graphemic substitution, and graphemic addition. These errors (Figure 10) are common in any written language such as English, Italian, and French.[8,9,25,36,37,40,46,51] In addition, some of the nonlinguistic errors such as stroke addition and stroke omission are also commonly observed in many written languages.[3,41,42,49]

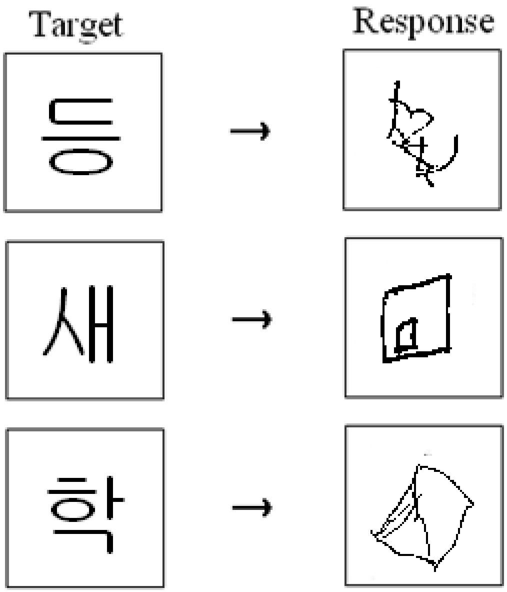


Figure 9. Examples of miscellaneous errors

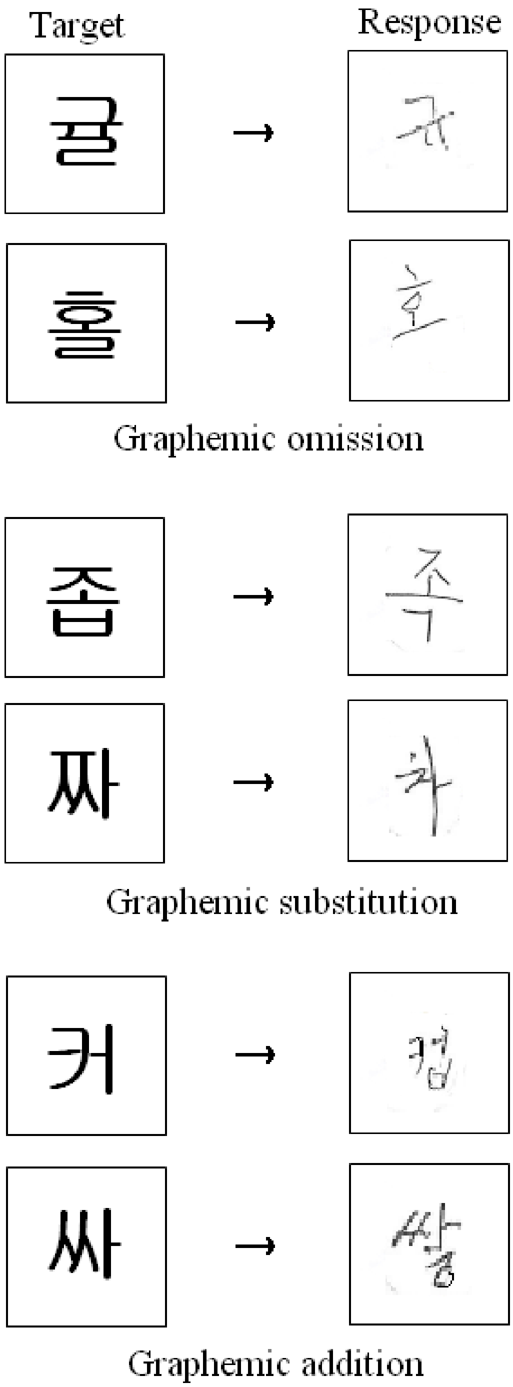


Figure 10. Examples of linguistic errors

2. Language-specific writing error patterns in Korean AD patients

Unlike the language-universal errors, graphemic misposition errors within a syllable (Figure 11) were only observed in our patients. The errors were also showed in the Korean patients with stroke.[23] The discrepancy between Korean and other patients[8,9,25,36,37,40,46,51] could be explained by the visuoconstructional nature of the Hangul script. Each grapheme of the Hangul has its own allocated space within a square structure (Figures 3, 4). In most alphabet-based languages, graphemes are arranged in a horizontal linear fashion to form words. Thus, in English, a slight either horizontal or vertical shift of grapheme with in a word (e.g., ‘r’ in ‘rain’) is permissible and would not change its meaning. However, graphemic shift would result in unintelligible and nonexistent syllabic form in Korean writing.

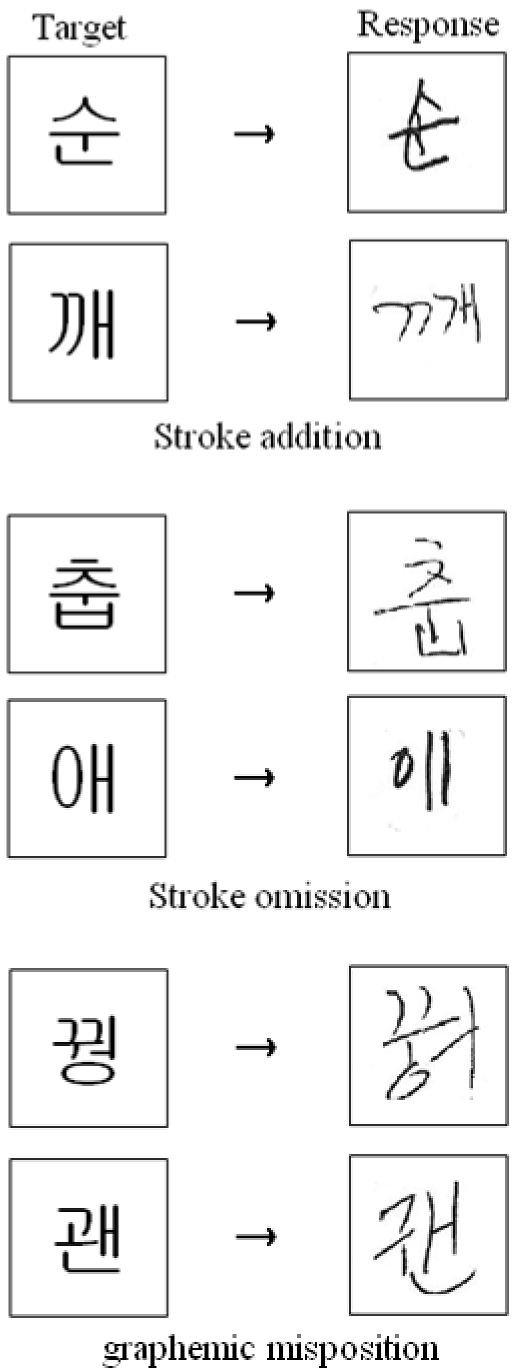


Figure 11. Examples of nonlinguistic errors

Another major finding was that the patients showed nonlinguistic errors even in the early stages of the disease, and this is the inconsistent results found in AD patients with Alphabetical writing.[38] Croisile[38] suggested that visuospatially disorganized handwriting appears later than linguistic abnormalities in the progression of the disease. Specifically, other previous studies[3,25,38] reported that deficits of central writing extend to graphic difficulties and alterations in handwriting spatial organization with disease progression. In severe stages, patients experienced more problems with letter formation and stroke placement.[3,45,46,49] The contrasting finding might be explained by the characteristics of constructing Hangul syllable which requires more spatial and constructional skills for arranging graphemes. In addition, these findings may be explained by the differences in patient. The previous studies[3,45,46,49] have shown that late onset (above 65 year olds) AD patients exhibit hypometabolism in the medial temporal lobe and lateral temporal region in the early stages; while patients in early stages of early onset (below 65 year olds) AD, exhibit hypometabolism in the frontal and parietal regions that is responsible for visuoconstructional dysfunction.[71] Moreover, McNeil and Tseng[21] reported that the parietal lobe processes visuospatial and constructional functions in writing. In the patient group, 20 early onset AD patients were included. Thus, according to the previous findings,[72] the early onset AD patients might experience more frontal and parietal dysfunction than late onset patients of the previous studies[3,45,46,49], who might have produced more diverse errors, including nonlinguistic (visuoconstructional) errors, in the early stages of the disease.

3. Relatively preserved Hangul representation

The performance of Hangul representation might be relatively preserved (41.5%) in the later stage of AD patients even though these patients showed low performance (6%) in the writing to dictation task. Based on the sub-score of the reading test of WAB[67], these CDR 3 patients could not read aloud or understand a context well. It can be concluded that Hangul representations in later stage of Korean AD patients might be partially preserved even though they could not read and write. This finding supports the notion that visual representation of graphemic shape and position within Hangul syllable may be extremely rigid.[20]

4. The relationship between performance of other neuropsychological or language testing and the performance of the writing task

Another major finding was that cognitive impairments in multiple domains such as attention, immediate memory, frontal executive, visuospatial, and language function were well correlated with the performance of Hangul writing. This is consistent with the findings of a previous study.[21]

First, functions of attention and immediate memory might take a part in the writing process by globally interacting with other processes such as semantically stored knowledge, lexically stored knowledge, and graphemic buffers. Thus, impaired attention and memory might be involved in the entire writing process and could result in letter substitution and omission errors.[40,73]

Second, frontal executive function such as planning, organizing behavior, disinhibition, and initiation[74] might also interact with the complexity of the writing process. Thus, patients with frontal lobe dysfunction could have difficulty maintaining the effort required for writing.[75]

Third, the visuospatially unique feature in Hangul writing would have relations with performance in such visuoconstructional task as RCFT. From the finding of the current study, the result of RCFT that focused on visuospatial abilities was highly associated with the performance of Hangul writing task. Generally, figure copying might be accomplished by the pictorial route (e.g., slavish or 'stroke-by-stroke' copying), while Hangul writing was generated by graphemic (spelling and writing) route. Unlike copying by the pictorial route, Hangul writing by the graphemic route can take advantage of stored knowledge of grapheme in long-term memory. However, these two tasks call for the visuospatial abilities for the generation of motor output, regardless of the route involved in the performances. This finding supports the notion that Hangul has visuoconstructional features and might share general visuospatial ability with picture drawing/copying.

Fourth, a similar correlation was also found between Hangul writings and WAB performance which are represented in the left hemisphere. Furthermore, the score of the Hangul writing task was very highly correlated (r=.914) with the score of the writing subtest of WAB. This result suggested that AD affects performance on 'parallel' verbal and written language task,[3, 55] and the writing to dictation single syllables could represent other levels of writing such as spontaneous writing and writing to dictation of sentences/words.

5. SPM analysis of FDG-PET

The behavioral manifestations observed in the error and correlation analyses of Hangul writing were objectively confirmed via PET findings. Significant associations between Hangul writing performance and regional metabolic activity were identified in the left temporal lobes, including the middle and inferior temporal areas and the left angular gyrus. It has been known that writing ability is usually related to the left hemisphere and agraphia is attributed to damage in the temporal lobe, angular, and supramarginal gyri in the left hemisphere. [2,51,64,76] Recently, Nakamura et al.[77] demonstrated activation in the left posterior inferior temporal area during Japanese writing, replicating the results of the previous studies.

Confirming our expectations, the voxels that showed significant correlations were also located in the right inferior temporal and occipital lobes. These two areas, including the "ventral visual stream", were associated with the functions of the orthographic and visual memories.[78] Patients with lesions on the right interior temporal cortex showed greater impairment in the processing of visual materials compared to patients with lesions in the left hemisphere.[79] In addition, significant positive correlation was found between Hangul writing performance and glucose metabolism in the right posterior cingulate gyrus. This area is connected to the occipital lobe and involved in visuospatial functions.[80] Due to the visuospatial configuration of Hangul syllables, the Hangul writing process might involve more nonlinguistic components than do other alphabetical writing systems. Thus, the hypometabolism in the right hemisphere might reflect the decline of the visuospatial-related features of Hangul writing in AD.

In contrast to my expectations, I did not identify any correlation between writing and metabolism in the parietal and frontal lobes. The whole writing process requires the coordination of linguistic and visuoconstructional-motor operations. In particular, the parietal lobe is involved in the ability to generate mental representations (motor engrams) of hand movements required for writing, and the premotor and motor regions in the frontal lobe translate these representations into the corresponding motor programs and appropriate hand movements.[2] However, there was no correlation in these two areas except for the left inferior parietal lobule (i.e., angular gyrus). I speculate that this unexpected result might reflect a false negative in the correlation analysis. AD is not a focal disease, and therefore, it is likely that each cognitive process under investigation requires the integrity of a much larger network of brain regions than we have observed. Due to the diffuse nature of the disease, we are only able to detect the strongest associations between cerebral metabolism and the writing process. These correlations could support that specific brain areas are involved in the writing process observed in patients with AD, but there are likely disruptions to a larger neural circuitry that underlies these deficits.[81]

When examining the correlation between the performance of AQ and cerebral metabolism, I also observed an association with the left temporal lobe. This result was consistent with that of existing literature[81,82] and suggests that this area may be sensitive to both oral and written language. In terms of the patterns of association, Hangul writing was associated more with inferior regional metabolism, and AQ had a higher relative metabolism in the middle region. This pattern is consistent with a previous finding that activation in the inferior temporal lobe may be specific to lexical orthographic processing. In the previous study[76], the task of writing-naming contrast showed a focus of activation associated with writing, but not naming, located in this region. Although identifying the pattern linking AQ and metabolism within the left temporal lobe was our main focus, associations with the right temporal lobe were also observed. This finding may reflect a functional role of this region in language and is consistent with previous work in AD.[83,84]

One of the supportive findings to our hypothesis was that the area most significantly associated with RCFT performance was located in the right occipitotemporal lobe. In the images, these regions were partially overlapped with the regions of Hangul writing. This pattern supported the concept that visuoconstructional abilities are related to drawing and copying and that Hangul writing may be processed in the right hemisphere.[81,85] However, 20 out of 22 patients completed RCFT test and, the statistic threshold value in RCFT was different from that of the other results. Future studies under the same condition may be needed.

V. CONCLUSIONS

The language-specific features our patients made may represent the unique arrangement of graphemes within the square form of a Korean syllable. Our study is noteworthy because it is the first to use PET to investigate the neural correlates of dysgraphia in AD patients using Korean language. The findings of this study provide objective support for the view that Hangul has both linguistic and nonlinguistic (visuoconstructional) characteristics, and impairment of Hangul writing performance in Korean AD patients might be closely related to a functional decline in both the right and left hemispheres.

The study of writing, other cognitive functions, brain functions, and their inter-relationships in AD are important for the following reasons. First, the data suggested that written language samples have greater power than oral language samples to differentiate older adults with high- and low-ability, and that it is necessary to assess both written and verbal language. There was no difference between CDR 0.5 and CDR 1 in all subtests of the language test, while there was a significant difference between CDR 0.5 and CDR 1 in the mean number of erroneous responses of Hangul writing task. Hence, the Hangul writing task may provide more sensitive targets than oral language tests for evaluating the early stages of AD. Second, the writing to dictation task could be used instead of the writing subtask of WAB in examining AD because a strong relationship between the one syllable dictation task and the subtest for writing was observed. With respect to the opportunity cost, the shorter administration time for the writing test could make this test more efficient. Third, our data suggests that writing impairment could be a possible clue to diffusely bilateral brain changes. The brain changes in AD patients may be linked to impaired writing during tasks of daily living and social behavior such as signing a document, proficiency at work, and composing a document.

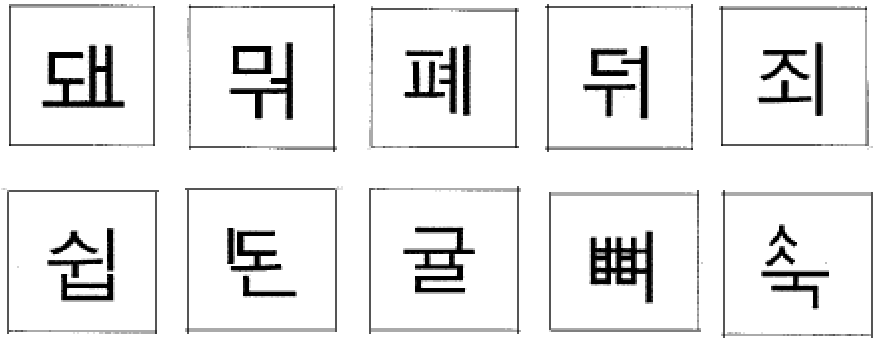
However, this study has limitations in that it mostly focused on the peripheral processes of writing and did not consider the central processes (e.g., lexical and phonological routes) or intermediate process (e.g., graphemic buffer) that could be involved in this patient population. Based on the results, the patients showed the linguistic errors in the early stages, and their writing abilities were associated with the immediate (working) memory function. The analysis on the deficits in the central and intermediate process may be useful in the detection of an early stage of AD. In addition to the underlying mechanisms involved between specific brain regions and Hangul writing, future studies are warranted to explore the specific brain regions related to each of these linguistic and nonlinguistic components in a larger number of patients.

APPENDIX

The stimuli of the Hangul writing to dictation task

Category	Stimuli									
Horizontal Writing	뼈	싸	때	처	내	짜	새	커	혀	깨
	애	꺼	야	배	펴	태	띠	매	태	떠
Vertical Writing	귤	순	춤	불	목	등	콩	쑥	똥	중
	봄	풀	곰	논	육	홀	국	좁	북	금
Mixed-Orientation Writing	왁	권	환	쉽	괜	월	꿩	된	광	훨
	집	화	병	꾀	뭐	학	줘	놔	길	쇠

The stimuli of the Hangul representation task: yes-no questionnaire)



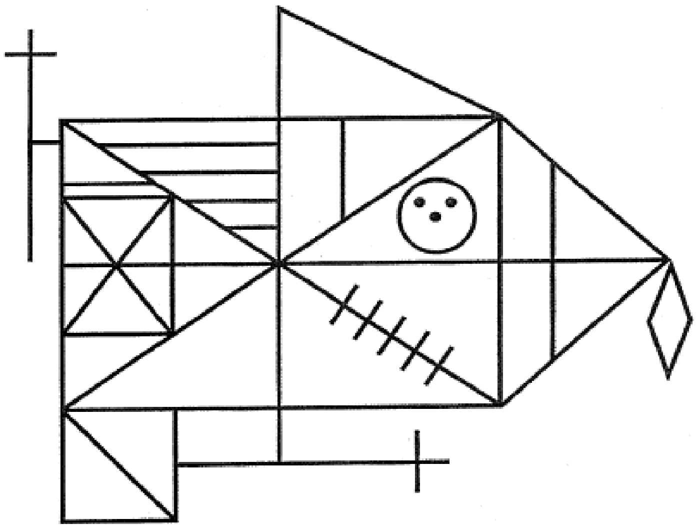
The stimuli of the Hangul representation task: multiple choice exercises)

The stimulus of Rey-Osterrieth Complex Figure Test (RCFT) of Seoul Neuropsychological Screening Battery (SNSB)

Seoul Neuropsychological Screening Battery **SNSB**

RCFT (Rey Complex Figure Test): Copy

반응 시간 : 분 초



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국 문 요 약

알츠하이머성 치매환자의 한글 실서증 특징

배경: 실서증은 각 나라에서 사용되는 문어 체계의 특징이 반영된 다양한 형태로 나타날 수 있다. 한글은 24개의 글자가 음소와 일대일로 각각 대응되는 음소문자에 속한다. 비언어적 측면에서는 자소들이 사각형의 형태 안에 일정한 규칙을 가지고 배열되는 시공간구성적 특징을 가진다. 이러한 관점에서 각 자소가 가로로만 배열되는 알파벳쓰기에 비하여 한글쓰기에서는 시공간구성적 기능이 더 많이 요구된다. 일반적으로 언어적 기능은 좌반구, 시공간구성기능은 우반구의 지배를 받는다. 한글은 언어적, 비언어적 특징을 모두 갖는 문자이므로 한글쓰기에서는 좌, 우반구 기능의 조화가 필요하다. 알츠하이머성 치매는 좌, 우반구에 아밀로이드 단백질이 침착되고, 특히 언어와 관련있는 측두엽과 시공간구성능력과 관련있는 두정엽에 위축이 생기는 질환이다. 따라서 알츠하이머성 치매환자는 한글 쓰기 수행 시 언어적, 비언어적 오류를 모두 보일 수 있다. **목적:** 본 연구에서는 1) 알츠하이머성 치매환자에서 나타나는 한글 실서증 특징과 치매 중증도에 따른 수행력, 2) 한글 음절에 대한 시공간구성적 표상능력, 3) 한글쓰기와 기타 인지기능과의 상관관계, 4) 한글 쓰기와 관련된 신경학적 기전을 확인하고자 하였다. **방법:** 75명의 알츠하이머성 치매환자와 20명의 정상인을 대상으로 한글 쓰기를 수행하도록 한 후, 오류척도에 따라 그 수행을 분석하였다. 또한 환자군에게는 한글표상능력 확인을 위한 판단과제와 인지기능 확인을 위한 신경심리검사를 시행하고, 포도당 유사체를 이용한 양전자방출단층촬영술을 통하여 휴지상태에서의 뇌의 대사량을 측정하였다. **결과:** 1) 환자군 내에서 치매중증도가 심할수록 수행력이 저하되며, 치매의 초기단계부터 비언어적 오류가 관찰되었다. 2) 중증도가 심한 환자군에서 한글쓰기 수행은 상당히 저하됨에도 불구하고 한글표상능력은 보존되어 있었다. 3) 한글쓰기 수행력은 주의력, 언어, 기억, 집행기능 및 시공간구성 능력과 높은 상관을 보였다. 4) 한글쓰기는 우반구 후두측두엽과 좌반구 측두두정엽의 포도당 대사와 연관이 있었다. **결론:** 환자들이 보인 오류는 사각 형태 안에 자소가 조합되는 한글의 특성에 기인한 것으로서, 한글에 언어적 측면과 비언어적 측면이 모두 내재되어 있다는 가설을 지지한다. 또한 한글 음절의 시공간구성적 형태에 대한 표상능력은 질환이 진행된 경우에도 견고하게 보존됨을 확인하였다. 마지막으로는 뇌영상 결과를 통하여 한글쓰기에는 양반구 기능이 모두 필요하다는 가정의 근거를 객관적으로 제시하였다. 본 연구 결과는 알츠하이머성 치매환자군의 문어능력 확인에 필요한 중요한 정보를 제공해주며, 더 나아가 뇌의 광범위한 변화에 대한 일종의 표식으로서 쓰기장애가 치매환자의 감별에 중요한 지표가 될 수 있을 것이라 생각된다.

핵심어: 한글, 쓰기, 실서증, 알츠하이머성 치매, 양전자방출단층촬영술