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Apraxic agraphia after thalamic lesion: three new cases

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ABSTRACT

Apraxic agraphia (AA) is a so-called peripheral writing disorder following disruption of the skilled movement plans of writing while the central processes that subserve spelling are intact. It has been observed in a variety of etiologically heterogeneous neurological disorders typically associated with lesions located in the language dominant parietal and frontal region. The condition is characterized by a hesitant, incomplete, imprecise or even illegible graphomotor output. Letter formation cannot be attributed to sensorimotor, extrapyramidal or cerebellar dysfunction affecting the writing limb. Detailed clinical, neurocognitive, neurolinguistic and (functional) neuroimaging characteristics of three unique cases are reported who developed AA following a thalamic stroke. In marked contrast to impaired handwriting, non-handwriting skills, such as oral spelling, were hardly impaired. Quantified Tc-99m ECD SPECT consistently showed a decreased perfusion in the anatomoclinically suspected prefrontal regions. The findings suggest crucial involvement of the anterior (and medial) portion of the left thalamus within the neural network subserving the graphomotor system. Functional neuroimaging findings seem to indicate that AA after focal thalamic damage represents a diaschisis phenomenon.

Keywords: thalamic stroke, apraxic agraphia

1. INTRODUCTION

Writing is a highly complex skill that requires the mastery and integration of a range of subskills involving cognitive operations, linguistic processing and sensorimotor functioning. Cognitive models of spelling and writing (Ellis, 1982, 1988; Caramazza, Micelli, Villa & Romani, 1987; Patterson & Shewell, 1987; Margolin & Goodman-Schulman, 1992) distinguish between the central processes (linguistic: phonological and lexical routes, graphemic buffer) involved in spelling, whatever the modality of output, and peripheral processes (motor: allographic system, graphomotor processing) that are specific to one particular output modality. In contrast to the central agraphias (e.g. surface (or lexical) agraphia, phonological agraphia, deep (or semantic) agraphia, graphemic buffer agraphia), the peripheral agraphias (e.g. afferent (or spatial) dysgraphia, micro/macrographia, apraxic agraphia, neglect dysgraphia, allographic dysgraphia) are characterized by a marked qualitative dissociation between inferior handwriting and superior non-handwritten forms of spelling, i.e. mental spelling, typing or block spelling (Heilman, Coyle, Gonyea & Geschwind, 1973; Heilman, Gonyea & Geschwind, 1974; Valenstein & Heilman, 1979; Mariën, de Smet E, de Smet HY, Wackenier, Dobbeleir & Verhoeven, 2013). Apraxic Agraphia (AA), a subtype of peripheral dysgraphia, results from the loss of or impaired access to the graphomotor engrams that contain information about the spatio-temporal characteristics of the hand movements necessary to form letters, i.e. relative size, position and order of strokes, but not their absolute size and duration or how they will be effected (Valenstein & Heilman, 1979; Rapcsak & Beeson, 2000). Distorted graphomotor output in AA cannot be attributed to sensorimotor, extrapyramidal or cerebellar dysfunction affecting the writing limb (Hillis, Chang, Breese & Heidler, 2004).

A third causative factor of AA might be impaired transmission of graphomotor patterns into movements necessary to produce letters (Lorch & Barrière, 2003). AA is either isolated or

associated with symptoms that cannot explain the writing impairment and is characterized by hesitant, incomplete and imprecise movements leading to illegible scrawls in severe cases (Valenstein & Heilman, 1979; Rapcsak & Beeson, 2000). Grapheme formation may improve during copying, as an effect of task-difficulty (spontaneous writing requires the expression of ideas while copying and writing to dictation has no such demands (Troyer, Black, Armilio & Moscovitch, 2004)), but is characterized by stroke-by-stroke execution (Rapcsak & Beeson, 2000). Croisile, Laurent, Michel and Trillet (1990) stated that pure agraphia without any accompanying neuropsychological deficits is extremely rare and its clinical features as well as the anatomical lesions are heterogeneous. Roeltgen (2003) proposed a further subdivision of AA in two subtypes: (1) AA with ideomotor apraxia and (2) AA with normal praxis. Semiologically, both subtypes are marked on the graphomotor level by illegible writing, spontaneously as well as to dictation.

AA has been documented in a variety of etiologically heterogeneous neurological conditions and is typically associated with causative lesions located in the dorsolateral and medial part of the prefrontal cortex (conversion of graphomotor plans to motor commands) or in the superior parietal lobe (storage of graphomotor plans) of the language dominant hemisphere. However, lesions in several other brain areas have also been reported to cause AA. Exner (1881); Aimard, Devic, Lebel, Trouillas and Boisson (1975); Coslett, Gonzales-Rothi, Valenstein and Heilman (1986); Rapcsak, Arthur and Rubens (1988); Anderson, Damasio and Damasio (1990); Hodges (1991) and Toghi, Saitoh and Takahashi (1995) documented AA after lesions of the left *prefrontal* cortex. Rubens (1975) and Watson, Fleet, Rothi and Heilman (1986) described AA due to a lesion in the left *supplementary motor area* (*SMA*), while Hillis et al. (2004) suggested that *Broca's area* plays a role in accessing orthographic representations. Left *parietal* lesions may also induce AA (Otsuki, Soma, Arai, Otsuka & Tsuji, 1999; Alexander, Fischer & Friedman, 1992; Roeltgen & Heilman, 1983;

Friedman & Alexander, 1983; Kapur & Lawton, 1983; Auerbach & Alexander, 1981; Basso, Taborelli & Vignolo, 1978). Magrassi, Bongetta, Bianchini, Berardesca and Arienta (2010) showed that damage to the left *superior parietal gyrus* (*SPG*) may lead to distorted grapheme production. The left SPG plays an essential role in sensorimotor integration but is not involved in language; rather it is involved in the initiation of on-line updating for early movement corrections (Tunik, Ortigue, Adamovich & Grafton, 2008). Lesions of the superior portions of the left *supramarginal* and *angular gyri* have been associated with AA (Fischer, McGrath, Bloch, Reinhalter & Otto, 1995; Otsuki et al., 1999; Rapcsak & Beeson, 2000). AA has been documented following damage to the left *temporal* lobe (Rosati & de Bastiani, 1979; Soma, Sugishita, Maruyama, Kitamura & Tsubaki, 1988; Yokota, Ishiai & Furukawa, 1990). In addition, there have been reports of subcortical lesions leading to AA. Laine and Martilla (1981) reported a 34-year-old ambidextral man with AA after a hemorrhage in the left *caudate nucleus* and *internal capsule*. Watson and Heilman (1983) described a 43-year-old right-handed woman who presented with AA due to vascular damage of the *corpus callosum*. Croisile et al. (1990) reported a 41-year-old right-handed man with a hemorrhage in the left *centrum semi-ovale* who presented with impaired grapheme production. The lesion spared both frontal and parietal cortex, but involvement of the body of the caudate nucleus could not be excluded. Nagaratnam, Plew and Cooper (1998), Assmus, Buss, Milkereit, Meyer and Fink (2007) and Krisnan, Rao and Rajashekar (2009) also found AA following vascular damage to the left centrum semi-ovale. Mariën, Verhoeven, Brouns, De Witte, Dobbeleir and De Deyn (2007) reported a 72-year-old right-handed man with AA, mild aphasia and dysexecutive disorder following right *cerebellar* damage. Mariën et al. (2007) hypothesized that AA, as documented by single photon emission computerized tomography (SPECT), resulted from crossed cerebello-cerebral diaschisis affecting the anatomoclinically suspected prefrontal language regions. In a recent review of 25 cases of vascular AA, De Smet, Engelborghs,

Paquier, De Deyn and Mariën (2011) confirmed that AA can be associated with lesions outside the language dominant parietal and frontal region. In their review three cases of cerebellar-induced AA were discussed.

During the last decades, a wealth of studies (e.g. Schmahmann, 2003; De Boissezon et al., 2005; Hillis, 2008; Crosson, 2013) has shown that the *thalamus* is crucially involved in language and cognition. De Witte, Brouns, Kavadias, Engelborghs, De Deyn and Mariën (2011) critically reviewed a study corpus of 465 patients with vascular thalamic lesions published between 1980 and 2008. The taxonomic label of thalamic aphasia was applied to 63.6% of the subjects with left thalamic damage. In addition, 65% of patients with left thalamic damage showed writing difficulties, i.e. paragraphias (Gorelick, Hier, Benevento, Levitt & Tan, 1984; Raymer, Moberg, Crosson, Nadeau & Rothi, 1997), perseverations (Ciemens, 1970; Archer, Illinsky, Goldfader & Smith, 1981) or kanji agraphia (Maeshima, Komai, Kinoshit, Ueno, Nakai & Naka, 1992). Unfortunately, in several cases (Alexander & LoVerme, 1980; Cohen, Gelfer, Sweet. 1980; Cappa, Pagagno, Vallar & Vignolo, 1986; Mori, Yamadori & Mitani, 1986; Fasanaro, Spitaleri, Valiani, Postiglione, Soricelli, Mansi & Grossi, 1987; Kumar, Masih & Pardo, 1996) only the severity level (ranging from mild to severe) of the writing disturbance was reported. Ohno, Bando, Nagura, Ishii and Yamanouchi (2000), Ikegami, Kojima, Maeda, Hojo and Fujihima (2006), Toyokura, Kaboyashi and Aono (2010), Sakurai, Yoshida, Sato, Sugimoto and Mannen (2011) and Osawa, Maeshima, Yamane, Uemiya, Ochiai, Yoshihara, Ishihara and Tanahashi (2013) explained both central and peripheral agraphia following thalamic damage by diaschisis phenomena of the left prefrontal or parietal cortex, reflecting the functional impact of a lesion in a distant but functionally connected region.

Besides clinical studies, brain-imaging studies using SPECT (Decety, Philippon & Ingvar, 1988), positron emission tomography (PET) (Petrides, Alivisatos & Evans, 1995),

functional magnetic resonance imaging (fMRI) (Beeson, 2004; Katanoda, Yoshikawa & Sugishita, 2001; Longcamp, Anton, Roth & Velay, 2003; Matsuo, Kato, Sumiyoshi, Toma, Dinh Ha, Moriya, Fukuyama & Nakai, 2003), diffusion weighted imaging (DWI) (Hillis, 2008) and intraoperative cortical mapping (Roux, Boetto, Sacko, Chollet & Trémoulet, 2003) tried to elucidate which regions are necessary for writing and which could possibly modulate this process. For example, Magrassi et al. (2010) noted that direct bipolar cortical stimulation in a limited area of the left anterior superior parietal gyrus induced complex writing deficits that were typical of both central and peripheral agraphias. They reported a full spectrum of alterations of writing, spanning from spelling errors with no or only slightly altered grapheme production to profound distortions of grapheme production, or even a complete writing stop. The writing impairment occurred without any associated spoken language, reading or calculation deficits. Magrassi et al. (2010) suggested that at least some of the patterns of deficits in these patients could be due to incomplete and unbalanced alterations in the function of the underlying neural circuits. Variations in the typology of the observed alterations in writing induced by stimulation of the same cortical area have also been described in studies in which the left frontal (Morris et al., 1984) and left supramarginal gyrus were stimulated (Roux et al., 2003). Following these stimulation studies, it could be hypothesized that at the thalamic level central and peripheral functions are deeply interwoven such that incomplete or unbalanced perturbation of the activity of the local circuits generates a complex spectrum of agraphias ranging from the central to the peripheral types.

In the literature only a handful of cases, mostly involving Japanese subjects, exists in which AA was induced by a thalamic lesion (Ohno et al., 2000; Maeshima, Osawa, Ogura, Sugiyama, Kurita, Satoh & Tanahashi, 2012; Vandenborre, van Dun & Mariën, 2015). Ohno et al. (2000) described a 78-year-old right-handed man who could not write in the alphabetic script (Roman alphabet), the non-alphabetic script (Kanji (ideograms) and Kana

(phonograms)) or Arabic numerals with either hand due to a left thalamic infarction in the dorsomedial nucleus. Copying, letter imagery and oral spelling of Kanji was intact. The majority of errors involved the partial omission or addition of characters. Scrawling, no reaction, neographism and complete substitution were not observed. Ohno et al. (2000) explained the AA from two different angles: (1) a neurocognitive explanation (the graphemic area was intact, but the patient failed to reach the correct graphemic motor pattern; he could compensate for the agraphia by building and copying a visual letter image) and (2) a pathophysiological explanation (thalamic destruction causes agraphia by exerting a remote effect on the left dorsolateral premotor area). In the alphabetic script, Vandenborre et al. (2015) recently described a 32-year-old ambidextrous man with a left frontal lobectomy who, following bilateral thalamic damage, developed AA. Vandenborre et al. (2015) advanced three hypotheses: (1) a neurological explanation (slow growth of the tumor in the left hemisphere might have gradually induced a transposition of the frontal writing centre to the homologue region in the right hemisphere), (2) a neurocognitive explanation (the thalamus might be involved in cognitive mechanisms subserving the graphomotor planning and execution (e.g. sustained attention) and (3) a neurolinguistic explanation (intact oral spelling and impaired grapheme formation imply a disturbance at the level of motor output). In the non-alphabetic script, Maeshima et al. (2012) described a 61-year-old, right-handed woman with Kanji agraphia and AA due to a left thalamic hemorrhage. She had difficulties writing Kanji characters (she could only write 46 of the 80 Kanji characters that are learned during the first grade), while she wrote correctly in Kana. Copying and oral spelling were intact. She could select each character within a word written in Kanji, but her ability to recall the shape of characters was damaged. Maeshima et al. (2012) explained the mechanism underlying agraphia by an overall reduction in the brain function due to the thalamic lesion. However, the Japanese language consists of a non-alphabetic writing system whereas Indo-European

language systems use an alphabetic writing system, i.e. the Roman alphabet (Shibatani, 1990; Miyagawa & Saito, 2008; Tranter, 2012). Evidence shows that the type of agraphia resulting from a brain lesion depends on the script system (Weekes & Chen, 2005; Yoon, Kim, Seo, Chin, Kim, Lee, Kim, Park, Suh & Na, 2012). Many differences exist between alphabetic and non-alphabetic writing scripts (Vandenborre et al., 2015): not only is the amount of characters different (Hadamitzky & Spahn, 1997), the degree of difficulty to learn to write the different characters (Hadamitzky & Spahn, 1997; Otsuki, 1999), the organization of the underlying neural networks (Paulesu et al., 2000; Siok, Perfetti, Jin & Tan, 2004) and the cognitive system subserving writing may substantially differ as well (Siok et al., 2004). For example, the Japanese writing system consists of two writing scripts: Kana and Kanji. Since Kanji characters are ideograms, i.e. graphically complicated constructs, visuo-spatial skills are crucially implicated in Kanji. In contrast to non-alphabetic writing scripts where each grapheme has its own allocated space within a square syllabic form, a slight horizontal or vertical shift of a grapheme in alphabetic writing does not change the lexical meaning. In this way it is difficult to differentiate between apraxic and visuo-spatial processes in Japanese handwriting.

In the present study we report clinical, neurocognitive, neurolinguistic and (functional) neuroimaging findings in three unique right-handed cases who developed AA in the alphabetic script after a unilateral thalamic stroke restricted to the anterodorsal nucleus (and the anteromedial nucleus).

2. CASE REPORTS

Case 1 (DA)

A 74-year-old right-handed man with normal developmental milestones and an education level of eight years was admitted to hospital due to reduced strength in the right body half and

twinkles in the right arm. On admission a CT scan of the brain revealed a hematoma in the left thalamus. Neurological examination showed only a very mild paresis of the right leg (Medical Research Council scale for muscle strength (MRC): upper limb: 5/5, lower limb: 4+/5). Medical history was characterized by arterial hypertension. He was a retired guard in social services. An axial T2-weighted MRI scan of the brain carried out three days postonset confirmed a small subacute hemorrhage in the left thalamus (Figure 1). As confirmed by a neuroimaging atlas (Kretschmann & Weinrich, 1992), the anterodorsal nucleus of the thalamus was involved. The ventral posterior nucleus was involved due to compression by oedema. Because of the extent of the hemorrhage there was compression of the posterior limb of the internal capsule. The anterior limb was intact. In comparison to normal database findings, i.e. ECD perfusion studies of fifteen healthy adults consisting of eight men and seven women with an age ranging from 45 to 70 years, quantified Tc-99m-ECD SPECT results showed a significantly decreased perfusion in the left prefrontal medial (-2.00 sd) and the right parietal region (-2.57 sd) (Figure 2). Neuropsychological investigations were performed four and 21 days after the stroke.

Insert F*igure 1 and 2 MRI and SPECT findings of DA* near here

Case 2 (CH)

A 77-year-old right-handed man with normal developmental milestones and an education level of twelve years was admitted to hospital due to reduced strength in the right arm and word finding difficulties. On admission the clinical neurological examination showed a mild right hemiparesis (MRC: upper limb: 4/5; lower limb: 4/5) and fluent but empty speech. Investigation of the cranial nerves was normal, no sensory deficits were found. A CT-scan of the brain revealed a hemorrhage in the left thalamus. Medical history was characterized by arterial hypertension, hypercholesterolemia, percutaneous transluminal angioplasty (PTA) of

the right vertebral artery and high-grade occlusion of the right carotid artery. Endarterectomy of the left carotid artery was performed four years before admission. He was a retired taxi-driver. An axial T2-weighted MRI scan of the brain carried out seven days postonset neurological symptoms showed a hematoma in the left thalamus with a clear mass effect (Figure 3). As confirmed by a neuroimaging atlas (Kretschmann & Weinrich, 1992), the anterodorsal and anteromedial nucleus of the thalamus were involved. The posterior limb of the internal capsule was compressed due to mass effects. In comparison to normal database findings quantified Tc-99m-ECD SPECT results demonstrated a significantly decreased perfusion in the left prefrontal lateral (-2.75 sd) and the left prefrontal medial region (-3.40 sd) (Figure 4). Neuropsychological investigations were performed two days after stroke and repeated one and eighteen months after stroke.

Insert *Figure 3 and 4 MRI and SPECT findings of CH* near here

Case 3 (LH)

A 70-year-old right-handed woman with normal developmental milestones and an education level of fifteen years acutely developed severe headache localized left frontal and oppressive in nature. Clinical neurological examination on admission showed a very mild paresis of the right arm (MRC: upper limb 4+/5, lower limb 5/5). Medical history was characterized by arterial hypertension. She was a retired teacher. Axial T2-weighted MRI scan of the brain carried out five days postonset revealed stroke in the left anterior thalamus (Figure 5). As confirmed by a neuroimaging atlas (Kretschmann & Weinrich, 1992), the anterodorsal and anteromedial nucleus of the thalamus were involved. In comparison to normal database findings quantified Tc-99m-ECD SPECT results showed a significantly decreased perfusion in the left prefrontal lateral (-3.68 sd), the left prefrontal medial (-6.08 sd), and the right

prefrontal medial region (-3.43 sd) (Figure 6). Neuropsychological investigations were performed two days, five days and three months after stroke.

Insert *Figure 5 and 6 MRI and SPECT findings of LH* near here

3. NEUROCOGNITIVE INVESTIGATIONS

Methods

Following the thalamic stroke formal neurocognitive and neurolinguistic investigations were carried out (see Table 1). To screen general cognitive functions, the Folstein Mini Mental State Examination (MMSE: Folstein, Folstein & McHugh, 1975) was administered. To investigate memory, visuo-spatial skills and attention the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS: Randolph, 1998; Hobart, Goldberg, Bartko & Gold, 1999) was used. Three drawing subtests were incorporated in the assessment: copying a simple figure (MMSE: Folstein et al., 1975) and copying and recalling a complex figure (RBANS: Randolph, 1998). Raven's Colored Progressive Matrices (CPM: Raven, 1938) were applied to assess visuo-spatial problem solving and inductive reasoning. Handedness was formally assessed by means of the Edinburgh Inventory (Oldfield, 1971). In order to exclude ideomotor and ideational apraxia subtests of the Hierarchic Dementia Scale (HDS: Cole & Dastoor, 1987) were used. Finger proprioception (up-down-test) and limb-kinetic apraxia (including three gesture productions, two on command and one on imitation) were screened in the clinical neurological examination. Neurolinguistic investigations consisted of standardized language batteries (Graetz, de Bleser, & Wilmes, 1992; Visch-Brink, Vandenborre, De Smet, Mariën, 2014; Kaplan, Goodglass & Weintraub, 1983; Bastiaanse, Bosje, Visch-Brink, 1995) supplemented with a detailed examination of written language. A comprehensive language profile was obtained by means of the Dutch version of

the Aachen Aphasia Test (AAT: Graetz et al., 1992) or by means of the Dutch version of the Comprehensive Aphasia Test (CAT-NL: Visch-Brink et al., 2014). Visual confrontation naming was additionally examined by means of the Boston Naming Test (BNT: Kaplan et al., 1983; Mariën, Mampaey, Vervaet, Saerens & De Deyn, 1998) and a verbal fluency task (unpublished norms) was performed, consisting of one-minute generation of words belonging to four different semantic categories, i.e. 'animals', 'clothing', 'means of transport' and 'vegetables'. Written language skills were assessed at different levels of complexity by means of the Dutch version of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA: Bastiaanse et al., 1995). The subtests phonological segmentation (PALPA 15 and 16), mirror reversed (PALPA 17), matching upper-lower case letters (PALPA 18 and 19) and writing to dictation (PALPA 37-44) were used. Subtests 'Writing to dictation' included nonwords and words from different morphological classes varying in length, imageability, frequency and regularity of spelling. In addition to writing to dictation, oral spelling (PALPA 37-44) and typing (PALPA 37 and 40) were also investigated by means of some subtests of the PALPA.

All tasks (praxis, writing and drawing) were examined with the dominant and the non-dominant hand.

Results

Case 1 (DA)

Insert *Table 1 Neurocognitive test results of all cases* near here

On admission cognitive screening was normal (MMSE: 26/30, sd: -0.4). Errors on the MMSE were found in delayed recall (2/3 words) and calculating backwards (3/5) (attention span or calculation). He correctly copied the simple figure of the MMSE. A strong right-hand

preference was confirmed by a laterality quotient of +90 on the Edinburgh Handedness Inventory. He obtained a maximum score on the HDS tasks for ideomotor and ideational praxis (10/10). Limb kinetic praxis and finger proprioception were normal. Four days poststroke, neurocognitive investigations by means of the RBANS (Table 1) only disclosed depressed attentional skills (index 75, sd: -1.7). Memory (index 90, sd: -0.7), visuo-spatial function (index 96, sd: -0.3), non-verbal problem solving (CPM: 22/36, pc: 75) as well as language (index 85, sd: -1; BNT: 52/60, sd: -0.2) scored within the normal range. Although he did not draw the outside cross of the complex figure of the RBANS (probably due to depressed attentional skills), visuo-spatial orientation and visuoconstruction (drawing and placement) were intact.

Insert *Table 2 Neurolinguistic test results of all cases* near here

Examination of verbal fluency resulted in a pathological score (total: 31, sd: -2.2). Written language skills were investigated nine days postonset (Table 2). Letter processing was normal: the patient obtained maximum scores on the phonological subtests (PALPA 15: 45/45; PALPA 17: 36/36; PALPA 18: 26/26; PALPA 19: 26/26), except for phonological segmentation (PALPA 16: 42/45, sd: -1.7). Writing to dictation, however, was significantly more impaired (Figure 7). He scored within the pathologically range for word length (PALPA 37: 13/24, sd: -18.5), word frequency and imageability (PALPA 38: 25/40, sd: -10.1), word class (PALPA 39: 14/20, sd: -14,7) and lexicality (PALPA 43: 14/24, sd: -10,3). A better, though still pathologically low score was seen when writing regular-irregular words (PALPA 42: 30/40, sd: -2,1). Most of the errors were illegible scrawls (22 out of 53) and letter deformations (14 out of 53), he made to a smaller extent stroke deletions (3 out of 53) and stroke additions (4 out of 53). Some phonological paragraphias (i.e. letter additions (10 out of 53)) were also seen. Graphomotor performances were executed in an effortful, slow and

laborious way, which resulted in illegible scrawls and spatial distortions. He could copy single letters, but when copying long words and sentences handwriting became illegible. There was no difference in legibility between upper- and lower-case writing. Oral spelling, on the other hand, scored within the normal range (PALPA 37: 23/24, sd: -1,1; PALPA 38: 38/40, sd: -0,9) and was not influenced by linguistic characteristics such as word class (PALPA 39: 20/20), lexicality (PALPA 43: 23/24, sd: -0.3) or regularity (PALPA 42: 38/40, sd: +0.2). Typing scored within the normal range and was not influenced by word length (PALPA 37: 24/24), lexicality or imageability (PALPA 40: 20/20).

Insert *Figure 7 Handwriting of DA* near here

Repeated neurocognitive investigations were performed twenty-one days poststroke. General cognition remained normal (MMSE: 26/30, sd: -0,4). This time he made one mistake calculating backwards (attention span or calculation). He could not name the day of the week correctly (temporal orientation) and recalled 2 out of 3 words presented to him after 5 minutes (delayed recall). On a more in-depth examination, attention (RBANS index 82, sd: -1.2), language (RBANS index 96, sd: -0.3) and visuo-spatial problem solving (CPM: 29/36, pc 90) improved. Naming (BNT: 53/60, sd: -0.1) and verbal fluency (total: 40, sd: -1.5) improved as well, but the discrepancy between intact oral spelling and distorted handwriting remained (e.g. PALPA 37 oral spelling: 24/24; PALPA 37 dictational writing: 14/24, sd: -16,2).

Case 2 (CH)

A general cognitive screening on admission (Table 1) disclosed a severely defective result (MMSE: 20/30, sd: -4.9). The patient could not recall any of the 3 words presented to him after 5 minutes (delayed recall). Orientation to place was impaired (0/5) and two mistakes

were made when calculating backwards (3/5) (attention span or calculation). He correctly copied the simple figure of the MMSE. A strong and consistent right-hand preference was confirmed by a laterality quotient of +100 on the Edinburgh Handedness Inventory. He obtained a maximum score on the HDS tasks for ideomotor and ideational praxis (10/10). Limb kinetic praxis and finger proprioception were normal. Six days poststroke neurocognitive examinations by means of the RBANS (Table 1) showed overall scores in the severely defective range as reflected by a memory index of 53 (sd: -3.1), attention index of 49 (sd: -3.4), language index of 69 (sd: -2.1) and visuo-spatial index of 57 (sd: -2.9). He correctly copied and recalled the complex figure of the RBANS. Visuo-spatial problem solving (CPM: pc 50) was not impaired. He scored within normal range on the BNT (51/60, sd: -0.4), but obtained a pathological result on the verbal fluency tests (total: 12, sd: -3.6).

Insert *Table 3 Neurolinguistic test results of case two* **near here**

Neurolinguistic investigations (Table 2 and 3), performed five days postonset, revealed a language profile consistent with transcortical sensory aphasia. Language comprehension (AAT: 66/120, sd: -4.2) was severely impaired. Written comprehension (AAT: 14/30, sd: -3.8) was significantly more impaired than auditory comprehension (AAT: 22/30, sd: -1.4). At the sentence level no difference was found between auditory (AAT: 14/30, sd: -3.8) and written comprehension (AAT: 16/30, sd: -3.2). He only focused on content words, which led to default mapping of semantics and pragmatics. Except for normal repetition (AAT: 150/150) language production was poor as well. Visual confrontation naming was impaired (AAT: 92/120, sd: -2.1) and he had difficulty describing pictures in grammatically correct and semantically complete sentences (AAT: 14/30, sd: -3.1). The patient's written language output was severely reduced (Figure 8): he could read aloud (AAT: 28/30, sd: -0.5) and build

up words with letter anagrams (AAT: 28/30, sd: -0.2), but dictational writing was impossible (AAT: 0/30, sd: -7.6). A more in-depth investigation of written language was conducted by means of the PALPA. Test results showed that letter processing and phonology (PALPA 15: 45/45; PALPA 16: 45/45; PALPA 17: 35/36, sd: -1.0; PALPA 18: 25/26, sd: -0.8; PALPA 19: 26/26) were normal. While oral spelling, typing and handwriting all scored within pathological range, a marked discrepancy was observed (for example PALPA 40 oral spelling: 17/20, sd: -3.8; PALPA 40 typing: 18/20, sd: -2.4; PALPA 40 dictational writing: 0/20, sd: -28.1). Handwriting was illegible, but he could orally spell words rather accurately. The pattern of errors in oral spelling was consistent: he made phonological paraphasias (i.e. transpositions (9 out of 26), deletions (8 out of 26), substitutions (7 out of 26) and additions (2 out of 26)) (PALPA 38: 36/40, sd: -2.3; PALPA 39: 18/20, sd: -4.7; PALPA 40: 17/20, sd: -3.8; PALPA 42: 27/40, sd: -3.0; PALPA 43: 20/24, sd: -3.7). When typing he made 3 phonological paragraphias (2 transpositions and 1 deletion). A discrepancy between copying and writing to dictation was observed as well: the patient's performance in copying single letters was better, but when copying long words and sentences handwriting rapidly deteriorated. There was no difference in legibility between upper- and lower-case writing.

Insert *Figure 8 Handwriting of CH* near here

Repeated neurocognitive and neurolinguistic assessments were performed one month after onset neurological symptoms. General cognitive screening (MMSE: 24/30, sd: -2.2) improved, though he still could not name the date and day of the week (temporal orientation) and was unable to recall any of 3 words presented to him after 5 minutes (delayed recall). Results on the RBANS memory (index 69, sd: -2.1), attention (index 72, sd: -1.9), language (index 82, sd: -1.2) and visuo-spatial subtests (index 92, sd: -0.5)) improved (see Table 1) as

well. As reflected by an increased score on the verbal fluency task, language dynamics (total: 37, sd: -1.7) improved as well. Visual confrontation naming normalised (BNT: 56/60, sd: -0.7), while visuo-spatial problem solving (CPM: 17/36, pc 30) declined. Language assessment by means of the AAT showed normal results (Table 3): language comprehension significantly improved (AAT: 114/120, sd: +0.5) as well as language production (AAT repetition: 149/150, sd: +0.6; naming: 118/120, sd: +1.0; reading aloud: 29/30, sd: +0.1). Handwriting improved (PALPA 37: 14/24, sd: -16.8) but remained severely impaired. A discrepancy between oral spelling (for example PALPA 40: 17/20, sd: -3.8) and typing (for example PALPA 40: 19/20, sd: -1.0) on the one hand and dictational writing (for example PALPA 40: 4/20, sd: -22.4) on the other hand was again observed. The pattern of errors in oral spelling remained consistent: he made phonological paraphasias (i.e. transpositions (6 out of 14), deletions (4 out of 14) and substitutions (4 out of 14)) (PALPA 38: 37/40, sd: -1.6; PALPA 39: 19/20, sd: -2.2; PALPA 40: 17/20, sd: -3.8; PALPA 42: 37/40, sd: -0.2; PALPA 43: 20/24, sd: -3.7). When typing he made 1 phonological paragraphia (an omission). Eighteen months postonset neurological symptoms, neurocognitive and neurolinguistic investigations were repeated. A further improvement of cognitive functions was reflected by increased index scores on the R-BANS (Table 1). Memory (index 100) and language (index 88, sd: -0.8) scored within the normal range. Attentional skills (index 75, sd: -1.7) remained slightly impaired and test results for visuo-spatial cognition declined (index 81, sd: -1.3). Visuo-spatial problem solving (CPM: 26/36, pc 82) restored and improved compared to the first examination in the acute phase. In-depth examination of written language was repeated (Table 2 and 3): handwriting was still distorted. Oral spelling evolved within normal range, except for spelling nonwords, where he made two phoneme transpositions (PALPA 43: 18/20, sd: -5.9). Test results on writing to dictation improved as well but the discrepancy between spelling aloud (for example PALPA

40: 20/20) and typing (PALPA 40: 20/20) on the one hand and dictational writing (PALPA 40: 10/20, sd: -13.8) on the other hand remained.

Case 3 (LH)

Cognitive screening performed five days poststroke showed a pathological result (MMSE: 23/30, sd: -2.6). She could not name the date and day of the week (temporal orientation) and could only recall 1 out of 3 words presented to her after 5 minutes (delayed recall). She correctly copied the simple figure of the MMSE. A strong right-hand preference was confirmed by a laterality quotient of +100 on the Edinburgh Handedness Inventory. She obtained a maximum score on the HDS tasks for ideomotor and ideational praxis (10/10). Limb kinetic praxis and finger proprioception were normal. Cognitive examination by means of the RBANS five days postonset showed severely impaired memory (index 53, sd: -3.1), language (index 51, sd: -3.3) and attention (index 53, sd: -3.1). She correctly copied the complex figure of the RBANS. When she had to recall the same complex figure, she could only correctly draw and place 5 out of 10 elements (due to impaired memory). Visuo-spatial cognition (index 105, sd: +0.3) was within the normal range (Table 1). Non-verbal problem solving was normal (CPM: pc 95). Neurolinguistic investigations were performed six days poststroke by means of the CAT-NL (Table 4), BNT and a test for verbal fluency (Table 2). She scored within normal range on language comprehension subtests (CAT-NL auditory comprehension: 61/66, cut-off score: 55; written comprehension: 56/62, cut-off score: 52). Only anomia was found: on the BNT: (32/60, sd: -5.0) and the verbal fluency task (total: 18, sd: -3.1), she scored within the pathological range; the CAT-NL only revealed discrete anomia (nouns: 36/48, cut-off score: 32).

Insert *Table 4 Neurolinguistic test results of case three* near here

Semantic (i.e. circumlocutions or cohyponyms) as well as phonological (i.e. phoneme transpositions or substitutions) paraphasias occurred. Written language skills were investigated one week postonset neurological symptoms (Table 2). Letter processing was normal. The patient scored normal on the phonological tests (PALPA 15: 45/45, PALPA 16: 45/45; PALPA 17: 36/36; PALPA 18: 26/26; PALPA 19: 26/26). Writing to dictation, however, was significantly impaired (Figure 9). She wrote with great effort and at a slow rate. Single letters, spontaneously written, were legible. When writing words, spontaneous cursive writing rapidly declined. Legibility improved when she wrote in upper-case letters. A marked discrepancy was observed between intact oral spelling (e.g. PALPA 37: 24/24; PALPA 38: 39/40, sd: -0.2) and typing (e.g. PALPA 37: 24/24) on the one hand and severely impaired dictational writing (e.g. PALPA 37: 21/24, sd: -4.5; PALPA 38: 32/40, sd: -5.2) on the other hand.

Insert *Figure 9 Handwriting of case three* near here

Repeated neurocognitive (three months after the stroke) and neurolinguistic (four months after the stroke) assessments were performed (Table 1). General cognition remained impaired (MMSE: 23/30; sd: -2.6) and the pattern of errors remained the same (temporal orientation and delayed recall). Although she improved on all subtests of the RBANS, i.e. memory (index 61, sd: -2.6), language (index 75, sd: -1.7), attention (index 68, sd: -0.6) and visuo-spatial skills (index 105, sd: -1.1), memory remained impaired. Neurolinguistic investigation revealed an improvement on all tasks (Table 2 and 4), especially for naming (BNT: 51/60, sd: -0.4; CAT-NL naming nouns: 44/48, cut-off score: 32). She scored on all language subtests within the normal range. Writing skills improved in time, but remained impaired. She

obtained maximum scores for oral spelling (PALPA 37: 24/24; PALPA 38: 40/40; PALPA 39: 20/20; PALPA 40: 20/20; PALPA 42: 39/40, sd: +0.4; PALPA 43: 24/24) and typing?, while handwriting remained slightly (PALPA 37: 24/24; PALPA 38: 37/40, sd: -1.6; PALPA 40: 19/20, sd: -1.0; PALPA 42: 34/40, sd: -1.0; PALPA 43: 22/24, sd: -1.4) to severely (PALPA 39: 17/20, sd: -7.2) impaired.

4. DISCUSSION

Three right-handed patients are reported who in addition to linguistic and cognitive disturbances presented with writing disturbances following a left thalamic stroke (a hemorrhage in case one and two; an ischemic infarction in case three). Although the cognitive and linguistic disturbances disappeared over time, writing was permanently impaired in all three patients. Since writing is a complex and over-learned movement involving motor control, sensory feedback, memory and language, we assessed proprioception, praxis, language, general cognition and written language processes to evaluate the exact nature of the observed writing disorder. Neurological examination excluded a sensorimotor deficit to explain the writing impairment. Since praxis was normal apart from a disruption of graphomotor execution and/or planning, all examinations point to AA. These case studies suggest the functional expansion of the role of the thalamus to the written language network, more specifically the execution and/or retrieving of the motor programs necessary to produce correctly formed graphemes (Vandenborre et al., 2015). This hypothesis is explained from different angles: a neurocognitive and -physiological, and a pathophysiological approach.

In the early acute phase of the stroke the neurocognitive and neurolinguistic profiles of the three cases were characterized by reduced verbal fluency, attention deficits and distorted, illegible handwriting (AA). Case two and three additionally presented with neurocognitive

deficits. While language was intact in case one, the second patient presented with transcortical sensory aphasia (TSA, a fluent aphasia syndrome characterized by impaired auditory comprehension and preserved repetition) (Kertesz, Sheppard & MacKenzie, 1982) and the third patient had anomia associated with semantic as well as phonological paraphasias. The anterior (and medial) portion of the left thalamus was involved in all three cases.

Neurophysiological theories of cognitive processing may explain the linguistic and writing impairments in these patients. Crosson (1999) stated that the thalamus is a critical element in an attentional ('selective engagement') system. Selective engagement serves to increase efficiency within the activated cortical unit and enhances the communication between various units that are engaged. The dorsomedial thalamic nucleus projects to the prefrontal association cortex, while the dorsoanterior thalamic nucleus projects primarily to the limbic association cortex (cingulate gyrus) (Engelborghs, Mariën, Martin & De Deyn, 1998). However, as pointed out by Barbas and Pandya (1989), intrinsic connections of the cingulate gyrus with other fronto-cortical areas are not limited to immediate adjacent areas, but there are also widespread connections with the more distant prefrontal regions. In all three cases the anterior (and medial) portion of the left thalamus was involved resulting in a range of deficits relevant to graphomotor and linguistic processing including (1) impaired attentional set-shifting resulting in executive dysfunctions (Troyer et al., 2004); (2) impaired memory (Sakurai et al., 2007); and (3) impaired use of internal cues for the control of attention, which may be employed by cortical motor areas to guide termination of ongoing movements and initiation of subsequent movements (Abutalebi et al., 2009). Therefore, the neurophysiological connections of the anterodorsal thalamic nucleus to the frontal and prefrontal cortical areas and its role in selective engagement may explain the apraxic writing disorder. The observed linguistic deficits after damage in case 2 and 3 can be explained by damage to the anteromedial thalamic nucleus (De Witte et al., 2011). We hypothesize that

anomia, phonological paraphasias and comprehension deficits were due to a failure of the thalamic system to selectively engage cortical mechanisms necessary for lexical retrieval based upon semantic information. The heterogeneous pattern of linguistic disturbances may underline between-subject variations (e.g. different lesion site in the thalamus). However, since neurocognitive deficits in all three cases significantly improved and language disturbances (TSA in case two and anomia in case three) completely resolved over time, it might be hypothesized that the neurocognitive and neurolinguistic deficits are caused by a mild, temporary structural-metabolic lesion or diaschisis (Kim, Suh, Lee, Park, Ku, Chung & Na, 2009). Handwriting with the dominant right hand, on the other hand, was impaired on admission and remained impaired in the lesion phase of the stroke in all three patients (Mazzocchi & Vignolo, 1979). Although cases two and three had (very) mild right-sided motor impairments, reduced strength in the right arm was not severe enough to explain illegible handwriting. As Harada, Okajima, and Takahasi (2010) reported from three-dimensional movement analysis of handwriting, handwriting in subjects with subcortical stroke resulting in mild paresis of the dominant hand is slow and lengthy, but the spatio-temporal characteristics of the hand movements necessary to form letters are maintained. In the three cases we report, however, handwriting was slow and laborious with distorted spatio-temporal characteristics (letter deformations and spatial distortions) as well. These spatio-temporal distortions associated with declining legibility with increasing word length, relatively preserved copying, and a marked discrepancy between oral spelling and dictational writing are consistent with a diagnosis of AA. In all three right-handed patients acute vascular damage to the left thalamus may be held responsible for the writing disturbance resulting from disturbed graphomotor planning and/or execution. In contrast to the linguistic disturbances which may be caused by a temporary disruption of general attention mechanisms resulting from compression by oedema, handwriting was permanently disturbed after focal

thalamic damage. This implies that the thalamus may be crucially involved in the network subserving graphomotor processing.

A pathophysiological explanation of thalamic induced AA is suggested by similar SPECT-results obtained in all three cases. Quantified Tc-99m-ECD SPECT revealed decreased perfusion in the left prefrontal region crucially involved in the execution of written language. A decreased perfusion in the right hemisphere was observed in two out of three cases (right parietal hypoperfusion in case one and right prefrontal hypoperfusion in case three). The functional disruption of the prefrontal brain regions reflects the functional impact of the thalamic lesion on a distant cortical region due to a lack of excitatory impulses. In line with the findings of Ohno et al. (2000), Ikegami et al. (2006), Toyokura et al. (2010), Sakurai et al. (2011), Maeshima et al. (2012), Osawa et al. (2013) and Vandenborre et al. (2015) these data suggest that the neural network responsible for writing is not restricted to the left superior parietal region (storage of graphomotor plans) and the left dorsolateral and medial premotor cortex (conversion of graphomotor plans to motor commands), but might also include the thalamus. The permanently disturbed handwriting of the three cases confirms a significant impact of the thalamus in the graphomotor planning and execution. Functional brain imaging indicates that AA in the alphabetic script may result from specific diaschisis phenomena affecting the prefrontal writing centre (Exner's area) (Engelborghs et al., 1998; Engelborghs, Mariën, Pickut, Verstraeten, & De Deyn, 2000). Exner's area is located in the posterior part of the left middle frontal gyrus (Exner, 1881; Anderson et al., 1990; Toghi et al., 1995) and is thought to contain the motor programs necessary for producing letters, as outlined by neuropsychological models for writing (Toghi et al., 1995). Decreased perfusion of the left prefrontal region may reflect the impaired recollection of the representation of the graphemes and the impaired generation of a motor program of written letters (Anderson et al., 1990; Longcamp et al., 2003). SPECT and positron emission tomography studies have revealed

major functional effects in frontal areas after discrete lesions in the dorsomedial thalamic nucleus (Engelborghs et al., 2000). It is possible that disruption of the striatal-ventral pallidal-thalamic-frontomesial limbic loop induces graphomotor distortions consistent with apraxic agraphia.

However, further research is needed to unravel the precise neurobiological substrate of the complex relationship between writing and the thalamus. Focal thalamic damage might lead to different types of agraphia in different script systems. In the non-alphabetic script, Ikegami et al. (2006) described a patient who developed pure agraphia and paragrammatism due to a left thalamic lesion. Toyokura et al. (2010) reported a 63-year-old right-handed man with pure agraphia, Kanji agraphia and paragrammatism following left thalamic damage. Sakurai et al. (2011) described two patients, a 58-year-old right-handed woman and a 52-year-old right-handed man. Both patients developed Kanji agraphia, grapheme deformation and micrographia following damage to the left ventral lateral and ventroposterolateral thalamus. Osawa et al. (2013) reported a 71-year-old right-handed man with Kana and Kanji agraphia due to a left thalamic lesion. In the alphabetic script, Vandenborre et al. (2015) reported a 32-year-old ambidextrous man with a left frontal lobectomy who developed AA following bilateral thalamic damage. Ohno et al. (2000) described a patient with AA both in the alphabetic and the non-alphabetic script due to a lesion of the dorsomedial portion of the left thalamus. However, it is not certain whether the patient Ohno et al. (2000) reported, presented with AA. Sakurai et al. (2011) defined AA as (1) presence of illegible graphemes in writing that cannot be accounted for by sensorimotor dysfunction; (2) grapheme production improves when copying; (3) preserved oral spelling or typing; and (4) disordered writing stroke sequences. The patient described by Ohno et al. (2000) seemed to meet only criterion (3). As a result, although impaired access to the graphomotor engrams, preserved oral spelling

and typing were evident in this case, hesitant, incomplete and imprecise movements leading to illegible scrawls, as a hallmark feature of AA, were not described. In line with Sakurai et al. (2011) we might conclude that the case reported by Ohno et al. (2000), is not a typical example of AA. The pattern of errors, i.e. partial omission or addition of characters, might be more suggestive for afferent or spatial agraphia than for AA. As Magrassi et al. (2010) indicated, the thalamus could be involved in both central and peripheral writing processes. The exact role of the thalamus in the motor and linguistic components of the writing process may therefore be of a very complex nature.

5. CONCLUSION

Unique clinical evidence in three patients using the alphabetic script was obtained suggesting a role for the anterior (and medial) portion of the left thalamus within the neural network subserving the planning and execution of graphomotor output. Quantified SPECT-results suggest that diaschisis may be the crucial pathophysiological mechanisms underlying "thalamic induced AA".

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Legend to figures

1) Brain MRI axial T2-weighted slices of case one showing a small subacute hemorrhage in the anterodorsal nucleus of the left thalamus with a clear mass effect on the posterior limb of the internal capsule.
2) Quantified Tc-99m-ECD SPECT perfusion scan of the brain (case one) demonstrating significantly decreased perfusion in the left prefrontal medial (-2.00 sd) and the right parietal region (-2.57 sd).
3) Brain MRI axial T2-weighted slices of case two showing a substantial hematoma in the anterodorsal and anteromedial nucleus of the left thalamus with a clear mass effect

on the posterior limb of the internal capsule.

4) Quantified Tc-99m-ECD SPECT perfusion scan of the brain (case two) demonstrated a significantly decreased perfusion in the left prefrontal medial (-2.75 sd) and the right parietal region (-3.40 sd).
5) Brain MRI axial T2-weighted slices of case three showing an acute subcortical stroke situated in the anterodorsal and anteromedial nucleus of the left thalamus.
6) Quantified Tc-99m-ECD SPECT perfusion scan of the brain (case three) demonstrating a significantly decreased perfusion in the left prefrontal medial (-3.68 sd) and the right parietal region (-6.08 sd).
7) Handwriting samples of case one (9 days poststroke)
    a. Cursive writing of lower-case letter ‘a’ and upper-case letter ‘h’.
    b. Copying one-syllabic Dutch words, i.e. mond [mouth], glas [glass], storm [storm] and worst [sausage] in lower-case versus upper-case letters
    c. Copying single letters ‘r, v, k, d, l, b, i, h, j’ in lower-case letters
8) Handwriting samples of case two
    a. Cursive writing of a Dutch word, i.e. wonde [lesion] one day poststroke
    b. Copying one-syllabic Dutch words, i.e. mond [mouth], glas [glass], storm [storm] and worst [sausage] in lower-case versus upper-case letters 10 days poststroke
    c. Copying single letters ‘p, s, t, w’ in upper- and lower-case letters 10 days poststroke
9) Handwriting samples of case three
    a. the alphabet in lower-case and upper-case letters (5 days poststroke)
    b. Cursive writing of single Dutch words, i.e. mens [human], groot [large], open [open], zien [to see] and hemel [heaven], in lower- versus upper-case letters (5

days poststroke)

c. Comparison copying one-syllabic Dutch words 1 week (left) and 4 months (right) poststroke, i.e. mond [mouth], glas [glass], storm [storm] and worst [sausage] in lower-case letters

Legends to tables:

1. d=days, m=months, po=postonset neurological symptoms, SS=Standard Score, SD=Standard Deviation, pc=percentile
2. d=days, m=months, po=postonset neurological symptoms, SD=Standard Deviation
3. SD=Standard Deviation