another patient. This "silent" mutation (c.750G>A, heterozygous) described earlier was found in conjunction with a novel heterozygous missense mutation that results in the replacement of a cysteine by a serine (p.Cys450Ser). The latter is considered pathogenic based on the following 4 arguments: (1) the cysteine residue and the protein region are highly conserved throughout evolution (see Fig 2); (2) the missense mutation was not detected in 210 control chromosomes; (3) compound heterozygosity for both alleles was detected only in the affected sibling and not in the 2 unaffected siblings and both parents; and (4) no additional mutations or splice aberrations were detected in the mRNA, making it unlikely that another mutation had been missed. It is notable that also in this patient the increase of α-AASA levels (urine: 4.7mmol/mol creatinine; plasma: 0.9μmol/L) is modest compared with other α-AASA dehydrogenase–deficient patients (n = 10; range, 9.6–75mmol/mol creatinine for urine, 0.8–8.0μmol/L for plasma). However, the limited number of patients tested does not allow any definitive conclusion on these metabolite levels, and further enzyme studies are warranted.

This study further emphasizes that increased urinary α-AASA is associated with pathogenic mutations in *ALDH7A1.* This illustrates that increased α-AASA levels should be used as a noninvasive pathognomonic marker in diagnostic laboratories. It may be desirable, at least in the Netherlands, but likely in a broader area, first to analyze the DNA for the presence of mutations in exons 14 (p.Gln399Glu), 9 (c.750G>A), and 4 (p.Arg82X) of *ALDH7A1,* before sequencing the complete open reading frame (ie, an additional 15 exons).

Furthermore, we detected an intriguing "silent" mutation that led to the introduction of a cryptic splice site that predicts to encode a truncated protein. Notably, a silent variant may also have an effect on *cis*-elements, resulting in erroneous splicing,[6] or it may even lead to different kinetics of mRNA (protein) translation.[7] This study illustrates the importance of mRNA studies when a seemingly nondisease-causing variant is detected or in the case where there is a strong suspicion of α-AASA dehydrogenase deficiency (ie, increased urinary levels of α-AASA) without the identification of one or both mutated *ALDH7A1* alleles. The fact that *ALDH7A1* is expressed in blood allows the inclusion of mRNA studies in such occasions.

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Hemineglect: Take a Look at the Back Space

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Visual hemineglect, the failure to explore the half of space, real or imagined, contralateral to a cerebral lesion with respect to body or head, can be seen as an illustration of the brain's Euclidean representation of the left/right axis. Here we present two patients with left-sided neglect, in whom only the left hemispace in front of an imagined and/or real body position was inaccessible, but the space behind them remained fully represented. These observations suggest that of the three Euclidean dimensions (up/down, left/right, and front/back), at least the latter two are modularly and separately represented in the human brain.

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We have the intuition that the space around us is Euclidean. This fundamental spatial fact is reflected in the way we perceive and cognitively structure the world and in the way we talk about the world, referring to three axes: up/down, front/back, and left/right. In patients with hemineglect, the right/left axis is typically impaired, in the sense that patients do not explore the half of space contralateral to their cerebral lesion. But how do these patients process the invisible sector of space that is behind them? Although there are numerous research reports on the way space is represented in the brain and deficits along the left/right but also up/down[1,2] axis have been described, there is a puzzling lack of research on how the space behind the subject is coded. Patients with spatial hemineglect provide an interesting model to oppose front and back space.[3,4] We report here the cases of two patients with hemineglect demonstrating that, although their right/left axis is perturbed, their back/front axis remains intact. This finding promotes the idea that space is encoded according to the three dimensions of Euclidean geometry, and that each of the axes is independently represented in the brain. Spatial hemineglect thus points to functional divisions of space, for which clinicians have largely remained blind.

Patients and Methods

Patient A is a 86-year-old right-handed man who suffered from an acute onset of dysarthria and left hemiparesis that recovered partially within 2 weeks. MRI showed a recent right thalamic ischemic stroke, involving the mediodorsal nucleus of the thalamus and the pulvinar. Neuropsychological assessment on the 5th day after admission showed no global intellectual deterioration or abstract reasoning difficulties and no visual field defects. To examine neglect in extrapersonal space,[5] we gave four different tasks both in near (NS) and far (FS) space[6]: a line bisection task and three cancellation tasks with letters, digits, or lines. In addition, in the NS condition, we included a landscape copying task, a star cancellation and a clock copying task, and word (n = 10 per condition) and sentence (n = 3 per condition) reading in horizontal, vertical, and mirror (only for words) positions.

Performance was flawless in all NS and FS conditions. There was no significant deviation in line bisection (mean deviation in NS = +3mm; mean deviation in FS = +3mm), and no omission in the cancellation tasks. Although he had no signs of neglecting the left half of the visual world when actually seeing it (no perceptual neglect), he omitted recognition of the left half of space when imagining it (representational neglect[7]). This neglect was dependent on the imaginary viewer position he was asked to take, in the sense that he was systematically neglecting what was standing at the left side of his imaginary viewpoint.

Patient B is a 62-year-old right-handed woman who suffered from an acute large right frontotemporoparietal ischemic infarct including the basal ganglia, probably caused by atrial fibrillation. She had a severe left hemiparesis and hemisensory loss without hemianopia, from which she recovered partly over 3 months. Comprehensive neuropsychological evaluation was normal except for severe left hemispatial neglect both in the perceptual and representational domain, an unawareness of this deficit (anosognosia), and some mild frontal executive signs. Two different tasks to assess perceptual neglect were given both in NS and FS: a line bisection task and two cancellation tasks with letters and bells. In addition, other tasks were given in the NS condition, including copies of figures and word and sentence reading in horizontal, vertical, and mirror (only for words) positions.

Performance demonstrated a perceptual neglect stronger in NS than FS tasks (mean deviation in line bisection in NS was +9mm and in FS +5mm; the letter cancellation test in NS 4/12 and in FS 7/12; Bell Cancellation Task in NS 20/35 and in FS 24/35). Exploration of the visual stimuli during the cancellation tasks was systematically started from the right side of paper sheets, demonstrating a consistent spatial bias overall. Copying and reading tasks were all impaired by neglect-related errors.

Assessment of representational neglect took place during the first month after stroke and was done following the procedure that Bisiach and Luzzatti[8] first described. The patients were asked both to verbally describe and to draw a map of two locations from different, opposite vantage points. The first location was the hospital room for Patient A and the home for Patient B; the second location was a famous square of Geneva (the "Place Neuve"). Two vantage points were systematically imposed, shifting the perspective by 180 degrees. An additional condition required the patients to locate themselves turning their back to the room/home or to the square. All these conditions were tested in random order on different sessions (back condition was not tested at each session, but when tested, this condition was counterbalanced with the others). Performances remained stable across sessions.

Results

A strong representational neglect was present throughout the different location imagery tasks in the different viewer-centered condition for both patients. Whichever location they were asked to describe, the patients systematically omitted the elements located on their left imaginary self-position, whether by drawing or verbal descriptions, suggesting that items in the mental image were spatially coded in a viewer-centered left-right axis. However, when asked to draw the "Place Neuve" and their room/home imagining that they were turning their back to it, the patients reported elements in both hemispaces, so that the total number of items recalled was increased, suggesting that this condition facilitated the evocation of space (Figs 1 and 2).

Discussion

Here we present two patients with left-sided neglect, in whom only the left hemispace in front of an imagined

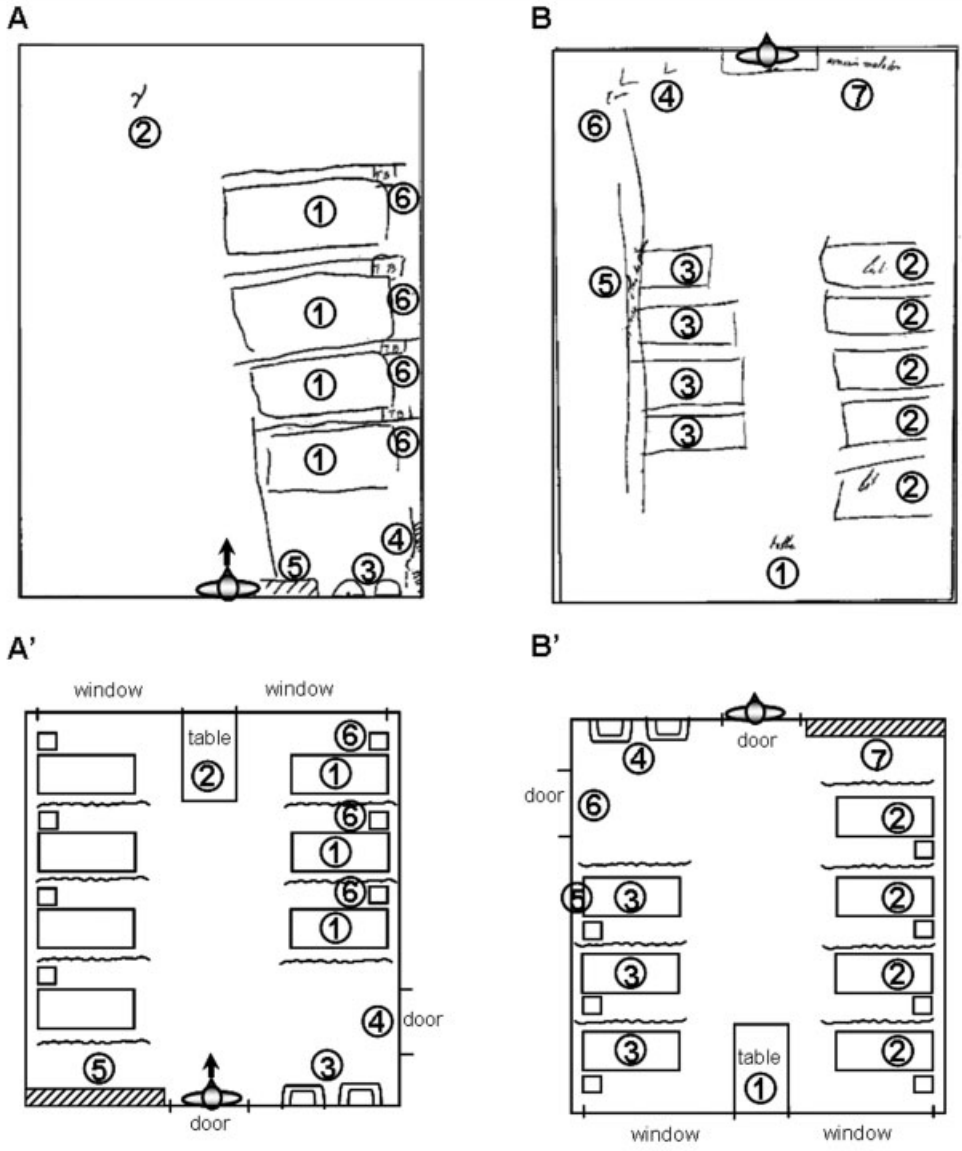

Fig 1. Examples of Patient A's drawings of his hospital room corresponding to the imposed imagined vantage points (arrow). *(A) Facing the table with his back against the room's door (room in front of him). (B) Drawing from the same imagined position but different orientation: the patient has to imagine that he turns his back to the room (room in his back, 180-degree imaginary shift). (A', B') Actual maps of the room with corresponding items indicated by numbers corresponding to the patient's placement, oriented according to the imagined vantage point.*

and/or real body position was inaccessible, but the space behind them remained fully represented.

We do not think that improved performance in backspace was simply due to an enhanced arousal associated with backspace imagery. Early experiments with healthy subjects[7] had evidenced worse, rather than better, performance if attention was directed to the back compared with the front of one's body. Imagery of frontal space involves a viewer-centered reference system when retrieving information in body-centered coordinates, whereas imagery of back space may rather depend on an orientation-free retrieval. Imagery of back space, even if visually mediated,[9] would therefore not share the same neural pathway as frontal space representation because it disrupts the possibility to adopt a viewer-centered reference frame. Even if the subject can claim to have "eyes in the back of his head," a proper viewer center of reference frame cannot be adopted.

This explanation opens a discussion about the orientation of humans toward visuomotor space. Humans are front/back oriented, and their body is programmed to act in the frontal space.[10,11] No movement planning is generally done in the space behind us; although with the aid of a mirror neglect, patients may be able to

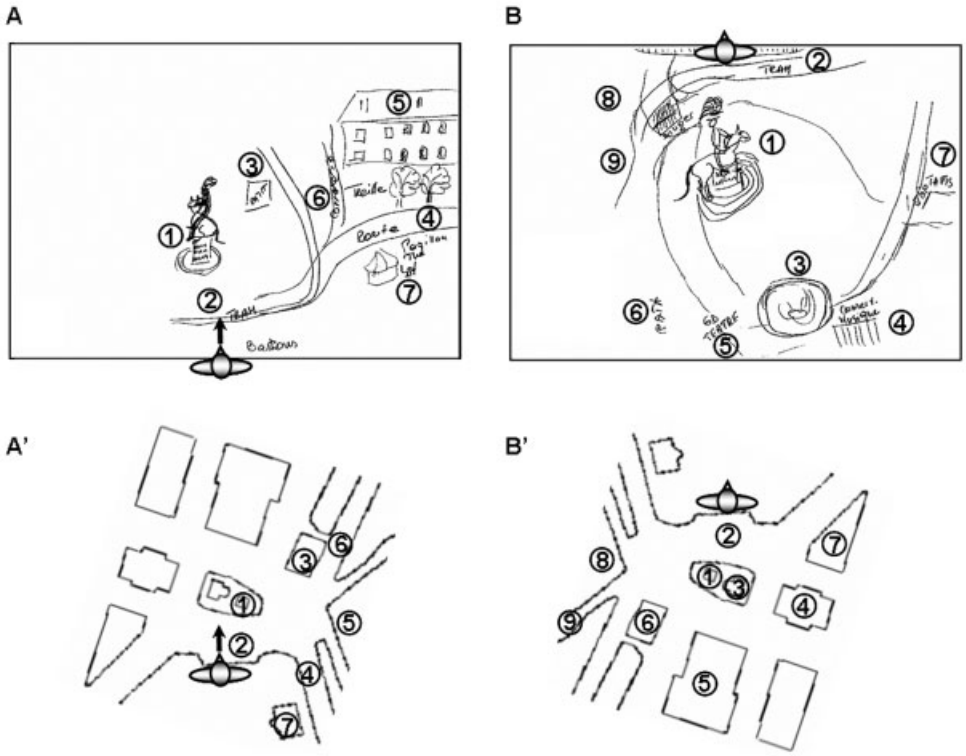

Fig 2. Examples of Patient B's drawing of the square corresponding to the imposed imagined vantage points (arrow). *(A) Facing the square. (B) Square in the back. (A′, B′) Actual maps of the square with corresponding items indicated by numbers, oriented according to the imagined vantage point.*

reach for objects placed behind their shoulder.[12,13] We thus hypothesize that the preserved representation of back space is due to the fact that no action directed to the visual imagery scene could be evoked. Many areas participating in space representation are motor areas,[14] and the posterior parietal cortex is involved in the initial stage of planning spatial movements.[15–17] It is plausible that visual imagery toward a space that cannot be coded motorically by actions involves different neural processes. In fact, recent work with healthy subjects[18] suggests that the terms *left* and *right* may loose their meaning if the hands are held in backspace for lateral decisions about a mental image.

If our interaction with the surrounding world were encoded according to Euclidian geometry, the three axes would be independent. The present observation addresses only the two dimensions left/right and front/back, and allows the conclusion that these must be represented separately. Our results show that the lesions that touched the left/right dimension did not touch the front/back dimension, at least not to a degree of becoming clinically relevant. This suggests that the representation of space is indeed organized in a Euclidian manner, and that the failure to organize space in the right/left dimension because of a lesion is not sufficient to disrupt the organization of the intact front/back dimension. Evidently, the top/bottom and back/front axes appear to have functional priority. The left/right axis cannot be defined until top/bottom and back/front are established. Therefore, the right/left axis is the least stable one.[19,20] These observations thus suggest that the three cardinal dimensions are likely represented as separate modular networks in the brain, and provide novel information and suggestions to foster further investigations on the nature of space representation in hemineglect, from a dissociation between a motor[21] (front) and a nonmotor (back) space.

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Mutations in the Cyclic Adenosine Monophosphate Response Element of the Tyrosine Hydroxylase Gene

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Tyrosine hydroxylase (TH) deficiency (OMIM 191290) is one cause of early-onset dopa-responsive dystonia. We describe seven cases from five unrelated families with dopa-responsive dystonia and low homovanillic acid in cerebrospinal fluid who were suspected to suffer from TH deficiency. Analysis of part of the TH promotor showed five homozygous and two heterozygous mutations in the highly conserved cyclic adenosine monophosphate response element. Our data suggest that, if no mutations are found in the coding regions of the gene in patients strongly suspected of TH deficiency, the search for pathogenic mutations should be extended to regulatory promotor elements.

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Typically, TH deficiency becomes manifest by the end of the first year and is characterized by ptosis, inexpres-

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