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<u>**Letter to the editor (case study) for the Annals of PRM**</u>

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Dear Editor

Handwriting is a complex task involving motor, linguistic, perceptual, and attentional skills predominantly controlled by the left hemisphere but requiring a spatial organization that depends on the right hemisphere[1]. Handwriting is often affected after right-hemispheric lesions, with a spectrum of signs related to the spatial layout of the written language,[2-5] constituting spatial dysgraphia/agraphia.[2,6,7] These signs are multi-faceted.[2-4,7] Most deal with spatial compression or mental rotation of the space and are related to spatial neglect: omitting the left half of the paper, overwriting or compressing some words, and omitting and substituting letters or graphemes. Others such as tilted writing and a progressive increase of the left margin cannot be interpreted as signs of spatial neglect and remain to be understood.

Here we present a case suggesting that these handwriting signs after stroke might be due to a counterclockwise tilt in representing the vertical, transposed on the sheet of paper referring to top and bottom.

JW was a 75-year-old right-handed male who had a right fronto-parietal hematoma (Fig. 1A and 1B) causing left hemiplegia with hemianesthesia, left hemianopsia and spatial neglect (US National Institutes of Health Stroke Scale score 13). At entry in rehabilitation (day 13 after the stroke), JW showed spatial neglect and pusher syndrome interpreted as a result of an extreme bias in the internal model of verticality [8]. He behaved as if he implicitly aligned his body posture onto a representation of the vertical, tilted counterclockwise. JW also presented a consistent and global counterclockwise tilt of his written production (Fig. 1E-G): drawing (-12°) and writing (left margin -9° with respect to the vertical, lines -11° with respect to the horizontal). He wrote without any space compression, deletions or omissions.

JW agreed to a further clinical investigation of these troubles to guide their rehabilitation, and also signed informed consent to be enrolled in the cohort DOBRAS (clinicaltrial.gov:NCT03203109). Several domains of spatial cognition were assessed at 2, 3 and 9 months post-stroke (M2, M3 and M9): spatial neglect by means of a battery of tests including the representation of the subjective straight ahead (SSA),[9] representation of the vertical (visual vertical [VV] and postural vertical [PV])[8], and drawing and writing on blank and cued (lined) paper as well as after a modulation of the verticality bias. Assessments involved using validated tests, devices, and protocols, all routinely used (details in additional material), except for a novel procedure to test handwriting. The SSA (10 trials) was compared to the actual straight ahead (0°), whereas deviations affecting the VV and PV (10 trials each) were compared to published normal values.[8]

To interpret JW's drawing and writing, we tested 12 right-handed healthy individuals (5 males), matched in age (mean [SD] 75.2 [2.8] years) and sociocultural level. All participants were tested in accordance with the Helsinki Declaration, with the approval of the local ethical committee (2019-04-09-1) after giving their written consent.

Statistical analysis involved using SPSS v23 (IBM Corp., Armonk, NY, USA). The existence of a systematic deviation (tilt) by comparison to the reference was tested by one-sample *t* tests. Negative values indicated a counterclockwise tilt (leftward, upward). Amplitudes and the significance of JW's tilts were analyzed with Z-scores (VV, PV) or T-scores (drawing, writing) calculated with control data. Conditions were compared by Wilcoxon test for paired samples or Friedman ANOVA. Significance was set according to Bonferroni corrections (bilateral tests). Data are presented as mean (SD).

JW's spatial neglect was severe at M2, affecting body and non-body spaces (Table 1), without any sign of spatial alexia. Only a few neglect signs persisted at M3 but no longer at M9, when the representation of the SSA, not tested earlier, was also normal (-0.7° [2.8], p=0.739).

JW's representation of verticality was tested under baseline conditions at M2 and M9 and also after a modulation procedure (M3). Thresholds of significance were corrected at 0.05/4=0.012. At M2, JW showed a severe transmodal counterclockwise tilt affecting the VV (-13.1°; 11.9*T-scores, $p<10^{-6}$) and PV (-11.2°; 12.4*T-scores, $p<10^{-6}$). This bias remained at M9 but was attenuated (VV= -5.3°; PV= -5.7°). As expected[10], the PV was modulated after 10 min of ipsilesional (right) whole body tilt in the dark at 30° (-9.8° before, 0.5° immediately after). JW's writing (9 lines and margins) was better oriented 20 min after the modulation procedure (before -10.2° (2.2) vs after -6° (1.5); p=0.008).

In controls and JW, *drawing orientation* was quantified by the tilt with respect to the horizontal for the 5 horizontal segments of the landscape to be copied (Fig. 1E)[11]. The corrected P-value was 0.05/4=0.012. The drawing was tilted counterclockwise: slightly for controls (-1.5° [0.57]; t=8.5, $p<10^{-6}$) and markedly for JW at M3 (-4.5°, t=5 and p=0.008; 5.3*T-scores, $p<10^{-6}$) and M9 (-8.4°, t=3.8 and p=0.02; 12.1*T-scores, $p<10^{-6}$). Because M3 and M9 data did not differ ($p=0.08$), they were pooled to show a substantial and remaining counterclockwise tilt (-6.7°) greatly deviated from the horizontal ($t=4.9$, $p<10^{-3}$), much greater than the control deviation (9.1∗T-scores, $p<10^{-6}$).

To analyze writing orientation, controls and JW were asked to copy the first 5 lines of the French version of the Brave Handwriting Kinder test[12] (Fig. 1G), a text standardized to diagnose dysgraphia in children. They were seated comfortably with the head and trunk aligned and wrote at a comfortable speed on a paper sheet that was blank or cued (lined) and was affixed to a graphic tablet (Wacom© Intuos 4 A5 USB) carefully centered in front of them on a slanted table (30°). The written samples were digitized, and 3 criteria were measured by an operator (CJ) who was blinded to the writer: the orientation of each of the 5 lines with respect to the horizontal, the orientation of the left margin with respect to the vertical (4 segments defined between the beginning of lines averaged to give a margin orientation per individual), and the mean time to write a letter calculated by using Ductus software[13].

For writing on blank paper, thresholds of significance were 0.05/6=0.008 for orientation and $p=0.05/3=0.016$ for time. The lines were tilted counterclockwise for all individuals: slightly for controls (-1.8° [1]; $t=6.4$, $p<10^{-4}$) and markedly for JW at M3 (-11.1° [2.6], 9.3∗T-scores, $p<10^{-6}$) and M9 (-8.2° [0.7], 6.4∗T-scores, $p<10^{-6}$). Because M3 and M9 data were comparable ($p=0.080$), they were pooled. JW showed a substantial deviation, far away from the horizontal (-9.9°; $t=13.8$, $p<10^{-6}$), and much greater than that for controls (7.4∗T-scores, $p<10^{-6}$). The left margin was vertical for controls (-0.4 [2.9]; $t=0.49$, $p=0.64$) but tilted counterclockwise for JW (8 values pooled for M3-M9: -8.1°, $t=20.4$, $p<10^{-6}$). After a transformation (90°), margins and lines did not differ for controls ($p=0.182$) or JW ($p=0.02$), which indicates that they remained orthogonal. Writing a letter took 0.5 (0.16) sec for controls but more time for JW at M3 (1.3 sec; 5∗T-scores, $p=10^{-6}$) and M9 (0.9 sec; 2.5∗T-scores, $p=0.012$).

For writing on a paper spatially cued, individuals were asked to copy the same text following lines tilted at 12° and 24° (Fig. 1H-K), counterclockwise (upward) or clockwise (downward). The corrected p-value was 0.05/10=0.005. Friedman ANOVA revealed no effect in controls ($p=0.118$); they followed the lines with negligible deviations at -24° (-0.1° [0.3]; $t=1.3$, $p=0.2$), -12° (-0.1° [0.3]; $t=1.3$, $p=0.2$), 12° (0° [0.6]; $t=0.23$, $p=0.82$), and 24° (-0.6° [0.7°]; $t=3.03$, $p=0.01$). In contrast, cueing had a strong effect on JW ($p<10^{-3}$ for pooled data for M3-

M9). He wrote above lines, and the deviation increased with the downward cueing (Fig. 1J,K). He followed lines at -24° (-0.6°; t=-2.9, p=0.017) but not lines at -12° (-1.3° [1.1]; t=-3.9, p=0.004), 12° (-4.1° [2]; t=-6.5, p<0.001), or 24° (-8.8° [2.5°]; t=11.2, p<0.001).

JW never wrote with the smallest sign of spatial dysgraphia but with a consistent vertically oriented bias persistent for at least 9 months (although attenuated), even though the spatial neglect disappeared and representation of the SSA was normal. This observation excluded a causal association between spatial neglect and tilted writing and helps in understanding why prism adaptation improves neglect-related signs of spatial dysgraphia but not line inclinations[7]. In contrast, JW showed disorders related to verticality bias, with a counterclockwise tilt consistent in magnitude for 2 modalities of verticality perception: drawing and both components of handwriting (i.e., left margin and lines), the writing keeping isotropic dimensions and orthogonality between margin and line deviations. Two ways to modulate spatial representation brought consistent additional information. When submitted to a procedure that should transiently attenuate his verticality bias, JW wrote with an attenuated tilt. When instructed to follow tilted lines, he failed to write on lines tilted to the side opposite his own verticality bias and only succeeded with the lines that greatly tilted in the same direction as his own verticality bias.

This case study demonstrates that tilted handwriting may result from a biased representation of the vertical. It argues for a multi-determined impaired spatial organization of writing after right hemisphere lesions[14], responding to several mechanisms: spatial neglect, feed-back related errors, or motor direction bias and also bias in the representation of the vertical. JW correctly constructed letters that excluded feed-back–related errors. His drawing was also homogeneously tilted, which excluded a motor bias error. This tilt had detrimental consequences on executing the task, slower than for controls.

This extends to handwriting the close link between perception and action with respect to the vertical, until now documented only for postural control. The detection of tilted handwriting could signal a biased representation of the vertical, which should be explored[15].

In conclusion, our case study brings new insights into tilted writing, which must be differentiated from other signs of spatial dysgraphia and may be caused by a bias in the representation of the vertical. Our observations open a new avenue for both clinical practice and research.

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TABLES AND FIGURES

Table 1. Spatial neglect in JW after right hemispheric stroke at 2, 3 and 9 months (M2, M3, M9) post-stroke

Peripersonal neglect was assessed by the Bells (cancellation) test (Gauthier et al., 1989), line bisection test (mean deviation for 2 lines of 200 mm), copying a landscape (Gainotti & Tiacci, 1970), text-reading, and overlapping figures test (Gainotti, D'Erme, & Bartolomeo, 1991). Personal neglect was assessed by the thumb-finding test (Bisiach, Perani, Vallar, & Berti, 1986), the reformulated comb-and-razor test (Beschin & Robertson, 1997; McIntosh et al., 2000) and the Fluff-Test (Cocchini et al., 2001). The Catherine Bergego Scale was also used, giving ecological information about both body and non-body neglect (Bergego et al., 1995). Asterisks indicate pathological scores. Details on these methodological references are in the references section of additional material.

	M2	M3	M9
Body neglect scores			
Bisiach test (0 to 3, cut-off > 0)	**1***	**3***	**0**
Comb test (% neglect index, cut-off > 11%)	**13***	**0**	**9**
Razor test (% neglect index, cut-off > 11%)	**21***	**0**	**0**
Fluff-Test (omissions 0 to 15, cut-off > 2)	**3***	**2**	**0**
Non-body neglect scores			
Bells cancellation test (total omissions, cut-off ≥ 6)	**1**	**1**	**1**
Line bisection (ipsilesional deviation in mm, cut-off ≥ 7 mm)	**20***	**5.5**	**-2**
Landscape copying (omissions 0 to 5, cut-off > 0)	**0**	**0**	**0**
Text reading (omissions, cut-off > 0)	**0**	**0**	**0**
Overlapping figures test (omissions, cut-off > 0)	**0**	**0**	**0**
Neglect in daily life score			
Catherine Bergego Scale	**6.3**	**4.4**	**0**

Figure 1. Some puzzling behaviors presented by JW after a right hemisphere stroke.

A) Axial Flair MRI slice and **B)** coronal FSE T2-weighted MRI slice 2 months after stroke, showing a right parietal hematoma in resorption. **C)** Leftward lateropulsion and pusher behavior in standing. **D)** Line bisection 1 month after stroke. The 21-mm ipsilesional deviation indicated severe spatial neglect (cut-off 6.5 mm). **E)** Copying a landscape (Gainotti and Tiacci, 1970) 1 month after stroke, showing signs of spatial neglect (left parts of the first tree and the house) associated with a -12° inclination of the main axis of the drawing. **F)** Short text written by JW before the stroke. Main line axes were approximately horizontal (0.5°). **G)** Short text written by JW after stroke showing a global counterclockwise tilt (plain blue lines). The dashed blue line represents the horizontal reference. Plain blue lines indicate the inclination of the orthogonal coordinate system. The mean tilt of lines was -9.4° and mean tilt of the left margin -9°. Finally, counterclockwise tilts observed after stroke were all congruent in direction and amplitude: drawing, margin and lines. **H-K)** JW’s handwriting on cued (lined) paper, with lines traced 24° upward (H), 12° upward (I), 24° downward (J) and 12° downward (K).

Figure

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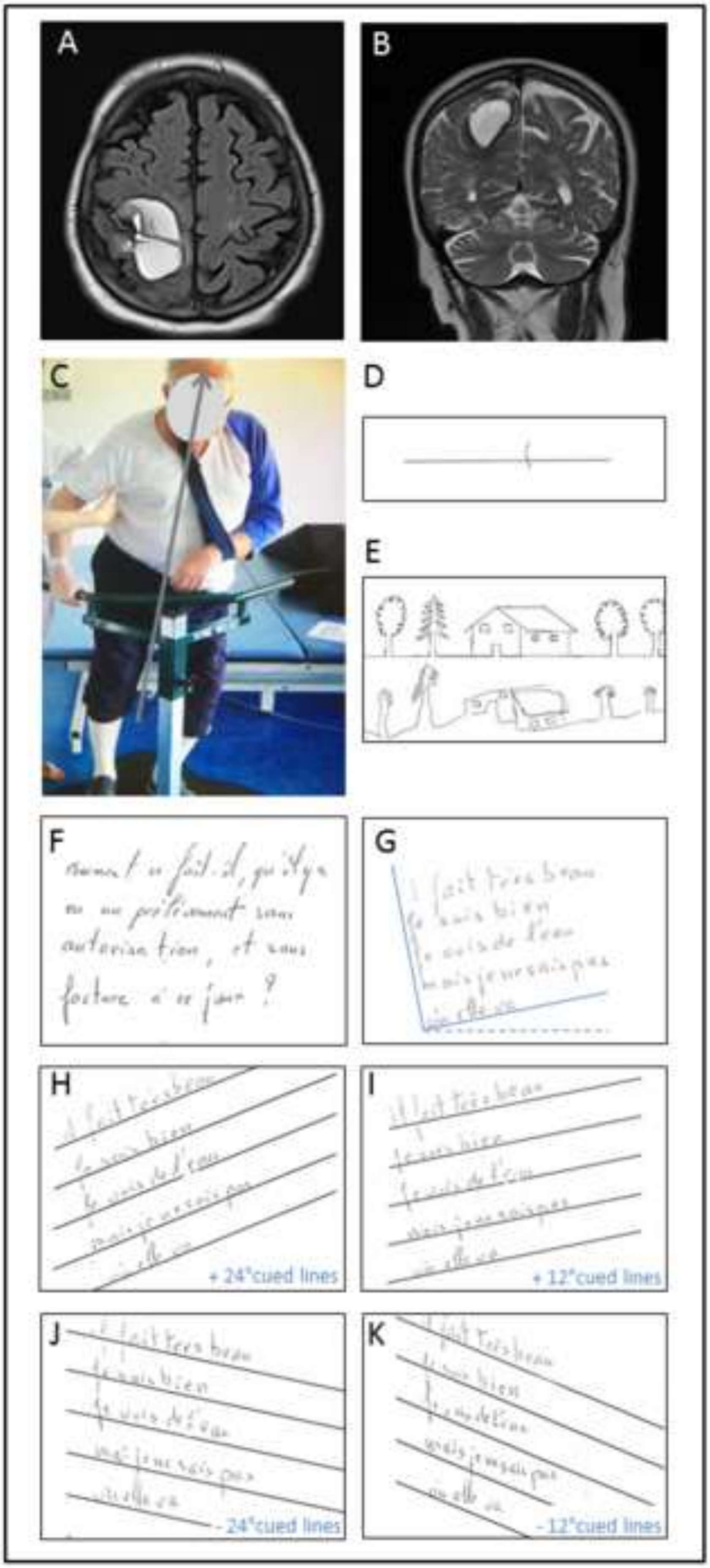

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