Adapted Morris Water Maze protocol to prevent interference from confounding motor deficits on cognitive functioning

De Coninck, Mattias; van Dam, Debby; Van Ginneken, Chris; De Deyn, Peter

Published in:
Somatosensory & Motor Research

DOI:
10.1080/08990220.2017.1372740

Publication date:
2017

Somatosensory & Motor Research

ISSN: 0899-0220 (Print) 1369-1651 (Online) Journal homepage: http://www.tandfonline.com/loi/ismr20

Adapted Morris Water Maze protocol to prevent interference from confounding motor deficits on cognitive functioning

Mattias De Coninck, Debby Van Dam, Chris Van Ginneken & Peter Paul De Deyn

To cite this article: Mattias De Coninck, Debby Van Dam, Chris Van Ginneken & Peter Paul De Deyn (2017) Adapted Morris Water Maze protocol to prevent interference from confounding motor deficits on cognitive functioning, Somatosensory & Motor Research, 34:3, 172-178, DOI: 10.1080/08990220.2017.1372740

To link to this article: https://doi.org/10.1080/08990220.2017.1372740

Published online: 10 Sep 2017.

SOMATOSENSORY & MOTOR RESEARCH, 2017
VOL. 34, NO. 3, 172–178
https://doi.org/10.1080/08990220.2017.1372740

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Adapted Morris Water Maze protocol to prevent interference from confounding motor deficits on cognitive functioning

Mattias De Coninck[a], Debby Van Dam[a,b], Chris Van Ginneken[c] and Peter Paul De Deyn[a,b,d,e]

[a]Laboratory for Neurochemistry and Behaviour, Institute Born-Bunge, University of Antwerp, Wilrijk, Belgium; [b]Department of Neurology and Alzheimer Research Center, University of Groningen and University Medical Center Groningen, Groningen, the Netherlands; [c]Applied Veterinary Morphology, University of Antwerp, Wilrijk, Belgium; [d]Department of Neurology and Memory Clinic, Hospital Network Antwerp (ZNA) Middelheim and Hoge Beuken, Antwerp, Belgium; [e]Biobank, Institute Born-Bunge, University of Antwerp, Wilrijk, Belgium

ABSTRACT

Purpose/aim of the study: Cognitive functioning in the Morris Water Maze (MWM) is assumed to be reflected by path length. In this study, the interference of motor deficits, as a confounding factor on cognitive functioning, was assessed by means of a lateralization study with hemicerebellectomized (HCX) mice. This model is characterized by motor deficits restricted to the lesion side, allowing comparison within the model itself (left vs. right), rather than the effect of the manipulation on this measure (experimental vs. control).

Materials and methods: Spatial learning was assessed after left or right hemicerebellectomy in adult mice by means of two MWM designs in which the location of the starting positions was altered for one condition in the adapted (Adap) MWM experiment, hypothesizing that motor impairments ipsilateral to the lesion side result in a difference in path length.

Results: When the starting positions were equal for both conditions in the traditional (Trad) MWM experiment, path length during the acquisition phase and spatial memory were more affected for the left HCX, while these effects disappeared after mirroring the starting positions in the Adap MWM, implying that motor phenotype and corresponding increase in task difficulty are responsible for the contradictory results in the Trad MWM experiment.

Conclusion: The differences found in the latter experiment were circumvented in the adapted MWM protocol, and therefore, excluding the motor deficit as a confounding factor on cognitive MWM parameters.

ARTICLE HISTORY
Received 7 July 2017
Accepted 24 August 2017

KEYWORDS
Hemicerebellectomy; motor deficits; laterality; spatial learning; acquisition

Introduction

The Morris Water Maze (MWM) is a frequently used and well-validated test for spatial learning and memory in rodents (for review, see D'Hooge and De Deyn 2001), originally developed for the discrimination of the proximal and distal sense of locality in rats: the animals have to find and learn the location of a (hidden) platform to escape a pool during the acquisition trials (Morris 1981). The characteristics of the animal, the set-up of the MWM, and the training protocol affect performance during acquisition trials, which is usually evaluated by the variables swim speed, escape latency, and path length. The latter variable is considered more appropriate to measure cognitive functioning, although it is inversely correlated with swim speed (Lindner 1997). Swim speed and escape latency are both influenced by non-cognitive factors, such as motivation and motor capacity of the animal. It is assumed that the effect of motor impairments is attenuated in a water maze as compared with the dry-land situation, while the motivational stimulus of a water maze is considered to be more stressful (Gage et al. 1984). To investigate the possibility of a motor interference on cognitive functioning in the MWM, as reflected by path length, a motor impaired animal model is required that allows comparison within the model itself, rather than the effect of the manipulation on this measure. The surgical ablation of one cerebellar hemisphere and hemivermis, or hemicerebellectomy (HCX), is a well-established model with known consequences on motor and cognitive abilities. HCX in adult rats resulted 4 months after surgery in extensor hypotonia, hindlimb hyperflexion, and hypermetric step all ipsilateral to the lesion side, while vestibular drop was observed contralateral to the hypotonic side (Molinari et al. 1990). HCX rats were able to swim with a good coordination and velocity (Federico et al. 2006), except for a slight body tilt to the lesion side (Molinari et al. 1990). Additionally, a lateralization study in rats was unable to demonstrate a functional specialization of the cerebellar hemispheres for spatial learning (Colombel et al. 2004), although the experimental design consisted of only motor-dependent MWM variables. Nevertheless, different MWM experiments revealed that HCX prevents acquiring new search strategies (Petrosini et al. 1996; Leggio et al. 2000;

CONTACT Peter P. De Deyn dedeyn@skynet.be Laboratory for Neurochemistry and Behaviour, Institute Born-Bunge, University of Antwerp, Universiteitsplein 1, 2610 Wilrijk, Belgium

Federico et al. 2006), and that these animals rely on the peripheral exploration of a maze (Petrosini et al. 1998). According to Mandolesi et al. (2003), this reduction in explorative behaviour results in impaired procedural learning, a prerequisite for building the entire spatial map of the maze, which can easily be overcome by adapting the environment to the (dis)ability of these animals.

Despite the fact that most behavioural research concerning the effects of a cerebellar lesion is performed in rats, mice are used for most mutant cerebellar animal models (Manto and Marmolino 2009). Neither the effect of a lesion in a normally developed cerebellum, nor a functional lateralization study in spatial learning has been investigated in mice. In this experiment, the effect of motor impairment on spatial learning was assessed after left or right HCX in adult mice by means of two MWM designs in which the location of the starting positions was altered for one condition, hypothesizing that these impairments ipsilateral to the lesion side result in a difference in path length.

Materials and methods

Animals

The 12- to 13-week-old, male C57BL/6 mice (Charles River, L'Abresle Cedex, France) were group housed ($n = 6$–8) in standard mouse cages under conventional laboratory conditions with food and water available *ad libitum*, constant room temperature and humidity, and a 12 h/12 h light–dark cycle (lights on at 8 a.m., lights off at 8 p.m.). The mice were randomly assigned (randomization.com) to one of the experimental conditions: the left (L-HCX) or right (R-HCX) unilateral removal of the cerebellar hemisphere. All experiments were carried out in accordance with the European Communities Council Directive on the protection of animals used for scientific purposes (2010/63/EU) and the Animals Ethics Committee of the University of Antwerp approved all protocols. Sample sizes were based on Mead's resource equation.

Hemicerebellectomy

Anaesthetized (100 mg/kg ketamine and 20 mg/kg xylazine, i.p.) mice were secured in a stereotaxic frame with non-puncturing ear bars. The muscles on the right (or left) side of the cranium were cut to clear the occipital bone of any tissue. A micro Trephine drill (Fine Science Tools, Heidelberg, Germany) was used to create a circular craniotomy of 5 mm in the occipital part of the skull, the dura was punctured, and the right (or left) cerebellar hemisphere and right (or left) hemivermis were ablated by aspiration. Extra caution was taken to avoid lesioning extracerebellar structures. The remaining cavity was filled with sterile GelFoam Sponge (Pfizer, Puurs, Belgium). The skull was closed with a layer of Bone Wax (Fine Science Tools) and carboxylate luting cement (Durelon™, 3M ESPE AG, Seefeld, Germany). Finally, the skin was sutured and the animal was allowed to recover from anaesthesia and surgery under an infra-red heating lamp. The overall well-being of the mice was monitored daily during the first week post-surgery and if necessary analgesia was administered (i.p. injection of 0.05 mg/kg buprenorphine, Vetergesic, Ecuphar, Oostkamp, Belgium). The MWM acquisition trials started 4 weeks after surgery.

Hidden-platform fast Morris Water Maze test

The influence of the motor impairments as a consequence of the HCX on path length was assessed by means of two MWM experiments: the starting positions of the R-HCX group were mirrored for the L-HCX group in an adapted (Adap) MWM protocol (Figure 1(B)), while in the traditional (Trad) MWM the starting positions remained equal for both HCX groups (Figure 1(A)). Each experimental group consisted of 10 mice at the start of the procedure.

The MWM set-up consisted of a circular pool (diameter: 150 cm, height: 30 cm) filled with opaque water kept at 25 °C. A round, acrylic platform (diameter: 15 cm) was placed in one quadrant. The set-up was surrounded by white walls with high-contrast visual cues surrounding the maze.

MWM training consisted of two daily acquisition trial blocks with an interval of 4 h on four consecutive days. An acquisition block was comprised of four trials starting from four different starting positions in a semi-random order and a 15 min inter-trial interval. Animals were placed in the pool with their nose towards the wall. In case an animal was unable to reach the platform within 120 s, it was placed on the platform during 15 s before returning to its home cage. Animals' trajectories were recorded using a computerized

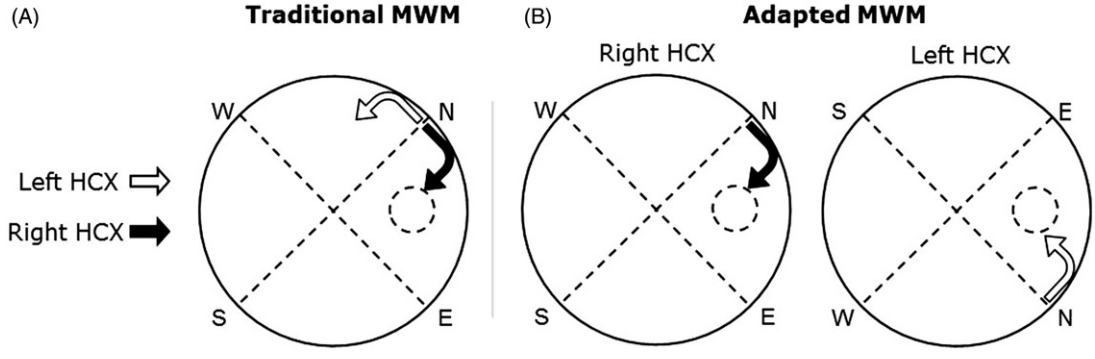

Figure 1. Orientation of the starting positions for both conditions in the traditional (A) and adapted (B) MWM experiments. Arrows indicate the preferred or natural circular swimming motion for both conditions starting from the N-location in the first trial, that is, without any learning effect. The small dotted circle in the NE quadrant represents platform location. HCX: hemicerebellectomy; MWM: Morris Water Maze; N: north; E: east; S: south; W: west.

video-tracking system (Ethovision 6, Noldus, Wageningen, the Netherlands) logging path length, escape latency, and swim speed. During the probe trial, performed 4 days after the final acquisition trial block, the platform was removed from the maze and each mouse was allowed to swim freely for 100 s. Spatial accuracy was expressed as percentage of time spent in each quadrant of the MWM and the number of crossings through the target position, that is, the specific location of the platform during the acquisition phase. Additional visual inspection of the probe trial trajectories was performed to increase insight in the exploration strategy. Mice that floated on all trials were excluded from data processing.

Gait analysis

Gait characteristics were analysed, to confirm motor deficits ipsilateral to the lesion side in the Trad MWM group, by applying ink to the animals' hind paws and letting them walk on a strip of paper, down a brightly lit alley (4.5 cm wide, 40 cm long), towards a dark goal box. Parameters scored were: (1) the toe spread for each paw (distance digit 1–5); (2) stride length (for both left and right paws); and (3) the distance between the left and right paw (Roth et al. 2015).

Stereology

After completion of behavioural testing, the anaesthetized animals (0.3 ml/mouse Nembutal, Ceva, Brussels, Belgium) were perfused transcardially with 4% buffered paraformaldehyde. The brain tissue was collected and further immersion fixated overnight. A rotary microtome (Microm HM 355 S, Thermo Scientific™, Merelbeke, Belgium) was used to cut the paraffin-embedded cerebellum in 5-μm coronal slices and every 30th slice was collected on a glass plate for Nissl staining. An Olympus BX50 microscope, equipped with a Sony CCD camera connected to a computer system running the software programme CAST-Grid (Olympus, Albertslund, Denmark) was used for quantitative analyses. The volume (V) of the remaining cerebellar tissue was estimated using a point-counting method on the Nissl-stained sections at a low magnification (4×). The volume V was calculated by means of the Cavalieri method: $V = \Delta t\ \Sigma P\ A(p)$. Where Δt is the distance between the sections (150 μm), ΣP is the sum of the number of test points that fell on the remaining cerebellar tissue (divided into grey and white cerebellar matter) for each slice, and $A(p)$ is the area that is associated with each test point of the point-count stereologic grid.

Statistics

Acquisition curves representing path length, escape latency, and swim speed were compared with a two-way repeated measures (RM) ANOVA. Trial block and Surgery (L-HCX and R-HCX) were considered as possible sources of variation. Two-way ANOVA (Factors: Quadrant and Surgery) was used to compare spatial accuracy during probe trial, number of entries through the former target position, and total path length travelled during probe trial were assessed with a one-way ANOVA. Bonferroni *post hoc* analysis was employed to determine differences for trial block, spatial accuracy, and the effect of surgery during the acquisition and probe trials. Independent Student's *t*-test was used to analyse gait patterns and differences in the grey, white, and total cerebellar volumes. Statistical analyses were performed using SPSS software version 23 (SPSS, Chicago, IL, USA); the level of probability was set at 95%.

Results

The experimental design of this study consisted of two MWM (Trad vs. Adap) experiments both containing two experimental conditions (R-HCX vs. L-HCX), resulting in TradR ($n = 10$), TradL ($n = 8$), AdapR ($n = 10$), and AdapL ($n = 9$) groups after exclusion of mice that floated on all MWM trials. The majority of the brains were used for stereological analysis (TradR: $n = 9$; TradL: $n = 8$; AdapR: $n = 9$; AdapL: $n = 6$), the remaining samples were excluded due to tissue processing issues.

Traditional starting positions

A two-way RM-ANOVA revealed an overall gradual decrease in path length [effect Trial block: $F(7, 112) = 7.967$; $p = .000$], escape latency [effect Trial block: $F(7, 112) = 2.408$; $p = .025$], and swim speed [effect Trial block: $F(7, 112) = 5.781$; $p = .000$] over the eight acquisition trials. The location of the HCX resulted in a significantly shorter path length for the R-HCX condition [$F(1, 16) = 6.728$; $p = .020$] (Figure 2(A)), while escape latency and swim speed were equal for both groups, respectively [$F(1, 16) = 1.930$; $p = .184$] and [$F(1, 16) = 3.365$; $p = .085$]. Similar progress over the trial blocks for both conditions during the acquisition phase was reflected in a lack of interaction effects (effect Trial blocks * Surgery) for path length, escape latency, and swim speed, respectively [$F(7, 112) = 1.026$; $p = .417$], [$F(7, 112) = 0.386$; $p = .909$], and [$F(7, 112) = 0.165$; $p = .992$].

The analysis of the probe trial results demonstrated differences in spatial memory functioning: the number of entries through the previous platform position was significantly higher in the R-HCX condition [$t(16) = 2.252$; $p = .039$], and a trend was observed for the preference patterns in the different MWM quadrants between the two groups [effect Quadrants * Surgery: $F(3, 64) = 2.701$; $p = .053$] (Figure 2(B)). Bonferroni *post hoc* analysis revealed that the mice spent more time in the quadrants located in the east side of the pool (target or NE and SE) as compared with the presence in the opposite half of the MWM (Figure 2(B)). Additional between-group analyses of the time spent in each quadrant revealed that the L-HCX visited the NW quadrant significantly longer. The visual trajectory analyses indeed demonstrated that the L-HCX condition used a more general exploration strategy of the entire maze, while the R-HCX mice focused on the target quadrant and the starting position (Figure 3(A,B)).

Gait analysis revealed a smaller toe span ipsilateral to the lesion side as compared with the contralateral hind paw

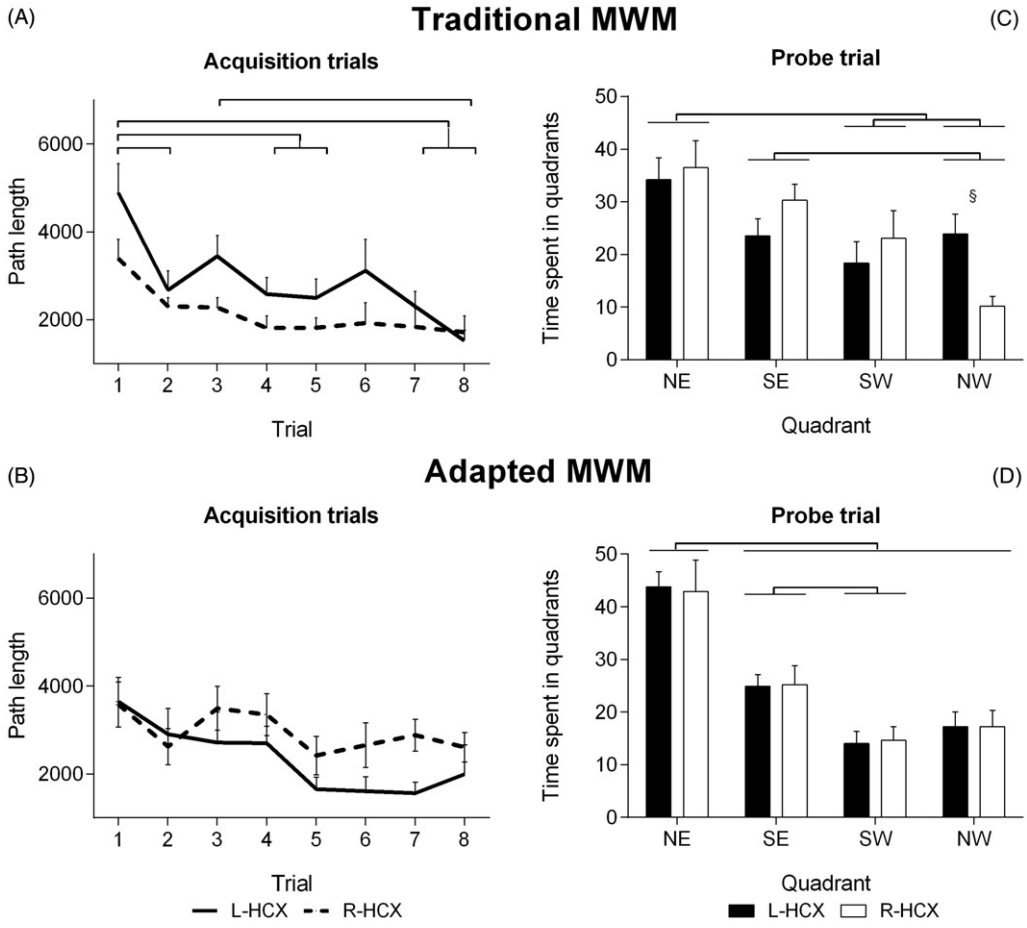

Figure 2. (A, C) Average path length (in cm) to reach the hidden platform during the acquisition phase for the traditional (A) and adapted (C) versions of the MWM. Brackets represent a significant difference (Bonferroni analysis $p < 0.005$) between the different trial blocks. (B, D) Time spent in the four quadrants during the probe trial for the traditional (B) and adapted (D) versions of the MWM. Brackets represent a significant difference (Bonferroni analysis $p < 0.005$) between the different quadrants. § represents a within-subjects effect of time spent in the quadrant. Error bars represent SEM. Group sizes were $n = 10$ for R-HCX and $n = 8$ for L-HCX in the traditional version, *vs*. $n = 10$ for R-HCX and $n = 9$ for L-HCX in the adapted version of the MWM. HCX: hemicerebellectomy; MWM: Morris Water Maze; N: north; E: east; S: south; W: west.

[$t(34) = -4.743$; $p = .000$], while stride and track width were unaffected. The remaining grey, white, and total cerebellar volumes were identical for both conditions, [$t(15) = 0.476$; $p = .641$], [$t(15) = 1.037$; $p = .316$], and [$t(15) = 0.828$; $p = .421$], respectively.

Adapted starting positions

Path length [$F(7, 126) = 3.313$; $p = .003$] and swim speed [$F(7, 126) = 6.485$; $p = .000$] decreased significantly over time (Figure 2(C)), in contrast to the escape latency, which remained constant [$F(7, 126) = 1.344$; $p = .235$]. While the L-HCX condition swam significantly faster [$F(1, 18) = 4.545$; $p = .047$], the learning curves of the two conditions were equal for both path length and escape latency, respectively [$F(1, 18) = 2.823$; $p = .110$] and [$F(1, 18) = 3.542$; $p = .076$]. Numbers of entries of the target quadrant [$t(17) = 1.095$; $p = .289$] and the interaction of the HCX and the time spent in each quadrant [Surgery * Quadrants: $F(3, 72) = 0.014$; $p = .998$] were identical for both groups. The animals were able to locate the hidden platform as they spent significantly more time in the target quadrant compared to the other quadrants [effect Quadrant $F(1, 72) = 23.538$; $p = .000$, Bonferroni *post hoc* $p > 0.01$] (Figure 2(D)). Visual trajectory analyses revealed no differences in exploration strategies during this probe trial (Figure 3(C,D)). Equal remaining grey, white, and total cerebellar tissue was found for both groups, [$t(13) = 0.522$; $p = .611$, $t(13) = 0.211$; $p = .836$, and $t(13) = 0.084$; $p = .935$, respectively].

Discussion

In this functional lateralization study of spatial learning in mice, the possible influence of motor deficits on MWM path length during acquisition, with the latter parameter being a reflection of cognitive functioning, was investigated by removing either the right or the left cerebellar hemisphere and hemivermis, resulting in motor deficits restricted to the lesion side. The latter was confirmed by means of a smaller toe span ipsilateral to the location of the cerebellar lesion, possibly due to the hypotonia (Molinari et al. 1990).

Despite the fact that path length is inversely correlated to swim speed (Lindner 1997), the influence of motor factors is difficult to measure, especially when comparing experimentally modified mice (surgically, chemically, or genetically) to their control counterparts. In contrast to a previous

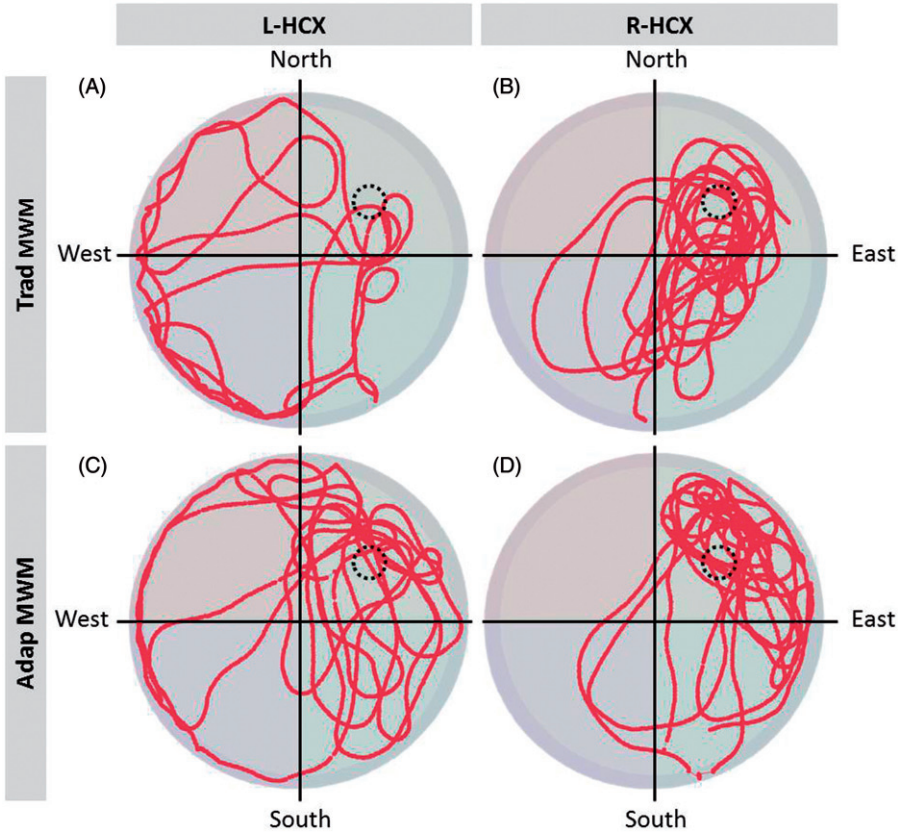

Figure 3. Typical trajectories during the probe trial (100 s) for every condition: (A) L-HCX and (B) R-HCX for the Trad MWM, and (C) L-HCX and (D) R-HCX for the Adap MWM. The dotted circle represents the location of the hidden platform. Adap MWM: adapted Morris Water Maze; HCX: hemicerebellectomy; Trad MWM: traditional Morris Water Maze.

performed lateralization study in rats (Colombel et al. 2004), the lateralization of the motor impairments after surgical ablation of a cerebellar hemisphere resulted in a longer path length during the acquisition phase for the L-HCX condition when the starting positions were equal for both conditions. The differences between the two groups in our study disappeared after mirroring the starting positions for the L-HCX condition to those of the R-HCX condition (Figure 1(B)), implying that the motor phenotype is responsible for the contradictory results in the Trad MWM experiment. The hypotonia in combination with the sequence of starting positions might be attributable to the difference in path length for the Trad MWM: when the R-HCX mice were placed in the pool at the N starting position, with their nose towards the wall, the hypotonia automatically resulted in a swimming motion towards the platform located in the NE quadrant, while the L-HCX condition swam away from the platform due to the motor phenotype, thereby travelling a larger distance to reach the platform (Figure 1(A)). In the lateralization study of Colombel et al. (2004) the first starting position was S oriented and the platform was located in the NW quadrant, resulting in a smaller difference in crossed quadrants (2 vs. 3) as compared with our protocol (1 vs. 4). The disparity in distance from the starting position to the location of the platform is a topic of discussion and a drawback of the MWM (Vorhees and Williams 2006). Also a smaller maze diameter can reduce task-related stress in certain rodent strains, hence allowing the animals to learn the immediate surroundings of the MWM and the location of the platform more successfully (Van Dam et al. 2006). In contrast to the 150-cm diameter maze used in our mouse study, the 90-cm MWM used in the study of Colombel et al. (2004) is rather small for rats (Morris 1981, 1984; Vorhees and Williams 2006). The latter researchers were most likely unable to detect whether the distance travelled to reach the platform was affected by the motor phenotype of the HCX rats in such a small-sized MWM. Especially when keeping in mind that the rats were tested 14 days post-surgery, a turning point in their motor recovery process (Burello et al. 2012), implying a larger effect of the cerebellar motor symptoms on their MWM performance as compared with our mice tested at 4 weeks after surgery. Until now, the effect of this (partial) motor recovery process on cognitive functioning has not been investigated in a traditional experimental design (HCX vs. control condition) and, additionally, it is hypothesized that some sort of cognitive recovery might be observed due to the possible neuroplasticity processes occurring at the level of the cerebellum. Therefore, it is hypothesized that the effect of a (partial) motor recovery needs to be taken into account when comparing the spatial learning capacity of a HCX animal to control animals without motor deficits.

Although the effect of the difference in path length appears negligible, spatial memory of the L-HCX mice in the Trad MWM appeared more affected than the R-HCX condition, in contrast to the probe trial performance of both conditions in the Adap MWM experiment. Stereological analysis confirmed that the remaining cerebellar tissue was equal for both conditions and as a consequence, an explanation

for these results has to be found in the nature of the task. Stress experienced during the acquisition phase is already described as a possible cause of variation in performance (Holscher 1999; Van Dam et al. 2006). As we mentioned earlier, the hypotonia and the location of the starting positions for the L-HCX condition resulted in a longer path length to reach the hidden platform. This increase in task difficulty and accompanying stress resulted in a learning deficiency for the L-HCX condition observed during the probe trial. Apart from the time spent in the target quadrant, the L-HCX group prefers a more generalized exploration strategy as they spent an equal amount of time in the non-target quadrants (Figures 2(B) and 3(A)), while on the other hand, the mice of the R-HCX condition spent most of their time looking for the platform in the two quadrants (SE and SW) near the starting position (S) (Figures 2(B) and 3(B)). In a previously performed MWM experiment, HCX rats were unable to acquire a praxic (a learned sequence of movements) or taxic (approach the platform using proximal cues) exploration strategy and relied on peripheral exploration of the maze, even when the platform was visible (Petrosini et al. 1996). This peripheral circling method is applied by young rats with incomplete cerebellar maturation and allows these animals to slowly acquire spatial relations in the presence of proximal and distal cues (Petrosini et al. 1996, 1998). As spatial map development progresses during the acquisition phase, HCX rats can abandon peripheral circling and make use of the place strategy to escape the pool (Petrosini et al. 1998). During an open-field experiment, spatial arrangement of the most explored objects was manipulated after a habituation phase. Object exploration of the HCX rats increased when the objects were relocated from the centre to the periphery, and performance was equal to the control rats for the latter location. Mandolesi et al. (2003) concluded that impaired spatial learning is caused by procedural ineffectiveness, such as peripheral circling, and that building the internal representation of the environment is route-based. The increase in time spent in the NW quadrant is a reflection of this inefficiency in exploration strategies due to the ipsilateral motor impairments of the L-HCX mice in the Trad experiment, and, most importantly, affects spatial memory performance.

It was hypothesized that the sensitivity of the gait analysis would allow capturing laterality differences: smaller stride and toe span ipsilateral to the location of the lesion. Due to the design of the used apparatus, the mice were able to use the support of the walls, which might result in an overestimation of their actual abilities. A second drawback of this study was the use of the stereological analysis since this technique does not allow the exact determination of the size of the lesions and the disconnection of the cerebellothalamic pathway, but is rather an estimation of the remaining cerebellar tissue.

This study demonstrates the negative impact of motor impairment on cognitive MWM parameters and the adequate circumvention of this effect by altering the start positions for the HCX model. In future research, these findings will allow the evaluation of visual spatial learning and memory in animal models with potential lateralization differences and, therefore, increase the validity of the MWM as a tool to assess cognitive functioning. Examples include the dopamine-related models such as the unilateral intranigral injection of 6-hydroxydopamine (Ungerstedt 1968, 1971a, 1971b) and the unilateral application of somatostatin to the striatum (Hathway et al. 2004); but also surgical models including the unilateral middle cerebral artery occlusion model (Krystal et al. 2010) and unilateral hemispherectomy (Krahe et al. 2000).

Disclosure statement

The authors report no conflicts of interest.

Funding

This work was supported by the Research Foundation-Flanders (FWO), Interuniversity Poles of Attraction of the Belgian Federal Science Policy Office [IAP7/16], Methusalem excellence grant of the Flemish Government, agreement between Institute Born-Bunge and University of Antwerp, the Medical Research Foundation Antwerp, the Thomas Riellaerts research fund, and Neurosearch Antwerp.

ORCID

Debby Van Dam http://orcid.org/0000-0003-4739-6076
Peter Paul De Deyn http://orcid.org/0000-0002-2228-2964

References

Burello L, De Bartolo P, Gelfo F, Foti F, Angelucci F, Petrosini L. 2012. Functional recovery after cerebellar damage is related to GAP-43-mediated reactive responses of pre-cerebellar and deep cerebellar nuclei. Exp Neurol 233:273–282.

Colombel C, Lalonde R, Caston J. 2004. The effects of unilateral removal of the cerebellar hemispheres on spatial learning and memory in rats. Brain Res 1004:108–115.

D'Hooge R, De Deyn PP. 2001. Applications of the Morris water maze in the study of learning and memory. Brain Research. Brain Res Rev 36:60–90.

Federico F, Leggio MG, Neri P, Mandolesi L, Petrosini L. 2006. NMDA receptor activity in learning spatial procedural strategies II. The influence of cerebellar lesions. Brain Res Bull 70:356–367.

Gage FH, Dunnett SB, Bjorklund A. 1984. Spatial learning and motor deficits in aged rats. Neurobiol Aging 5:43–48.

Hathway GJ, Humphrey PP, Kendrick KM. 2004. Somatostatin induces striatal dopamine release and contralateral turning behaviour in the mouse. Neurosci Lett 358:127–131.

Holscher C. 1999. Stress impairs performance in spatial water maze learning tasks. Behav Brain Res 100:225–235.

Krahe TE, Filgueiras CC, Caparelli-Dáquer EM, Schmidt SL. 2000. Contralateral rotatory bias in the free-swimming test after unilateral hemispherectomy in adult Swiss mice. Int J Neurosci 108:21–30.

Krystal L, Schaar KL, Brenneman MM, Savitz SI. 2010. Functional assessments in the rodent stroke model. Exp Transl Stroke Med 2:13.

Leggio MG, Molinari M, Neri P, Graziano A, Mandolesi L, Petrosini L. 2000. Representation of actions in rats: the role of cerebellum in learning spatial performances by observation. Proc Natl Acad Sci USA 97:2320–2325.

Lindner MD. 1997. Reliability, distribution, and validity of age-related cognitive deficits in the Morris water maze. Neurobiol Learn Mem 68:203–220.

Mandolesi L, Leggio MG, Spirito F, Petrosini L. 2003. Cerebellar contribution to spatial event processing: do spatial procedures contribute to formation of spatial declarative knowledge? Eur J Neurosci 18:2618–2626.

Manto M, Marmolino D. 2009. Animal models of human cerebellar ataxias: a cornerstone for the therapies of the twenty-first century. Cerebellum 8:137–154.

Molinari M, Petrosini L, Gremoli T. 1990. Hemicerebellectomy and motor behaviour in rats. II. Effects of cerebellar lesion performed at different developmental stages. Exp Brain Res 82:483–492.

Morris RGM. 1981. Spatial localization does not require the presence of local cues. Learn Motiv 12:239–260.

Morris RGM. 1984. Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods 11:47–60.

Petrosini L, Molinari M, Dell'Anna ME. 1996. Cerebellar contribution to spatial event processing: Morris water maze and T-maze. Eur J Neurosci 8:1882–1896.

Petrosini L, Leggio MG, Molinari M. 1998. The cerebellum in the spatial problem solving: a co-star or a guest star? Prog Neurobiol 56:191–210.

Roth L, Van Dam D, Van der Donckt C, Schrijvers DM, Lemmens K, Van Brussel I, De Deyn PP, Martinet W, De Meyer GR. 2015. Impaired gait pattern as a sensitive tool to assess hypoxic brain damage in a novel mouse model of atherosclerotic plaque rupture. Physiol Behav 139:397–402.

Ungerstedt U. 1968. 6-Hydroxy-dopamine induced degeneration of central monoamine neurons. Eur J Pharmacol 5:107–110.

Ungerstedt U. 1971a. Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiol Scand 82(Suppl. 367):69–93.

Ungerstedt U. 1971b. Striatal dopamine release after amphetamine or nerve degeneration revealed by rotational behaviour. Acta Physiol Scand 82 (Suppl. 367):49–68.

Van Dam D, Lenders G, De Deyn PP. 2006. Effect of Morris water maze diameter on visual-spatial learning in different mouse strains. Neurobiol Learn Mem 85:164–172.

Vorhees CV, Williams MT. 2006. Morris water maze: procedures for assessing spatial and related forms of learning and memory. Nat Protoc 1:848–858.