# Titre

Space representation in 3D

# Description

* The aim of this research project is to investigate the three-dimensional (3D) nature of space representation in the healthy subject.
* In every day life, our cognitive system uses multiple representations of space, depending on the frame of reference (coordinate system) used to encode afferent sensory signals. In the horizontal plane, space can be mapped relative to the body or specific body segments (Rizzolatti et al., 1997). In the frontal plane, space can be oriented relative to gravity, the only absolute coordinate system on earth (Dakin & Rosenberg, 2018).
* These ego-centred and gravity-centred space representations are geometrically orthogonal, driven by different sensory signals, though to rely on different neural resources (Rousseaux et al., 2013), and can thus be considered as independent representations. Nevertheless, recent evidences challenged this view.
* In the rodent, a population of neurons in the medial temporal lobe discharged in response to rotation of the animal in orthogonal planes. Some neurons coded the animal’s orientation relative to both gravity (frontal and sagittal planes) and visual landmarks (horizontal plane) (Angelaki et al., 2020; Finkelstein et al., 2015, 2016). These observations suggest that the brain can build allocentric 3D space representations, at least in the rodent.
* In the human, mouting evidence have shown that right-brain damaged (RBD) patients often exhibit concurrent space perception disorders in both horizontal and frontal planes (Baier et al., 2012; Brandt et al., 1994; Funk et al., 2010; Kerkhoff, 1999; Kerkhoff & Zoelch, 1998; Yelnik et al., 2002). These patients fail to respond to or orient to their left hemi-space (spatial neglect), and perceived the gravity vector as tilted toward the counterclockwise (contralesional) direction. It has been thus proposed that spatial neglect might bear not only on lateralized but also on graviceptive sensory signals, leading to space perception disorders in multiple planes after right-brain damage (Pérennou, 2006).
* In sum, animal and human studies showed that space representations (ego- and allo-centred) in the horizontal plane might not be strictly independent from gravity-centred space representations in the frontal plane.
* Thus, one might ask whether space representation is mapped and oriented in a 3D frame of reference, combining the body and gravity as co-dependent coordinate systems. To test this hypothesis, we will evaluate in the healthy subject both ego-centred (horizontal plane) and gravity-centred (frontal plane) space representations either after an “experimental intervention” or after a “control intervention”. We will use as interventions the prism adaptation (Prablanc et al., 2020) at the one hand, and the virtual-tilted room (VTR) (Odin et al., 2018) at the other hand, known to bias the ego- and gravity-centred space representations in the horizontal and frontal planes, respectively.
* Subjects will undergo the prism adaptation intervention in three conditions: right prisms/ left prisms (experimental conditions) or plain glasses (control condition). Similarly, subjects will undergo the VTR intervention in three conditions: right tilt/ left tilt (experimental conditions) or uprightness (control condition).
* If the brain represent the horizontal and frontal planes in a 3D co-dependent coordinate system, then each experimental condition, compared to the corresponding control condition, should both give rise to ego-centred and gravity-centred spatial after-effects (defined here as [experimental condition bias – control condition bias]). Moreover, we expect these ego-centred and gravity-centred spatial after-effects to be correlated.
* The coordinates of the ego-centred space representation will be assessed by the proprioceptive straight-ahead (PSA) task (Rossetti et al., 1998). The coordinates of the gravity-centred space representation will be assessed by the visual vertical (VV) task (Pérennou et al., 2014; Piscicelli et al., 2016; Piscicelli & Pérennou, 2017).

# Hypotheses

In RBD patients, the PSA is usually shifted rightward, whereas the VV is usually shifted leftward ( Baier et al., 2012; Chokron & Imbert, 1995; Rousseaux et al., 2013, 2014). Reverse spatial biases are observed in left-brain damaged patients (Baier et al., 2012; …).

Thus, we made the prediction that in healthy subjects left prism adaptation give rise to a rightward PSA after-effect and a leftward VV after-effect. Conversely, right prism adaptation should give rise to a leftward PSA after-effect and a rightward VV after-effect.

Similarly, we made the prediction that left VTR give rise to a rightward PSA after-effect and a leftward VV after-effect. Conversely, right VTR should give rise to a leftward PSA after-effect and a rightward VV after-effect.

This way, the experimental conditions should reproduce a pattern of pseudo neglect and pseudo verticality bias in conformity with the litterature, according to the left or right side of the experimental condition.

Moreover, we expect these after-effects to differ from 0, indicating a difference between the experimental and the control conditions.

Finally, we expect a negative correlation between the PSA and the VV after-effects. That is, the more positive the spatial after-effects in the horizontal plane, the more negative the spatial after-effects in the frontal plane, and vice-versa.

# Study Design

Each participant will perform two sessions, one for each intervention (prism adaptation or VTR). Each session will follow a mixed design, with the intervention condition (experimental vs control) as a within subject design, and the side of the experimental condition (left vs right) as a between subject variable. Thus, whereas the experimental and control conditions will be performed *within* the same participants, the side of the experimental condition will be determined *across* the participants (the side will be the same for both prism adaptation and VTR interventions).

The order of the session of will be counterbalanced across the subjects. During each session, the order of the intervention conditions will be fixed, with the control condition always performed in the first place. The order of the spatial tasks (VV or PSA) will be fixed within a subject (and thus the same across the two sessions), but counterbalanced across the subjects.

# Randomization

For each participant, the order of the two sessions (prism adaptation or VTR) will be randomly determined. The random number list used to create these sequences will be created using the web applications available at http://random.org (option "Integer Set Generator").

# Data collection procedures

Participants will be recruited through an advertisements published on the web address of the Laboratory of Psychology and Neurocognition (Grenoble, France) : https://lpnc.univ-grenoble-alpes.fr/Experimentations-en-cours-590. Students in psychology course will be paid with bonus mark (1 hour = 1 point). The other participants will not be remunerated.

# Sample size

Our target sample size ranges from 20 to 30, according to time constraint and missing data.

# Sample size rationale

Because the present study is a pilot study, we don’t plan to recruit a large sample. Nevertheless statistical power will be optimized by setting the variable “intervention condition” (control vs experimental) as a within subject factor.

We will perform one sample t-tests to test whether PSA or VV after-effects (experimental – control condition) are different from 0. With this design, Gpower estimates that 19 participants are enough to reach a power = .70, with a cohen’s d = 0.05 (medium effect size), and an alpha rate = .05.

# Stopping rule

# Variables

## Manipulated variables

Our independent variables will be Intervention Condition (control vs experimental) as within-subject variable and Experimental Side (left vs right) as between-subject variable.

## Measured variables

Our outcomes will be the PSA and the VV, both measured in degrees. Signed and absoluted values will be used.

# Analysis Plan

## Statistical models

First, we expect the after-effects (defined here as [experimental – control] conditions) of the left and right experimental conditions to be of opposite sign, by mimicking opposite patterns of pseudo neglect (PSA task) and pseudo verticality bias (VV task). Thus, for both interventions, we will test the effect of Experimental Side (left vs right) on both PSA and VV after-effects with an independent t-test.

Second, we expect these after-effects to be significantly different from 0 in terms of magnitude, indicating a significant difference between the experimental and the control conditions. In this view, we will first test the effect of Experimental Side on absolute after-effects, to test if the left and right experimental conditions differ in terms of magnitude. If the independent t-test is non significant, the absolute after-effects of the left and right experimental conditions will be pooled and tested against 0 with a one sample t-test. Otherwise, we will run separate one sample t-tests with each experimental conditions.

Finally, we will test Pearson correlations whether the PSA and the VV after-effects are negatively correlated.

Welch t-tests will be used if the variance between the Experimental Side levels is unequal beyond a factor 4. The non parametric Mann-Whitney test and Spearman correlation will be used if the data don’t follow a gaussian distribution.

# Statistics

If data distribution is Gaussian, both SA and VV after-effects will be analysed with a one-tailed paired t-test with Perturbation (leftward, control) as within-subject variable. Otherwise, SA and VV data will be applied a log transformation (before calculating the after-effect, which can take negative values) to follow a Gaussian distribution. If transformations are inoperative, SA and VV after-effects will be analysed with a non-parametric one-tailed Wilcoxon test (aka Mann-Withney-Wilcoxon test).

To investigate the correlations between the SA and VV after-effects, we will first calculate SA and VV delta scores from the Perturbation conditions (eg., SA leftward – SA control). These delta scores will provide “corrected” after-effect measures, controlled for the after-effect obtained without leftward perturbation. Correlations between these delta SA and VV after-effects will be calculated with Pearson or Spearman correlations, depending on the Gaussian distribution of the data.

# Data exclusion\*

First, the presence of outliers will be check graphically with boxplots. Second, studentized residuals will be examine to check whether one observation has extreme influence (“pulling”) on statistical estimates. By convention, studentized residuals above 4 are considered as highly influent. Analyses will be run with and without outliers (Judd et al., 2017).

# Missingness\*

Missingness (eg, one participant realizes three out of four sessions only) will be handled by using Linear Mixed Model (LMM, aka multilevel model) thanks to the R library “lme4” (Bates et al., 2015). If the LMM doesn’t converge properly, we will estimate statistical parameter with a multilevel Bayesian approach, thanks to the R library “brms” (Bürkner, 2017). Because a Bayesian procedure constrains the model with a priori knowledge (“prior”), statistical parameters can be more easily approximated.

# References\*

Angelaki, D. E., Ng, J., Abrego, A. M., Cham, H. X., Asprodini, E. K., Dickman, J. D., & Laurens, J. (2020). A gravity-based three-dimensional compass in the mouse brain. *Nature Communications*, *11*(1), 1855. https://doi.org/10.1038/s41467-020-15566-5

Baier, B., Suchan, J., Karnath, H.-O., & Dieterich, M. (2012). Neural correlates of disturbed perception of verticality. *Neurology*, *78*(10), 728–735. https://doi.org/10.1212/WNL.0b013e318248e544

Bates, D., Mächler, M., Bolker, B. M., & Walker, S. C. (2015). Fitting linear mixed-effects models using lme4. *Journal of Statistical Software*, *67*(1). https://doi.org/10.18637/jss.v067.i01

Brandt, T., Dieterich, M., & Danek, A. (1994). Vestibular cortex lesions affect the perception of verticality. *Annals of Neurology*, *35*(4), 403–412. https://doi.org/10.1002/ana.410350406

Bürkner, P. C. (2017). brms: An R package for Bayesian multilevel models using Stan. *Journal of Statistical Software*, *80*(1). https://doi.org/10.18637/jss.v080.i01

Chokron, S., & Imbert, M. (1995). Variations of the egocentric reference among normal subjects and a patient with unilateral neglect. *Neuropsychologia*, *33*(6), 703–711. https://doi.org/10.1016/0028-3932(95)00007-P

Dakin, C. J., & Rosenberg, A. (2018). Chapter 3 - Gravity estimation and verticality perception. In B. L. Day & S. R. Lord (Eds.), *Handbook of Clinical Neurology* (Vol. 159, pp. 43–59). Elsevier. https://doi.org/10.1016/B978-0-444-63916-5.00003-3

Finkelstein, A., Derdikman, D., Rubin, A., Foerster, J. N., Las, L., & Ulanovsky, N. (2015). Three-dimensional head-direction coding in the bat brain. *Nature*, *517*(7533), 159–164. https://doi.org/10.1038/nature14031

Finkelstein, A., Las, L., & Ulanovsky, N. (2016). 3-D maps and compasses in the brain. *Annual Review of Neuroscience*, *39*(1), 171–196. https://doi.org/10.1146/annurev-neuro-070815-013831

Funk, J., Finke, K., Müller, H. J., Utz, K. S., & Kerkhoff, G. (2010). Effects of lateral head inclination on multimodal spatial orientation judgments in neglect: Evidence for impaired spatial orientation constancy. *Neuropsychologia*, *48*(6), 1616–1627. https://doi.org/10.1016/j.neuropsychologia.2010.01.029

Judd, C., MacClelland, G., & Ryan, C. (2017). *Data Analysis: A Model Comparison Approach to Regression, ANOVA, and Beyond.* (3rd ed.). Routledge.

Kerkhoff, G. (1999). Multimodal spatial orientation deficits in left-sided visual neglect. *Neuropsychologia*, *37*(12), 1387–1405. https://doi.org/10.1016/S0028-3932(99)00031-7

Kerkhoff, G., & Zoelch, C. (1998). Disorders of visuospatial orientation in the frontal plane in patients with visual neglect following right or left parietal lesions. *Experimental Brain Research*, *122*(1), 108–120. https://doi.org/10.1007/s002210050497

Odin, A., Faletto-Passy, D., Assaban, F., & Pérennou, D. (2018). Modulating the internal model of verticality by virtual reality and body-weight support walking: A pilot study. *Annals of Physical and Rehabilitation Medicine*, *61*(5), 292–299. https://doi.org/10.1016/j.rehab.2018.07.003

Pérennou, D. A. (2006). Postural disorders and spatial neglect in stroke patients: A strong association. *Restorative Neurology and Neuroscience*, *24*(4–6), 319–334. http://files/748/2006-21796-010.html

Pérennou, D. A., Piscicelli, C., Barbieri, G., Jaeger, M., Marquer, A., & Barra, J. (2014). Measuring verticality perception after stroke: Why and how? *Neurophysiologie Clinique/Clinical Neurophysiology*, *44*(1), 25–32. https://doi.org/10.1016/j.neucli.2013.10.131

Piscicelli, C., Barra, J., Sibille, B., Bourdillon, C., Guerraz, M., & Pérennou, D. A. (2016). Maintaining trunk and head upright optimizes visual vertical measurement after stroke. *Neurorehabilitation and Neural Repair*, *30*(1), 9–18. https://doi.org/10.1177/1545968315583722

Piscicelli, C., & Pérennou, D. (2017). Visual verticality perception after stroke: A systematic review of methodological approaches and suggestions for standardization. In *Annals of Physical and Rehabilitation Medicine* (Vol. 60, Issue 3, pp. 208–216). Elsevier Masson SAS. https://doi.org/10.1016/j.rehab.2016.02.004

Prablanc, C., Panico, F., Fleury, L., Pisella, L., Nijboer, T., Kitazawa, S., & Rossetti, Y. (2020). Adapting terminology: clarifying prism adaptation vocabulary, concepts, and methods. In *Neuroscience Research* (Vol. 153, pp. 8–21). Elsevier Ireland Ltd. https://doi.org/10.1016/j.neures.2019.03.003

Rizzolatti, G., Fadiga, L., Fogassi, L., & Gallese, V. (1997). The space around us. *Science*, *277*(5323), 190–191. https://doi.org/10.1126/science.277.5323.190

Rossetti, Y., Rode, G., Pisella, L., Farné, A., Li, L., Boisson, D., & Perenin, M.-T. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature*, *395*(6698), 166–169. https://doi.org/10.1038/25988

Rousseaux, M., Honoré, J., & Saj, A. (2014). Body representations and brain damage. *Neurophysiologie Clinique/Clinical Neurophysiology*, *44*(1), 59–67. https://doi.org/10.1016/j.neucli.2013.10.130

Rousseaux, M., Honoré, J., Vuilleumier, P., & Saj, A. (2013). Neuroanatomy of space, body, and posture perception in patients with right hemisphere stroke. *Neurology*, *81*(15), 1291–1297. https://doi.org/10.1212/WNL.0b013e3182a823a7

Yelnik, A. P., Lebreton, F. O., Bonan, I., Colle, F. M. C., Meurin, F. A., Guichard, J. P., & Vicaut, E. (2002). Perception of verticality after recent cerebral hemispheric stroke. *Stroke*, *33*(9), 2247–2253. https://doi.org/10.1161/01.STR.0000027212.26686.48

Finally, we are also interested in the correlation between different types of after-effects. An index of after-effect can be obtained by extracting for each subject his/her [Time X Perturbation] interaction slope value for a given measure.

With this method, we will test the correlations between :

- prism after-effect on SSA AND prism after-effect on VV

- VR after-effect on SSA AND VR after-effect on VV

- VR after-effect on SSA AND prism after-effect on VV

# DRAFT

----------------------------------------------

1) Hypotheses tested by ANOVA

----------------------------------------------

According to the "3D hypothesis", the recalibration of the egocentric spatial coordinates in the horizontal plane should recalibrate the gravitocentric spatial coordinates in the frontal plane too, and vice-versa.

First, we expect a significant effect of LPA on both SSA and visual vertical. The SSA after-effect (ie, posttest - pretest) should be oriented rightward, whereas the visual vertical after-effect shoud be oriented leftward.

Second, we expect a significant effect of the virtual reality immersion (leftward tilt) on both SSA and visual vertical. The SSA after-effect (ie, posttest - pretest) should be oriented rightward, whereas the visual vertical after-effect shoud be oriented leftward.

Importantly, we expect that the control conditions (sham prism adaptation and upright virtual reality) shouldn't give rise to significant after-effects on either SSA or visual vertical. To control for this possibility, we will test the interaction between the Condition variable (control vs biased) and the Time variable (pretest vs posttest) for each intervention (prism adaptation and virtual reality). We expect a significant interaction explained by a simple effect of Time in the biased condition but not in the control condition. These simple effects should be directed in the predicted direction, without being necessarily significant. Note that we are particulary interested in the 2x2x2 interaction, because the effects of each intervention on SSA or visual vertical are by no means comparable.

----------------------------------------------------

2) Hypotheses tested by correlations

---------------------------------------------------

The effect of each intervention on the dependent variables will be evaluated by extracting for each individual the interaction slope value between Time and Perturbation. Concretely, this interaction slope indicates the after-effect difference between the control and the deviation conditions. The larger the interaction slope, the larger the deviation condition has biased the SSA or the visual vertical compared to the control condition. Thus, we will assess for each intervention the correlation between the interaction slopes for SSA and those for visual vertical. We aim to examine if participants who showed a "large" interaction in one plane (horizontal or frontal, SSA or visual vertical) showed a "large" deviation in the other plane too.

Finally, we will test whether the two “trans-dimensional” after-effects —effect of prism adaptation on visual vertical; effect of virtual room tilt on SSA— are correlated within the same participants. Indeed, if egocentric and gravitocentric spatial representations rely on the same cognitive process, we expect that a “large” trans-dimensional after-effect in one direction should result in a similar “large” trans-dimensional after-effect in the other direction. To test this hypothesis, we will examine the correlation between two measures : the individual interaction slope values (Perturbation X Time) for the visual vertical in the prism adaptation intervention ; the individual interaction slope values (Perturbation X Time) for the SSA in the virtual reality intervention.

To investigate these hypotheses, we will submit healthy participants to leftward prism adaptation (LPA), a visuo-motor adaptation training known to bias egocentric spatial perception rightward (Prablanc et al., 2020). When the subject is asked to point toward a visual target, prism wearing induces a leftward error pointing. Then the error signal triggers an adaptation process that realigns proprioceptive coordinates of the hand and retinal visual coordinates, in the rightward direction (Bastian, 2008). After prism removal, SSA is usually shifted rightward after LPA, as compared with the pre-test SSA orientation (the so-called "after-effect" [AE]).

According to the "3D hypothesis", the recalibration of the egocentric spatial coordinates in the horizontal plane should recalibrate the gravitocentric spatial coordinates in the frontal plane too. At the operational level, we expect a correlation between rightward after-effects bearing on the SSA, and leftward (counterclockwise) after-effects bearing on the visual vertical tasks. We thus expect to induce a pseudo-neglect in the horizontal plane sided by a pseudo vertical bias in the frontal plane.

Crucially, we will also test the mirrored prediction that a specific intervention known to bias the visual vertical should in turn bias the SSA orientation. In this view, we plan to expose the same healthy participants to a virtual environment tilted 18° leftward in the frontal plane. This paradigm is perfectly suited to bias the visual vertical (Odin et al., 2018; Witkin & Asch, 1948). According to the "3D hypothesis", we should observe a rightward rotation of the SSA after a sustained immersion of the subject (4 minutes) in the virtual tilted room.

Finally, we will test whether the two “trans-dimensional” after-effects —effect of prism adaptation on visual vertical; effect of virtual room tilt on SSA— are correlated within the same participants. Indeed, if egocentric and gravitocentric spatial representations rely on the same cognitive process, we expect that a “large” trans-dimensional after-effect in one direction should result in a similar “large” trans-dimensional after-effect in the other direction.