KU LEUVEN

DEPARTMENT OF MOVEMENT SCIENCES

MOVEMENT CONTROL AND NEUROPLASTICITY GROUP

Provisional doctoral plan

Role of neurochemicals (GABA) in motor learning and task transfer

Hong Li

Promotor: Prof. Stephan P. Swinnen
Affiliation: Movement Control and Neuroplasticity Research Group

Co-promotors: Dr. Sima Chalavi and Dr. Kirstin-Friederike Heise
Affiliation: Movement Control and Neuroplasticity Research Group

Department of Movement Sciences
Tervuursevest 101, 3001 Heverlee

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1. Introduction and background

Learning various kinds of motor skills is a fundamental ability of human beings to expand their behavioral repertoire and cope with difficulties in life even though the inter-individual capacity for learning such skills can be substantially different. Indeed, there is a considerable variation across individuals in their learning capacity, the brain regions involved and their interactions, learning outcome, and memory strength. The underlying reasons for this diversity are still unknown. Therefore, a better understanding of the role of learning-dependent brain areas and the underlying training-induced dynamical changes in neurochemical composition is mandatory to optimize the obtained learning outcomes and better master various motor skills. Based on past evidence, the task-dependent GABAergic modulation of inhibition has been demonstrated to be related to behavioral improvement[1]. Specifically, magnetic resonance spectroscopy (MRS) has revealed that the γ-Aminobutyric acid (GABA) level in the left primary sensorimotor cortex (left SM) steadily decreased during practice of a motor task, which supported the hypothesis that a reduction in regional GABA concentration accompanies cortical functional reshaping as a result of practice[2,3]. Research conducted by our group has also confirmed that task learning is associated with a decrease of GABA even though this depends on the training context[4]. Basically, it is assumed that a reduction in GABA, the major inhibitory neurotransmitter in the brain, promotes interactions among neurons that constitute the neurobiological basis of learning. However, to date, what exactly the role of GABA is in different training stages and whether it also accounts for the performance of task transfer is still elusive. Therefore this project aims to contribute to this knowledge gap.

Here, I will study the role of GABA modulation in learning-related brain regions during different learning stages. For this purpose, I will utilize a modified version of the bimanual tracking task (BTT), which has been shown to be optimally suited to study skill learning in healthy populations[5,6]. Previous research demonstrated that different training modes or types of practice organization are associated with distinct degrees of modulation of GABA level[7]. Here, I will investigate whether and how different modalities of sensory information sources for supporting learning may have differential impacts on GABA level modulation in specific brain areas that are specialized for processing these types of sensory information sources. More specifically, this refers to the availability of real-time augmented visual feedback (in the form of a moving cursor on the screen) during task performance or lack of such augmented feedback, which directly increases the importance of somatosensory information processing for task execution and learning. Furthermore, the difference between the neurochemical underpinnings of task training and alteration in motor performance variables in the context of initial training and overtraining remains elusive. Therefore, I will investigate the degree of training-induced GABA modulation in the beginning stage (early learning) and after sufficient training of the task (late learning).

In addition, I will also investigate how a previous learning experience (task A) impacts the acquisition of a new skill (task B), i.e., proactive interference. Furthermore, how does the new memory trace affect the previously encoded information, i.e., retroactive interference? I will investigate the potential role of GABA modulation in the context of task transfer. Thus, the assumption is that when a solid memory trace is formed and a specific brain circuit is activated while mastering a new skill, it will induce resistance or negative transfer towards learning another (related) motor task. Conversely, positive transfer may occur when learning similar skills might involve the same brain circuits such that the previously mastered skill may provide a sound basis for learning another related skill. The critical factor is the relation between the skills.

The motor control and neuroplasticity research group, directed by Prof. Swinnen, is devoted to a better understanding of the processes of brain function, structure, connectivity and neurochemicals

in the context of motor control and motor learning. Therefore, a combination of neuroimaging techniques and behavioral task training paradigms will be employed. In the past few years, research on the role of the brain in motor training and learning has been initiated in our group to better understand training-induced alterations in the brain associated with the learning process. However, to date, the neurochemical changes associated with the learning process remain largely unknown. Accordingly, the purpose of this project is to explore the neurochemical basis of learning under different contextual conditions (sensory information availability), during the early and late stages of learning and during transfer.

2. General hypothesis and specific aims

Phase 1
I will prepare a comprehensive review of existing literature on the relationship between neurochemicals, especially GABA, and motor task performance and learning. I will summarize the existing evidence on neurotransmitter modulation in relation to the behavioral training as well as the relationship between baseline levels of GABA and subsequent behavioral changes as a result of motor learning. This will provide a solid basis for future research.

Phase 2
I will primarily focus on two specific sensory processing regions in the human brain, namely the primary somatosensory cortex (S1), a dedicated area for processing of proprioceptive information, and a visual processing region that is highly specialized for processing moving visual stimuli (human MT/V5), embedded in the occipital cortex. I will investigate whether the availability of augmented visual information feedback versus no visual feedback will have a differential effect on the modulation of GABA in the brain regions specialized for the processing of these different types of sensory information sources.

Firstly, I will focus on identifying the brain regions in which baseline GABA levels are the best predictor of subsequent bimanual task learning and overlearning. Secondly, I will study whether there is neural specificity in GABA modulation based on the type of sensory information made available during task practice, i.e., I assume higher modulation of GABA in the visual processing region (MT/V5) than in the somatosensory processing region (S1) during provision of augmented visual information feedback, and, vice versa in the absence of augmented visual information. Thirdly, I will investigate whether the MRS-assessed GABA measurement is differentially modulated during the initial training phase (early learning) vs. overtraining phase (late learning).

I hypothesize that (1) the baseline GABA levels obtained from the prominent learning-related brain regions can predict the future amount of task learning; (2) task training with availability of augmented visual information will be associated with a specific decrease of GABA level in the visual processing region whereas task training with exclusive availability of proprioceptive information will be associated with a unique decrease of GABA levels in the somatosensory processing region. (3) the modulation of GABA level is more pronounced during early learning (when plasticity is maximal) than during late learning (when task-related plasticity is reduced).

Phase 3
I will investigate GABA modulation during task transfer. More specifically, I will investigate whether previous learning of a task (Task A) affects learning a new task (Task B) and whether this is associated with GABA modulation in order to inhibit or suppress the tendency for interference from learning Task A into acquisition of Task B. I assume that coping with interference effects may require extra processing in more generic brain regions for error detection, correction and movement planning [e.g., dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC)] as well as in more specific

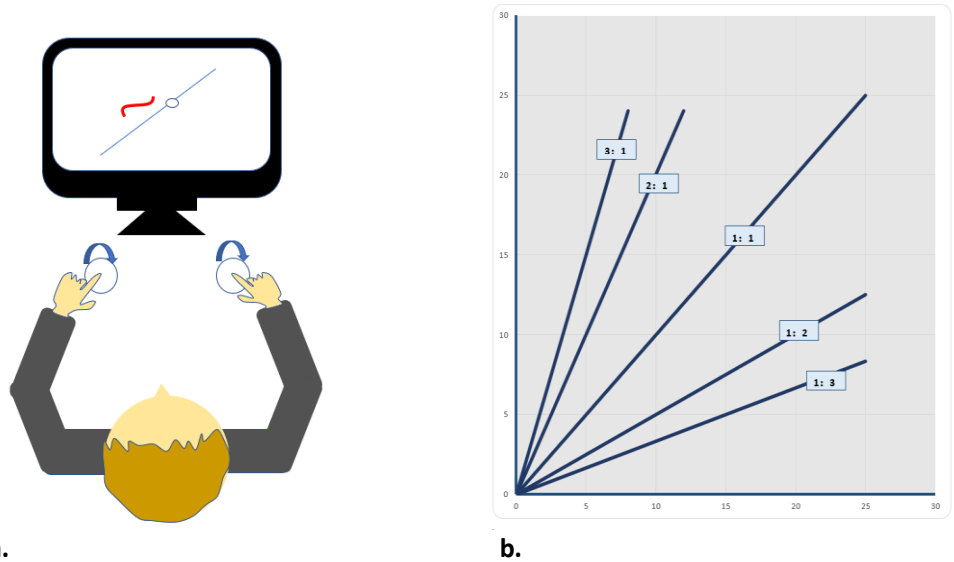
brain regions involved in sensory processing (see Phase 2). The effect of baseline levels of GABA in these regions on transfer will be investigated as well as regionally-specific modulation of GABA during Task B training. There are 2 groups: one group has extensive Task A training (solid memory trace) and another has not (fragile memory trace). Both are subjected to subsequent Task B learning.

I hypothesize that (1) learning new skills requires overcoming pre-existing (preferred) movement patterns or previously acquired motor skills. Compared with the fragile memory group, the solid memory group will suffer from negative transfer from practice of Task A to learning Task B (behavioral hypothesis); (2) modulation of GABA levels will be more prominent in the solid memory group as compared to the fragile memory group in order to overcome the negative transfer from the pre-existing task A onto acquiring Task B (neurochemical hypothesis).

3. Methodology

3.1 Bimanual tracking task (BTT)

In order to implement the learning paradigm, a refined version of the BTT will be used, which allows us to investigate the influence of visual information and proprioceptive information on memory encoding. The adjusted BTT has models with two different feedback conditions: visually-based motor learning condition and proprioception-based motor learning condition. Both conditions will constitute the practice of 5 variations (1:1, 2:1, 3:1, 1:2, 1:3) within 1 quadrant, which means that the target line can be with one of the 5 slopes 1:1, 2:1, 3:1, 1:2, 1:3. The task device is a non-ferromagnetic apparatus with two dials controlled by two hands. The left dial controls the movement along the y-axis and the right dial along the x-axis, and the participant's two hands can rotate clockwise (CW) and counterclockwise (CCW) with different speeds to manipulate the direction and speed of the target moving on a computer screen. In the visually-based condition, the blue target line, the moving white dot on the target line, and the movement trace of the cursor controlled by hands are shown on the screen. Subjects are expected to adjust the movement of both hands dependent on the visual feedback. In the proprioception-based condition, only the blue target line is shown on screen and the subjects are expected to adjust the movement of both hands dependent on their proprioceptive input. Information about task success is only provide after trial completion in the both groups. An auditory imperative stimulus marks the start and the end of each trial in both conditions.



a. **b.**

Figure 1: Bimanual tracking task (BTT) (a. the setup of BTT; b. example variants)

3.2 Brain imaging technique

In this study, I will make use of *Magnetic Resonance Spectroscopy (MRS)*, more specifically the MEGA-PRESS sequence (Puts & Edden, 2012), which the most common approach being J-difference spectral editing. This sequence is specialized for GABA measurement in a low concentration. More specifically, I will obtain baseline measures of GABA in different brain areas: left DLPFC, left S1, left middle temporal visual area (left MT/V5), left dorsal premotor cortex (left PMd), and left striatum. Additionally, I will obtain measures of dynamical modulation of GABA in left S1 and left MT/V5 prior to and following a practice session in Phase 2 and left DLPFC and left ACC in Phase 3. In order to assure a consistent MRS voxel position between participants and measurement sessions, the voxels are set based on the anatomical marker on T1 weighted image.

3.3 Procedure

Phase 1. Literature review on the role of GABA in task performance and learning as well as training-induced GABA modulation. Three databases are searched and the following studies are included: 1) involving a cognitive or motor training or learning task; 2) using the MRS technique to quantify the GABA level at baseline or dynamically. Then two rounds of screening are carried out by a different person successively to avoid a bias in paper selection. After that, data extraction and paper quality assessment are implemented. In this review, I will summarize existing evidence about the relationship between GABA modulation and learning.
(In progress, one manuscript).

Phase 2. Participants are divided into three subgroups (Group 1: visual-FB dependent motor learning; Group 2: no-visual-FB dependent motor learning; Group 3: Control Group). On day 1, baseline GABA levels are measured in left DLPFC, left S1, left MT/V5, left dorsal premotor cortex (left PMd) and left striatum among all subjects. On day 2, we mainly focus on obtaining the dynamic GABA level in left MT/V5 and left S1 in each group. MRS data are collected before initiation of training(pre-test) and after training (mid-test) of the BTT, and after completion of training (post-test). Sensory voxel assessment (visual vs. proprioception) is counterbalanced. An overview of the study protocol of day 1 and day 2 is below.

<table>
<tr><th>Groups</th><th>Day 1</th><th colspan="5">Day 2</th></tr>
<tr><td>Group 1</td><td rowspan="4">Baseline MRS</td><td rowspan="4">MRS (Pre)</td><td>BTT with visual FB training</td><td rowspan="4">MRS (Mid)</td><td>BTT with visual FB overtraining</td><td rowspan="4">MRS (Post)</td></tr>
<tr><td>Group 2</td><td>BTT without visual FB training</td><td>BTT without visual FB overtraining</td></tr>
<tr><td>Group 3</td><td>Rest</td><td>Rest</td></tr>
</table>

Figure 2: Training protocol of phase 2

Phase 3. Young adults are divided into two groups: solid memory group (Solid group) and fragile memory group (Fragile group). Young adults in the Solid group need to learn Task A sufficiently before learning Task B, while young adults in the Fragile group are not familiar with Task A and then learn Task B directly. Task A has 2 variations in quadrant 1 (both clockwise, left: right=1:2 and 1:3) and Task B has 2 variations in quadrant 1 (option 1) or quadrant 2 (option 2). We will decide for the right option based on some piloting studies. The amount of learning on Task B will be related to baseline GABA level in the aforementioned brain areas. Moreover, GABA modulation in the prefrontal brain

areas (DLPFC and ACC) will be measured in both groups of participants prior to and following practice of Task B.

Groups	Day 1					
Group 1	Baseline MRS	Learning Task A extensively	Rest	MRS (Pre)	MRS (Mid) Learning Task B	MRS (Post)
Group 2		No learning of Task A				

Figure 3: Training protocol of phase 3

4. Milestones and timing of the PhD project

The expected timeline of this PhD project is shown below.

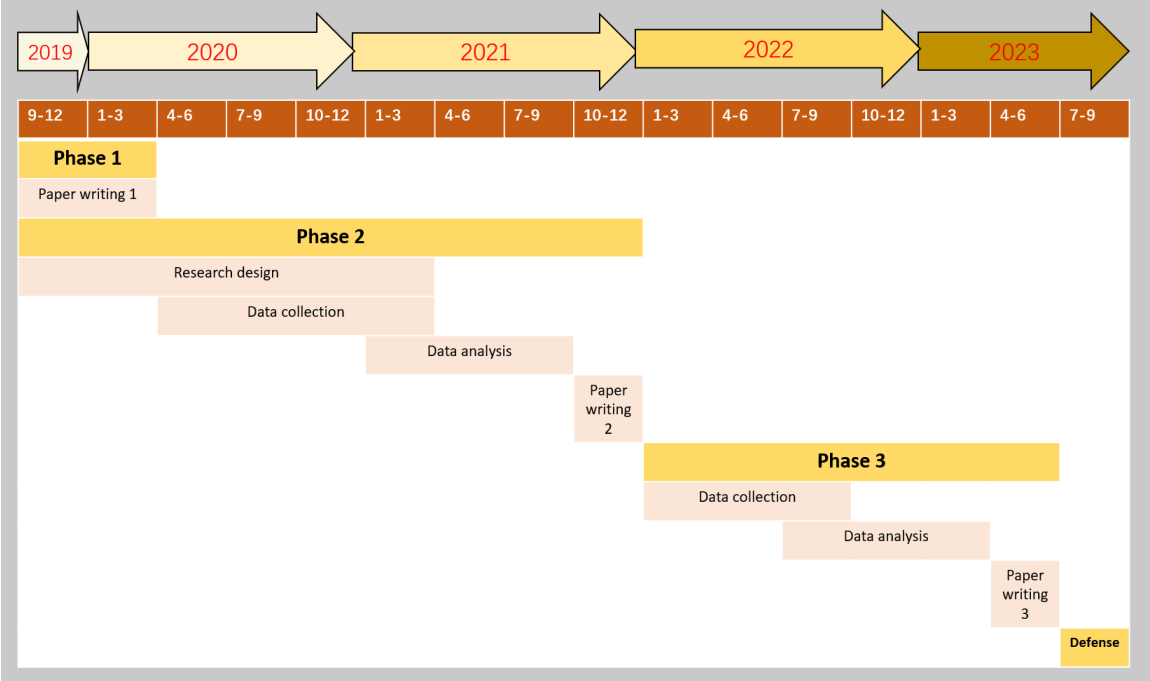


Figure 5: Timeline of this PhD project

5. Conclusion

In conclusion, this doctoral thesis will shed light on the neurochemical basis of task training and overtraining under different sensory conditions and on the neurochemical basis of transfer from one task to another.

6. References

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