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**CORTICAL STRUCTURAL AND FUNCTIONAL COMPONENTS
OF VISUAL PERCEPTUAL LEARNING**

(A VIZUÁLIS PERCEPTUÁLIS TANULÁS
AGYKÉRGI STRUKTURÁLIS ÉS FUNKCIIONÁLIS KOMPONENSEI)

PhD thesis booklet

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General background and aims

By encountering visual stimuli, we become more accurate in identifying and discriminating them, and we might also be able to detect previously undetectable features. Visual perceptual learning is a form of skill learning, reflecting performance improvement in visual tasks through experience or practice. Perceptual learning is mediated by experience induced changes at low level sensory cortices (Karni & Sagi, 1991; Adab & Vogels, 2011), however, several models emphasize the possible contribution of higher-level cortical areas (see e.g., Petrov et al., 2005; Ahissar & Hochstein, 2004). Learning brings on short-term modifications in the efficiency of synaptic transmission and long-term alterations in the structure and number of synapses (Kandel, 2001). Although much has been clarified about the neuronal base of skill learning and procedural memory over the last century, the complex processes underlying learning are still relevant topics of neuroscience.

In my work, I searched for the cortical structural and functional components of perceptual learning by employing the Contour Integration (CI) task (Kovács & Julesz, 1993). The CI task was originally developed to investigate the orientation selective neurons with similar preference in the primary visual cortex (V1). Observers are assumed to rely on the long-range horizontal connections of these neurons to ‘bind’ the small contour elements embedded in random noise. Shape dependent contextual processing seems to be present at this early visual level (Kovács & Julesz, 1994; Li et al., 2006; Mathes & Fahle, 2007), and neuronal correlates were found in the visual cortex with imaging techniques in monkeys (Kinoshita et al., 2009; Kourtzi et al., 2003) and in humans as well (Altmann et al., 2003). The prolonged maturation, extending into late childhood, of long-range horizontal connections in layer II/III of the human primary visual cortex has been demonstrated (Burkhalter et al., 1993).

The developing brain has a high degree of plasticity, and the adult brain also retains some plasticity, making it possible to learn new skills. The developing brain’s greater plasticity is explained on one hand by its higher cortical synaptic density (Huttenlocher, 1984), on the other hand, by the elevated brain metabolic rate during childhood, which continues until 16-18 years of age (Chugani et al., 1998). The developmental aspects of perceptual learning and the corresponding topic of neural plasticity have not been investigated systematically by behavioral techniques. In Thesis I. I discuss the typical developmental trend of contour integration, along with the comparison of the different age groups’ perceptual learning capacity.

Visual performance enhancement in perceptual learning tasks occurs during two major phases (Karni & Sagi 1991): an early ‘fast learning’ phase followed by a slower improvement in the absence of the stimuli. The former is a consequence of fast neuronal changes (Gilbert, 1994), while the later is a result of the reorganization of cortical representations (Karni & Sagi, 1993). The second phase is sleep-dependent, this is the stage where the consolidation of experience induced changes takes place (Karni & Sagi, 1993; Stickgold et al., 2000). The role of sleep was confirmed

by several studies applying Texture and Orientation Discrimination tasks (Karni & Sagi, 1994; Stickgold et al., 2000; Matarazzo et al., 2008). Contour integration involves higher level (longer range) spatial integration than the above mentioned processes. In Thesis II, I report the modulatory role of sleep in CI, which has not been investigated in this type of task before.

The third main topic of my investigations is perceptual learning in atypical development. Genetically determined neurodevelopmental disorders involve impairment in the growth and development of the central nervous system (e.g., Down, Rett, fragileX, Williams syndromes), which leads to a variety of disorders of brain functions. Reduced capacity to learn is one of the most prevalent and general symptoms of these disorders. Discovering the underlying factors behind this impaired capacity is crucial for successful neurorehabilitation. I investigated learning capacity in Williams syndrome (WS), in which population there are individual differences in the degree of genetic injury (the hemizygous microdeletion of the long arm of the chromosome 7 affects cc. 20-30 genes, but the magnitude of the deletion varies individually; see e.g., Botta et al., 1999), and in the cognitive and learning skills as well. Besides an overall brain volume reduction, there is a specific parieto-occipital reduction in WS (Chiang et al., 2007). Morphometric studies showed altered neural density and morphology in the primary visual cortex in WS (Galaburda et al., 2002). As in many neurodevelopmental disorders, disturbed sleep pattern has been found in WS (Arens et al., 1998; Gombos et al., 2011). In Thesis III, individual performance of WS subjects was analyzed by comparing the performance of each WS subject to the learning patterns of entire typically developing age-groups. By exploring individual differences and looking at each subject individually instead of grouping and averaging them together, we could avoid information loss. Difference in individual WS performance patterns might indicate different underlying structural and/or functional impairments, which we can assume based on the deviations from typically developmental patterns.

To summarize, the thesis and the relating publications will discuss the following three main issues:

I) *The typical developmental trend of contour integration and perceptual learning.* How is contour integration baseline performance related to the structural/ functional maturation of V1? What are the learning capacities of different age-groups?

II) *Clarifying the role of sleep.* What are the phases of perceptual learning in contour integration? What modulatory role does sleep have in these different phases?

III) *Factors that determine initial performance and perceptual learning in WS.* Based on the comparison with typically developing population patterns, what are the factors behind impaired contour integration and perceptual learning performance in WS?

New scientific data

Thesis I.: The typical developmental trend of contour integration and perceptual learning.

a) We studied baseline and perceptual learning performance of six typically developing age-groups ($n=60$, 7-21 year) in the contour integration task. Participants practiced in the same task through five days with an approximately twenty-four hour shift between the practice sessions, and we estimated perceptual threshold on each practice day. Perceptual learning was compared to motor learning. In order to avoid the dissimilar cognitive loads in the initial phases of the two different tasks, we defined baseline performance as perceptual threshold on Day 2. Learning curves of the age-groups were drawn based on the measured perceptual thresholds during the course of the training, and the overall and between-session improvements were analyzed as well.

According to our results, the structural developmental changes in V1 affect baseline performance in the Contour Integration task. In the typically developing population, contour integration shows prolonged age-dependent improvement, and reaches adult level only by the age of 14. All age-groups showed significant learning in the task. After comparing the learning pattern of the age-groups, it became apparent that the performance of younger age-groups change faster and in a greater degree (steeper learning curves) in the early period of the training.

b) The participant population of the first study was extended with additional forty subjects ($n=100$, 7-23 years), and data were reanalyzed to get a more accurate depiction about the typically developing trend of contour integration and perceptual learning. The age-groups were the followings: 7-8 years, 9-10 years, 11-12 years, 13-14 years, adults (mean 21,5 years). In this analysis, the baseline was defined as Day 1 performance, and learning was expressed as the difference between the perceptual thresholds on Day1 and Day5.

The new results strengthened earlier findings: contour integration reaches the adult level only in late childhood, 13-14 years old age-group showed no significant difference compared to the adult group. Age-groups 7-8 years and 8-9 years showed significantly lower baseline performance than all the older age-groups. Learning performance was

significantly lower in the adult group than in the child age-groups, except in the 13-14 years old group, whose learning did not differ significantly from that of the adults. Learning was similar across the different age groups in children.

Thesis II.: The role of sleep in the two phases of perceptual learning.

In this work, we attempted to distinguish the time and sleep dependent phases of perceptual learning. To separate the daytime (time dependent) and nighttime (time and sleep dependent) offline modulations the following experimental design was employed: two groups of subjects practiced five times in CI through two and a half days, at 8 a.m. and 8 p.m. (12 hours between training sessions). The Morning Group (MG) started the five-session training course at 8 a.m., while Evening Group (EG) at 8 p.m. By the fifth session (the end of the experiment) the two groups practiced the same amount and all participants slept two times, however in Session2 and 4 the two groups differed in respect whether they had have sleep before the session or not.

Based on our results, we could distinguish two phases of perceptual learning in CI. In the early phase of learning sleep is not crucial for performance increment between two sessions, by Session2 both groups' performance increased significantly, even though MG had no sleep between the two training sessions. Even if sleep is not sufficient, performance enhancing effect of sleep was presents in this early stage as well: by Session2 EG (had sleep between the two training sessions) showed significantly greater amount of learning than MG (had no sleep between the two training sessions). After Session3, in the later phase of learning performance enhancement is sleep-dependent: by Session4 only EG (had sleep before the session) performance increased significantly, while MG (had

no sleep before session) showed no relevant performance increment during daytime. These results might implicate that initial phase involves higher-level cognitive and attentional processes, and the second phase is more specific to low-level cortical changes.

Thesis III.: Dissociation of structural vs. plasticity factors in perceptual learning

Nineteen WS subjects with wide range of age (7-30 years) and hundred typically developing subjects (7-23 years) participated in this study. Each participant practiced in CI task with the same experimental design through five days. Two values of the subjects were analyzed: the baseline performance (Day1) and the learning performance (improvement by Day5). We normalized the data of all subjects (z-score) and on learning data an additional correction was also performed. This correction was necessary for the valid comparison of the typically developing and WS subjects' performances. In typically developing population, there is a correlation between the baseline and the amount of learning: the lower the baseline, the greater the improvement is during the five-day learning course. Learning values had to be corrected to avoid the false conclusions about the learning capacity of WS subjects because of their low baseline performance. Instead of pooling the very inhomogeneous results of WS subjects together, we evaluated individual performance by expressing it in terms of the deviation from the average performance of the group of typically developing subjects with similar age. This approach helped us to reveal information about the possible origins of poor performance of WS subjects in contour integration.

In line with the expectations, the performance patterns of the WS subjects were very inhomogeneous. Subjects' performances showed four major patterns: (1) subjects performing in the normal range (or even above) both in terms of baseline performance and learning rate, (2) subjects in the normal range in terms of baseline, but handicapped in learning, (3) subjects in the normal range in terms of learning, but handicapped in terms of baseline performance, (4) subjects handicapped both in terms of baseline performance and learning. Case (2) and (3) are especially interesting, since these allow us to make conclusion on the potential dissociation between factors determining baseline and learning performance. Low baseline performance presumably indicates structural, functional impairment in primary visual cortex since the horizontal connections of the orientation selective neurons in V1 are assumed to find the

CORTICAL STRUCTURAL AND FUNCTIONAL COMPONENTS OF VISUAL PERCEPTUAL LEARNING

PhD thesis booklet

contour in the noise (the structural and functional immaturity of these connections in childhood leads to lower baseline performance, see Thesis I.). There might be a number of different factors behind reduced learning capacity in WS. From one hand, it is the potential lack of genes (e.g. Linkk1, Stx1, Cyln2) determining dendritic spine growth and synaptic transmission likely underlie learning. On the other hand, disturbed sleep pattern could be another possible factor determining reduced learning capacity in WS (learning in CI is sleep dependent, see Thesis II.).

Conclusions and further directions

I studied the structural and functional factors determining perceptual learning in contour integration. The Contour Integration task is an optimal tool for these investigations, since the underlying mechanisms and neuronal background are well explored. We plotted the developmental curves of contour integration and perceptual learning based on the results of a large typically developing population ($n=100$, 7-23 years): (i) the new results strengthened earlier findings: contour integration reaches the adult level only in late childhood, (ii) younger age-groups demonstrated a greater capacity to learn, however, significant learning was present in all studied age-groups. In a further investigation, we identified two phases of perceptual learning in CI: sleep is not crucial for performance improvement in the early phase of learning, while after this initial fast learning phase, there seems to be a sleep-dependent stage of learning.

After defining the performance determining factors in CI, we employed the task in an atypically developing population to look at individual performances. We evaluated individual WS performance by expressing it in terms of the deviation from the average performance of typically developing subjects of similar ages. This approach helped us to dissociate different factors behind poor performance in WS. The dissociation of these factors in patients with a well-determined genetic, neuroanatomic and behavioral profile has a great potential both in developing more effective treatment procedures, and in the better understanding of basic learning mechanisms of the human brain

In future work we attempt to verify our above mentioned assumptions in a series of behavioral, polisomnographic and genetic investigations. In a preliminary study (Gombos et al., 2010) polisomnographic and behavioral data of WS subjects were analyzed together, the results showed enhanced left hemispheric Beta activity in individuals with higher learning capacity (compared to those who showed reduced learning capacity).

List of publications related to the theses

Thesis I.

1. Gervan, P., Berencsi, A., Madarasz, T., Kovacs, I. (2010). Development and plasticity of primary visual and motor function in humans. *Learning & Perception*, Supplement 1, p. 25.
2. Gervan, P., Berencsi, A. & Kovacs, I. (2011). Vision First? The Development of Primary Visual Cortical Networks Is More Rapid Than the Development of Primary Motor Networks in Humans. *PLoS One*, 6(9), 25572, 1-9.
DOI:10.1371/journal.pone.0025572
3. Gervan, P., Gombos, F. & Kovacs, I. (2012). Perceptual Learning in Williams Syndrome: Looking Beyond Averages. *PLoS One*, 7(7), 40282, 1-8.
DOI:10.1371/journal.pone.0040282

Thesis II.

4. Gervan, P. & Kovacs, I. (2007). Sleep dependent learning in contour integration. *Journal of Vision*, 7(9), p. 48a., Paper 48.
5. Gervan, P. & Kovacs, I. (2010). Two phases of offline learning in contour integration. *Journal of Vision*, 10(6), 24, 1-7.
DOI: 10.1167/10.6.24

Thesis III.

6. Gervan, P. & Kovacs, I. (2009). Dissociating structural abnormalities and epigenetic factors in WS individuals. In: Wiring the Brain: From Genetic to Neuronal Networks. Adare, Ireland, p. 46., Paper P1.26.
7. Gervan, P., Gombos, F. & Kovacs, I. (2012). Perceptual Learning in Williams Syndrome: Looking Beyond Averages. *PLoS One*, 7(7), 40282, 1-8.
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