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CORTICAL STRUCTURAL AND FUNCTIONAL COMPONENTS OF VISUAL PERCEPTUAL LEARNING

PhD thesis

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Contents

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Glossary of abbreviations

AMPA	Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid
BDNF	brain-derived neurotrophic factor
ERP	event-related brain potential
FMRP	fragile X mental retardation protein
GABA	gamma-aminobutyric acid
GluR1	Glutamate receptor 1
LTD	long-term depression
LTP	long-term potentiation
MEG	magnetoencephalography
NMDA	N-Methyl-D-aspartate
NREM	non-rapid eye movement
PLMS	periodic leg movements during sleep
REM	rapid eye movement
SWA	slow wave activity
VERP	visual event-related brain potential
Zif268	zinc finger protein 225

Abstract

Experience-dependent cortical plasticity is fundamental for the ability to acquire or improve skills through learning, which is an essential capacity throughout human life. Exploring perceptual learning provides an opportunity to understand cortical plasticity, perception and behavior in a coherent way. I investigated the cortical structural and functional factors underlying visual perceptual learning in typically developing children and young adults and in people living with a genetically based neurodevelopmental disorder (Williams syndrome, WS).

The first goal was to determine the typical developmental trend of perceptual learning capacity in a visual integration task. The contour integration (CI) task specifically addresses the spatial range of long-range horizontal connections in the primary visual cortex that have been shown to have a prolonged maturational period in humans. Our results (n=100, 7-23 y) are consistent with earlier findings in terms of the slow development of spatial integration, and reveal age-dependent improvement reaching the adult level only by the age of 14 years in CI. Furthermore, younger age-groups demonstrated a greater capacity to learn, however, significant learning was present in all studied age-groups.

The second goal was to determine the role of sleep in perceptual learning in CI, since previous findings claimed its sleep-dependent nature in several other tasks. Two phases of perceptual learning were identified 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.

The third goal was to determine the spatial integration and perceptual learning capacities in WS, where it is known that abnormalities in the structure and connectivity of the visual cortex, as well as sleep disorders can be a component of the syndrome. 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 on an individual basis: low baseline performance in CI indicating structural impairment in the primary visual cortex; while low learning capacity indicating abnormal sleep patterns and/or a potential lack of genes underlying synaptic plasticity. 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.

Kivonat

Új készségek elsajátítása vagy már meglévők fejlesztése tanulás útján nélkülözhetetlen képességünk egész életen keresztül, melyhez elengedhetetlen a tapasztalatfüggő kérgi plaszticitás. A perceptuális tanulás vizsgálata lehetőséget ad arra, hogy a kérgi plaszticitás, a percepció és a viselkedés összefüggéseit megértsük. Munkám során a vizuális perceptuális tanulást meghatározó kérgi strukturális és funkcionális komponenseket vizsgáltam tipikusan fejlődő gyerek és fiatal felnőtt populációban, valamint egy genetikailag meghatározott fejlődési zavarban, Williams szindrómában (WSZ).

Az első cél a perceptuális tanulás tipikus fejlődési trendjének meghatározása volt egy vizuális integrációs feladatban. A kontúrintegrációs feladat specifikusan az elsődleges látókéreg hosszú távú horizontális összeköttetéseit célozza meg, mely összeköttetések elnyújtott érése figyelhető meg humán szinten. Eredményeink (n=100, 7-23 év) összhangban vannak a korábbi vizsgálatokkal, miszerint a téri integráció lassú életkori fejlődést mutat és csak körülbelül 14 éves korra éri el a felnőtt teljesítmény szintet. Továbbá, a fiatalabb életkori csoportok nagyobb tanulási kapacitást mutattak, mindamellett, hogy szignifikáns tanulás minden korcsoportban jelen volt.

A második cél az alvás szerepének meghatározása volt a kontúrintegrációs feladatban mutatott perceptuális tanulásban, mivel korábban alvásfüggő jellegét számos más feladat esetében kimutatták. A perceptuális tanulás két fázisát azonosítottuk: a korai fázisban az alvás nem elengedhetetlen a tanuláshoz, majd a kezdeti gyors szakaszt követően a tanulás már alvásfüggőséget mutat.

A harmadik cél a téri integráció és a perceptuális tanulási kapacitás feltérképezése volt Williams szindrómában, amely szindróma elsődleges látókérgi strukturális- és összeköttetésbeli eltéréseket, valamint alvászavarokat is okozhat. Az egyes WSZ alanyok teljesítményét a hasonló korú tipikusan fejlődő életkori csoport átlagteljesítményétől való eltérésük szerint értékeltük. Ez a megközelítés segített abban, hogy a WSZ alanyok gyenge teljesítménye mögött rejlő oki tényezőkről feltételezéseket fogalmazzunk meg: az alacsony kontúrintegrációs alapteljesítmény feltehetően az elsődleges látókéreg strukturális, funkcionális sérülését jelzi, míg a gyenge tanulási kapacitás hátterében valószínűleg sérült alvás mintázat és/vagy a szinaptikus plaszticitást befolyásoló, potenciálisan hiányzó gének állhatnak. Ezeknek a tényezőknek a disszociálása olyan alanyok esetében, akiknél a genetikai, a neuroanatómiai és a viselkedéses profil alaposan feltérképezett, segítséget nyújthat egyfelől a hatékony kezelés kialakításában, másfelől az emberi agy alapvető tanulási mechanizmusainak megértésében.

I. Introduction

I.1.Learning and brain plasticity

The human brain has a great capacity to acquire new skills, both in the perceptual and motor domains. Although much has been clarified about the neural basis of skill learning and procedural memory over the last century, the complex processes underlying learning are still progressing research topics of neuroscience. Procedural learning, including learning by 'doing' or by 'experiencing' is usually distinguished from the declarative learning of factual knowledge (e.g., Cohen & Squire, 1980).

A popular view on procedural learning claims that skill learning is subserved by functional and structural changes within the brain systems repeatedly involved in the performance of the task, and exposed to the same experience (Karni, 1996). These functional and structural changes are unimaginable without the brain's dynamic potential to reorganize itself, in other words, without brain plasticity. Greenough and colleagues (1987) distinguished two types of experience driven plasticity: experience-expectant vs. experience-dependent. Experience-expectant plasticity refers to the process when during critical or sensitive periods of development there is selection among the overproduced synaptic connections driven by sensory experience, which results either in establishing the used or eliminating the unused connections. During sensitive periods, lack of exposure to normal external input results in impaired functioning of neural circuits. On the other hand,

experience-dependent plasticity is present throughout life, and neural connections are formed in response to specific experience of the individuals to incorporate environmental information into their neuronal networks. The type of learning I will discuss here is a form of experience-dependent plasticity.

A vast amount of data shows that connections in the human low level sensory cortices (visual, auditory, somatosensory) can be shaped by experience (for a review see Calford, 2002), and it is generally assumed that these changes are caused at the neuronal level by Hebbian plasticity (see e.g., Kirkwood and Bear, 1994). The theory of Hebbian plasticity postulates that the strengthening or weakening of neuronal connections depends on the relative timing of neuronal activity (i.e. similarities or differences in the firing pattern of neurons; Hebb, 1949). When presynaptic and postsynaptic neurons are active simultaneously, the connection between the two neurons becomes stronger. Therefore, if two stimuli constantly emerge together, the neurons receiving input from those paired stimuli consequently fire together, which leads connection strengthening between them. These changes in synaptic connectivity could lead to modifications in the topography of the cortical structure (e.g., Pons et al., 1991). For example, if a body part is involved in more behavioral activity its representation becomes larger in the somatosensory cortex, however, after deafferentation of the body parts, the cortical representation shrinks (e.g., Recanzone et al., 1992; Merzenich et al., 1983a,b).

I.1.1.Learning and plasticity in neuroselectionist learning theories

The question, how do experience and environment form our mind throughout learning, had arisen well before the emergence of cognitive neuroscience. Through the history of human cultures, there have always been metaphors for learning,

plasticity and memory formation, because it used to be (and still is) a puzzling phenomenon. This issue was considered even by the ancient philosophers, such as Plato, who formulated a very plastic description of the process of learning (in, Wagoner, 2012, p.2):

"I would have you imagine that there exists in the mind of man a block of wax. When we wish to remember anything we have seen, or heard, or thought in our own minds, we hold the wax to the perceptions or thoughts, and in that material receive the impression of them as from the seal of a ring. Whatever is so imprinted we remember and know so long as the image remains. – Plato, Theatetus, 191D-E "

By the early 20th century, the metaphors which described learning as writing or recording information into wax or on a tablet, had been replaced with models about filing cabinets in which mind stores knowledge. Outlining even briefly the history of theories of memory and learning from antiquity to the 21th century would go well beyond the scope and aim of this work. By keeping in mind that numerous versions of learning theory could be found in psychology and cognitive sciences, I would like to focus on two neuroselectionist theories, since these theories attempt to integrate the cognitive and neural perspectives on learning, and seem to explain the origins of specificity and variety.

In his theory of Neural Darwinism, Edelman (1987, 1989, 1993) claims that the theory of group selection could be used to understand how neural networks are shaped by experience. Edelman (1978) emphasizes that in the human brain extremely large numbers of unused connections are present not only in childhood, but through adulthood as well. The unused connections offer possibilities for learning, however, the author debates that merely genes or environment would be sufficient in itself to govern the types and patterns of innumerable distinct neuronal connections. He also maintains that selection should take place at the level of neuron populations rather

than at the level of a single synapse, since cognitive functions originate from the connectivity of numerous neurons (1989). The Theory of Neuronal Group Selection states that we learn throughout perceiving and interacting with a continuously changing environment, and only those groups of neuronal connections are selected that are functionally adaptive. Edelman assumes that selection takes place through Hebbian mechanisms (see above activity dependent synaptic strengthening and weakening), which mechanisms show captivating parallels with Darwinian natural selection. According to his concept, perceptual experience leads to re-entrant signalling between neurons establishing reciprocal connections within and between different levels of nervous system. As Edelman describes "Reentry can be defined as ongoing parallel signalling between separate neuronal groups occurring along large numbers of ordered anatomical connections in a bidirectional and recursive fashion.(Edelman, 1993 p. 117)" As a result of the re-entry, new properties of the network connectivity emerge, i.e. learning takes place. Edelman formulated three basic mechanisms of selection (1987): (i) developmental selection, (ii) experimental selection, (iii) re-entrant mapping. During developmental selection, the anatomical development of the neural network takes place where the physical process of cell organization and connection establish the 'primary repertoire'. The experimental selection is the modification of connection weights in the network via usage leading to formation of interconnected maps and maintaining the 'secondary repertoire'. Re-entrant mapping is the process of indirect selection of maps by other connected maps (stimulation).

Another neuroselectionist model of learning was formulated by Jean-Pierre Changeux, and the foundation of his theory is the idea of 'resonance' between the percept evoked by external stimuli and the internal 'pre-representations' of the

organism (Changeux, 1985). The pre-representations sprout from the recombination of pre-existing sets of neuronal groups, and are characterized with great diversity. This selectionist model proposes that first the genesis of multiple and transitory pre-representations takes place, which is followed by the selection of the 'adequate' internal representation of the external word. The hypothesized resonance accounts for the internal selection and the selected pre-representation will be stored. Later on, Dehaene and Changeux (1989, 1991) claimed that the pre-representations produced by a neuronal 'generator of diversity', and it is the release of rewards that modulates the synaptic strength in the neuronal network. The pre-representations are selected by positive reward signals that, following the classical Hebbian rule, tend to stabilize the recent activation. Positive reward occurs as a consequence of successful interaction with the environment of the organism. On the other hand, a negative reward, as consequence of anti-Hebbian rule, will diminish the probability of the ongoing activation. Unsuccessful interaction with the environment will destabilize the system and lead to construction of new pre-representations. In their renewed theory of learning,) By introducing the 'auto-evaluation' loop' in their model the anticipation of reward was taken into account by Dehaene and Changeux (1991). By the help of this function, each action could be associated with increase or decrease in the probability of the reward. This internal mode of simulation accelerates learning and equally importantly helps to avoid risky actions without trying them out in the external world.

Neuroselectionist theories provide a link between the process of learning and neuronal architectural changes as a consequence of learning. Models, based on these concepts, demonstrate a promising framework for studying neuronal networks. However, as Fernando and Szathmary (2010) pointed out, neither Edelman's nor

Changeux's models could explain transmission of a favorable trait of one group to non-group material, which is a fundamental feature of natural selection and learning as well.

I.1.2.Experience –dependent plasticity and learning at the cellular level

The dominant conceptual model for activity-dependent synaptic plasticity is the Hebbian synapse (Hebb, 1949), discussed above. By the discovery of long-term potentiation (LTP) and long-term depression (LTD) the candidate mechanisms for learning and memory at the cellular level have been found (Bliss & Collingridge, 1993; Bliss & Lomo, 1973; Lynch & Baudry, 1984; Lynch et al., 1977). The stimulation of NMDA (N-Methyl-D-aspartate) receptors is essential in LTP, since the increased calcium entering through the NMDA channel leads to phosphorylation of AMPA (Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionic Acid) receptors and insertion of more AMPA receptors into the postsynaptic membrane (Malinov & Malenka, 2002). The increase in the number and activity of AMPA receptors induced by NMDA receptor stimulation leads to enhanced excitatory response when the synapse is stimulated later. The enhanced activity of the NMDA receptor channel complex in the immature brain is thought to be responsible for the intensified LTP at younger ages (e.g., McDonald & Johnston, 1990).

The following properties of LTP and LTD make them excellent candidates as physical and biochemical substrates of learning and memory at the cellular level (Schiller et al., 1998): (i) LTP and LTD occur almost universally in the CNS; (ii) LTP can be induced fast and it persists after the stimulus disappears for several hours or days, just like the formation of memory itself; (iii) LTP is input-specific.

The correlation of learning with LTP and LTD should be found at the behavioral level as well. In fact, studies have consistently reported improvements in learning when LTP occurs and impairment in learning and disruption in memory consolidation when LTP is blocked in a variety of learning paradigms (see review by Martin et al., 2000). Traditionally, LTD has been viewed as a counterpart for LTP, as a mechanism reversing effect (Bear & Malenka, 1994). Later on, investigators have identified a much broader role for LTD in formation of certain types of memories (Manahan-Vaughan & Braunewell, 1999), in preventing saturation of neural networks (Dayan & Willshaw, 1991). Therefore, it appears that both LTP and LTD are importantly linked to maintenance of the normal functioning in nervous system and memory formation.

Synaptic refinement and stabilization of neuronal circuits are equally important mechanisms in activity-dependent learning and memory (Cohen-Cory, 2002; Sheng & Kim, 2002). Both types of processes involve stimulation of neurotransmitters and other cell surface receptors, activation of intracellular signaling cascades and gene transcription, along with synthesis of new proteins that change the physical shape and number of synapses (see e.g., Johnston et al., 2001).

I.1.3.Factors affecting plasticity

Neural plasticity is influenced by a number factors such as aging (Kramer et al., 2004), psychoactive drugs (e.g., stimulants, THC; Robinson & Kolb, 2004), gonadal hormones (Kolb & Stewart, 1991), stress (Liston et al., 2006), neurotrophic factors (e.g., NGF, FGF-2; Kolb et al., 1997), electrical stimulation (Teskey et al., 2003), sleep (Karni et al., 1994). These factors might affect both the structural and functional levels. In the followings, the focus will be on aging and sleep.

I.1.3.1.Age and plasticity

It is generally believed that the nervous system is the most plastic during its development. In humans, neurobiological development is a prolonged process extending well into adolescence. Because of the elongated development, important steps of the neurobiological development take place after middle childhood (for a review see Spear, 2000). The prolonged maturational period allows a shift from genetically determined cortical specification toward epigenetic control in brain development (Cicchetti & Tucker, 1994). Allowing both the environment and the experience to have an impact on the functional specialization of the cerebral cortex (Johnson, 1999).

During the course of development, the highly dynamic system of the human brain undergoes numerous diverse phases from cell formation to the rapid growth and subsequent elimination of unused synapses before finally entering into a more stable phase following puberty (e.g., Huttenlocher, 1984, 1990). During development, neural systems become more and more stable, tending to reach an optimal pattern of functioning, while plasticity becomes less pronounced. However,

plasticity never disappears from the adult human nervous system (Stiles, 2000). In adulthood, during learning and memory formation, synaptic changes are similar to that of childhood maturation (Kolb et al., 2011). However, Johnston (2003) in his review pointed out, there are qualitative differences between adult and child plasticity, since during early years there are extra synaptic connections present in the child's brain. This surplus of connections allows „changes to occur at the level of axonal and dendritic branching, while in older individuals changes are restricted to more localized formation and activity-dependent rearrangement of synaptic spines" (Johnston, 2003, p.107).

It is widely accepted that neuroplasticity is continuously changing during aging (e.g., Heuninckxet al., 2008; Nieto-Sampedro & Nieto-Diaz, 2005). Kleim and Jones (2008) collected several factors likely contribute to the decline of plasticity in normal aging, which are the followings: decreased experience-dependent synaptic potentiation, reduced synaptogenesis, widespread neuronal and synaptic atrophy, and physiological degradation. In addition, Huttenlocher proposed (2002) that some neural mechanisms for plasticity disappear during development. "One such mechanism may be the functional specification of unspecified, labile synapses for the construction of new neuronal circuits." (Huttenlocher, 2002, p.188).

I.1.3.2.Sleep, learning and experience-dependent plasticity

The idea, that sleep enhances plasticity and learning through reactivation of the wake-active neural networks, is a long-standing concept in neuroscience. Several studies reported reactivation in animals (e.g.,Wilson & McNaughton, 1994; Skaggs & McNaughton, 1996), and increased metabolic activity and synchronization in specific brain areas in humans as well (e.g., Maquet et al., 2000). More recently, neuronal activation sequences have been found that were learned during the day in fast-forward off-line replays during sleep (Euston et al., 2007; Sara, 2010). Replays were observed in prefrontal cortex in transient episodes during slow wave sleep (SWS). These sequences were compressed in time (6-7 times faster) compared to the average activity during behavior in the hippocampus (Euston et al., 2007). This off-line replay might play a crucial role in consolidation of memories during sleep. As Buhry et al. (2011) in their review emphasized, the offline replay and reactivation clearly has the properties to drive LTP (i.e. to contribute to plasticity), since it has similar features to that of spike-timing-dependent plasticity and tetanic stimuli (a high-frequency sequence of individual stimulation, commonly used to induce long-term potentiation).

Another hypothesis about the role of sleep in plasticity and learning was formulated by Tononi and Cirelli (2003), and it emphasizes the homeostatic function of sleep. They suggested that wakefulness is associated with synaptic potentiation in several cortical circuits, while NREM (non-rapid eye movement) sleep is associated with synaptic downscaling. Downscaling leads to an improved signal-to-noise ratio, which can be accounted for the beneficial effects of sleep on performance (Tononi & Cirelli, 2006; Cirelli & Tononi, 2008). Vyazovskiy et al. (2008) reported that the level of GluR1 (Glutamate receptor 1) subunit containing AMPA receptors during

wakefulness is elevated, while during sleep it is decreased, indicating potentiation of synaptic transmission during wakefulness, followed by depotentiation during sleep. The authors suggested that these results are in line with the synaptic homeostasis hypothesis.

The connection between plasticity related gene expression and sleep also has been studied in the last decades. Huber et al. (2007) studied the relationship between exploration-rich wakefulness and cortical expression of plasticity-related genes and slow wave activity (SWA) during a subsequent night of sleep in rats. They found, that the level of exploratory behavior during waking had a strong connection with the SWA response during sleep. Furthermore, they reported that high level of induction of brain-derived neurotrophic factor (BDNF) in the cerebral cortex during waking resulted in strong SWA response during sleep. This indicates a link between sleep slow wave activity, experience-dependent neural activity and synaptic plasticity.

Ribeiro and colleagues (1999) found that exposure to an enriched environment resulted in up-regulation of zif-268 (zinc finger protein 225, also known as nerve growth factor-induced protein A) during REM (rapid eye movement) sleep in rats, suggesting that brain gene expression during REM sleep depends on previous waking experience. In a further experiment, the same research group induced hippocampal long-term potentiation in awake animals, which led to increased zif-268 expression following REM sleep in extrahippocampal areas such as amygdala, entorhinal, auditory, somatosensory and motor cerebral cortices. It has been suggested that REM sleep „constitutes a privileged window for hippocampus-driven cortical activation, which may play an instructive role in the communication of memory traces from the hippocampus to the cerebral cortex" (Ribeiro et al., 2002; p. 10914).

I.1.4.Disorders of plasticity

As we emphasized above, neuronal plasticity is essential not only for normal brain development, but also later on for maintaining and shaping the established neuronal networks. In case of injured plasticity mechanisms, the neuronal system may become abnormally reactive to environmental inputs or, on the contrary, less responsive to experience. Abnormal neuronal plasticity is a central characteristic in neurodevelopmental disorders (NDDs). NDDs involve impairment in the growth and development of the central nervous system and refer to a variety of disorders of brain functions which can affect social behavior, emotions, learning ability and memory. Neurodevelopmental disorders can be distinguished by genetic (e.g., FragileX, Down Syndrome.) and environmental causes (e.g., lead poisoning, nutritional deficiencies, infections.), the nature and site of dysfunction (e.g., metabolic disorder, immune disorder), and by the time course of cognitive and behavioral deficits during development (pre-, peri- or postnatal).

Here I will focus on NDDs with a known genetic basis causing abnormalities in the central nervous system. These disorders are easy to characterize by animal models, well defined in terms of mechanisms, and very promising in terms of the better understanding of neural plasticity.

The majority of neurodevelopmental disorders are caused by genetic abnormalities that may be classified into several categories, such as chromosomal disorders, single gene disorders and polygenic disorders (Tager-Flusberg, 2005). Chromosomal disorders are characterized by lacking or duplicating either entire chromosomes (e.g., Down syndrome, Turner syndrome), or segments of a chromosome (e.g., Williams Syndrome, Prader-Willi syndrome). Single gene disorders formulate a further category, in which impairments are caused by a single

gene mutation (e.g., phenylketonuria, fragile-X syndrome). A third group of disorders is referred to as polygenic or complex subgroups of NDDs, since they are assumed to be caused by several interacting genes (e.g., Autism Spectrum Disorder).

One of the most common problems in NDDs is the imbalances between excitatory and inhibitory networks (Wetmor & Gardner, 2010, Chattopadhyaya & Cristo, 2012). Cc. 20–30% of all cortical neurons are inhibitory neurons or interneurons, which predominantly utilize gamma-aminobutyric acid (GABA) as a neurotransmitter. GABAergic interneurons have a crucial role in brain development and in controlling adult plasticity. Lehmann et al. (2012) list several mechanisms where inhibitory interneurons contribute to normal functioning, such as cell migration and differentiation, timing the onset of critical period, generation of temporal synchrony and oscillation among networks of excitatory neurons, as well as experience dependent refinement of neuronal connections. In line with this, Wetmore and Garner (2010) highlighted that the imbalance between excitatory and inhibitory networks is crucial in several neurodevelopmental disorders: inhibitory networks abnormally dominate in Down syndrome, Rett Syndrome and neurofibromatosis type I, while overexcitation occurs in Fragile X Syndrome and Tuberous sclerosis.

Abnormal translation of proteins near synapses is another common cause of dysfunction in NDDs (Alves-Sampaio & Montesinos, 2007; Wetmor & Garner, 2010). Alteration in translation can lead to abnormal cell proliferation, irregular dendritic arborisation and spine numbers, and impaired synaptic plasticity as well (Alves-Sampaio & Montesinos, 2007). Fragile X mental retardation protein (FMRP), coded by the human gene FMR1, normally inhibits the translation of mRNA (messenger Ribonucleid acid). In mouse models of fragile X Syndrome, reduced

fragile X mental retardation protein (FMRP) function causes extreme translation responsible for abnormally enhanced plasticity (Oostra & Willemsen, 2009). Similarly, altered protein translation was found in other neurodevelopmental disorders such as Rett Syndrome, tuberous sclerosis and in neurofibromatosis type 1 (Wetmor & Garner, 2010).

Impaired communication between the synapse and the nucleus (such as calcium signaling) also could lead to cognitive deficits in NDDs (Cohen & Geenberg, 2008). Normal and effective signaling is essential not only for maturation of the nervous system, but also indispensable for experience-dependent plasticity. Genetical mutations that affect components of signaling networks have been identified in Timothy syndrome, in Coffin-Lowry syndrome, in Rubenstein-Taybi syndrome and Rett syndrome (Cohen & Geenberg, 2008).

In spite of the enormous effort in the last decades, which lead to discoveries about the molecular, genetic and neurophysiological mechanisms, many unanswered questions remained about the underlying factors of impaired plasticity in NDDs. It should be emphasized that most of the results are based on mouse models, which gives strong limitations to the interpretations of the data. Besides the obvious differences in the complexity of the human and mouse central nervous systems, it should be noted that the effect of epigenetic factors in humans is much more profound than in inbred laboratory animals.

Finally, with respect to impaired plasticity in NDDs, a last notion should not to be missed: sleep disturbances are extremely common in NNDs, the reported prevalence rates ranging from 13% to 86% (e.g., Didden & Sigafoos, 2001; Harvey & Kennedy, 2002). For example, in Down syndrome obstructive sleep apnea or sleep-disordered breathing were found to be present between 45 and 100% of the

cases (Marcus et al., 1991; De Miguel-Diez et al., 2003; Dyken et al., 2003). Young et al. (2007) reported as high as 80 % prevalence of sleep disorders in Rett syndrome (e.g., night-time laughter, night-time seizures). In fragile X syndrome 32% of the population was reported to have sleep problems (Kronk et al., 2010). Since sleep is proved to be essential to learning and to encode long-term memories throughout life (e.g., Karni et al., 1994; Walker et al., 2002) a link between sleep problems and learning disabilities in NDDs might be presumed. Correspondingly, significant negative relationship between disturbed sleep and attention, learning, behavior and academic functioning in childhood has been reported (e.g., Blunden & Beebe, 2006; Bourke et al., 2011), leading to the suggestion that sleep problems in neurodevelopmental disorders potentially play an important role in cognitive deficits and learning difficulties in this population.

The impaired plasticity and sleep with respect to Williams syndrome will be discussed in chapter I.3., separately from the above covered NDDs.

I.2. Visual Perceptual Learning

In addition to research efforts at the molecular and cellular levels, developing a tool to investigate the factors underlying impaired plasticity and learning abilities in NDDs at the behavioral level would also be advantageous. What factors influence plasticity and learning capacity in NDDs? Furthermore, what are the sources of large individual differences in NDD populations? These and similar questions are especially important from the clinical and educational points of view, and might contribute to successful rehabilitation in NDDs.

Perceptual learning paradigms have the potential to become useful tools to study plasticity in the human central nervous system since they might provide a possibility to connect cortical plasticity, perception and behavior. The phenomenon of perceptual learning has been extensively studied, and it has a well-established neuronal background offering the opportunity for controlled and specified investigations. Moreover, the application of perceptual learning tasks might be considered a particularly appropriate way of investigating learning abilities in atypically developing groups as it aims learning at a low cognitive level requiring low cognitive load.

I.2.1. Perceptual learning – general mechanisms and characteristics

The conceptualization of procedural memory was indicated by neuropsychological studies reporting patients with hippocampal amnesia and spared ability to learn new skills (Cohen & Squire, 1980). Procedural learning refers to gradual acquisition of skills over several sessions of practice or following prior

exposure to stimuli. In the procedural domain of learning and memory, motor and perceptual skill learning are traditionally distinguished, however these two subtypes of learning share several common attributes. Paz and colleagues (2004) suggested similar principles of neural coding and computation in both domains concluding that sensory and motor learning are determined and directed by changes in neuronal tuning functions in low cortical areas (such as primary visual, auditory, somatosensory and motor cortices). Censor et al. (2012) have summarized the analogies between perceptual and motor learning lately in a comprehensive review. They highlighted that (i) the two types of learning go through similar stages of initial fast acquisition and slower between session learning and memory stabilization; (ii) in spite of the high specificity of learning reported earlier, evidence for generalization was shown later in both domains; (iii) sleep plays a pivotal role in both forms of learning due to several suspected mechanisms such as promoting LTP and LTD, preventing neural network saturation, and reactivating neural circuits; (iv) there is evidence for the involvement of higher-order brain areas in learning especially in the initial phase of learning and in generalization. This chapter will discuss these phenomena of procedural learning with respect to its perceptual form, concentrating on the visual domain.

The observation that performance in perceptual tasks can improve with practice has been reported in several modalities for a wide variety of perceptual tasks. Performance enhancement was registered in very simple sensory discriminations, such as tactile frequency and pattern discrimination (Recanzone et al., 1992; Spengler et al., 1997; Nagarajan et al., 1998), visual texture, orientation and motion discrimination (Karni & Sagi, 1991; Schoups et al., 1995; Ball & Sekuler, 1987), auditory pitch discrimination (Recanzone et al., 1993) and odor

discrimination (Stevenson, 2001; Wilson and Stevenson, 2003). These improvements in perceptual tasks following repeated exposure to sensory experience are referred to as perceptual learning.

Perceptual memory formation goes through various stages. Fast learning takes place in the early phase of learning when individuals start to practice in a new task, and it leads to initial encoding or acquisition of memory (Karni & Sagi, 1993). This rapid performance improvement might occur even within the first period of exposure to the stimuli, and instead of involving structural and functional changes, it seems to be an effect of familiarity with the task (Karni & Sagi, 1993). After this rapid initial phase, performance enhancement slows down, and usually takes place between the practice sessions without any exposure to the stimuli. This phase involves sleep-dependent mechanisms and relies on structural and functional changes (see later). At this stage, memory consolidation takes place resulting in more stable memories, which become resistant against other interfering stimuli and decay (i.e. forgetting).

The typical features of perceptual learning are generally thought to be different from the features of other forms of learning. First, the timescale within which perceptual learning emerges is highly variable among tasks. For example, Poggio and colleagues (1992) reported learning within several hundred trials in a vernier acuity task, while in another study, orientation discrimination learning occurred over weeks (Schoups et al., 1995). Another characteristic feature of perceptual learning is its high specificity to the properties of the trained stimulus and task. Learning was shown not to transfer within different stimulus types (e.g., it was orientation specific in Fioretini &, Berardi 1980; Schoups et al., 1995), retinal locations or parts of the visual field (Karni& Sagi, 1991; Shiu & Pashler, 1992) or

tasks (e.g., from vernier acuity task to orientation discrimination, Crist et al., 1997). However, this high-level specificity seems to be challenged in more recent studies (see later, in the next subchapter). Furthermore, in perceptual learning, unlike in many other forms of learning, feedback is not required for performance enhancement (e.g., Karni& Sagi, 1991; Fahle & Edelman, 1993). Taken together, these above described features of perceptual learning led to the conclusion that neural mechanisms underlying perceptual learning are at relatively early stages of sensory processing (Gilbert, 1994). However, the extent of specificity in perceptual learning has been reconsidered recently. The level of specificity in learning was suggested to depend on the difficulty of the trained conditions, and was found to be the highest for very difficult tasks (Ahissar and Hochstein, 1997). Evidence was found for global components and generalization in perceptual learning studies (e.g. Ahissar & Hochstein, 1997; Censor & Sagi, 2009; Jeter, et al., 2009). These findings, along with experimental data with respect to the role of attention and feedback from higher cortical areas (see later in I.2.2.2.) are commonly interpreted as evidence for the role of higher cortical areas in perceptual learning.

Finally, a common feature of perceptual learning across modalities is its sleep-dependent nature. The role of sleep in learning has been shown in several modalities, such as in the visual (e.g., Karni et al., 1994; Stickgold et al., 2000a,b), auditory (e.g., Gaab et al., 2004; Fenn et al., 2003) and somatosensory domains (e.g., Kattler et al., 1994; Bergmann et al., 2008).

I.2.2. Visual perceptual learning

Visual perceptual learning (VPL) has been studied in different visual tasks, including paradigms involving the discrimination of textures (Karni and Sagi, 1991; Schoups et al., 1995), detection of motion direction (Ball & Sekuler, 1987), spatial phase discrimination (Fiorentini & Berardi, 1981), stereoscopic vision (Ramachandran & Braddick, 1973), hyperacuity (Poggio et al., 1992; Fahle & Edelman, 1993; Fahle, 1994), orientation discrimination (Shiu & Pashler, 1992; Schoups et al., 1995) and object recognition (Furmanski & Engel, 2000).

The level of processing at which perceptual learning takes place is still a subject of debate. The two most important factors considered as 'indicators' of the cortical level of learning are (i) specificity vs. non-specificity of learning (i.e. transfer) and (ii) attention free vs. attention dependent manner of learning. High level stimulus specificity suggests that learning takes place within low level cortical areas, since in these areas neurons are selective for basic stimulus properties (see e.g., Karni & Sagi, 1991). On the other hand, transfer of learning to other tasks would imply that higher central cognitive processes are involved beyond local low-level visual processes (see e.g., Xiao et al., 2008). As for attention, perceptual performance enhancement for unattended stimuli would suggest that perceptual learning occurs without the contribution of higher-level central processes (see e.g., Seitz & Watanabee, 2003). On the other hand, the involvement of attentional processes in learning points to a crucial role for higher brain areas in controlling changes at early visual processing levels, or in reading out information from early cortical inputs (see e.g. Ahissar & Hochstein, 1993; Petrov et al., 2005). In the followings, evidence and theories with respect to low-level vs. higher-level learning will be discussed.

I.2.2.1.Evidence for early cortical plasticity in perceptual learning

Early behavioral studies found visu0al perceptual learning to be specific for retinal location (e.g., Karni & Sagi, 1991; Shiu & Pashler, 1992; Schoups et al., 1995), for stimulus orientation (e.g. Fiorentini & Berardi, 1980; Poggio et al., 1992) and for the trained eye (e.g., Fahle, 1994) leading to the assumptions that learning occurs at low-level cortical areas.

In an electrophysiological study in monkeys, Li et al. (2008) found practice induced changes in V1, but these changes disappeared when animals were anesthetized leading to the assumption that they resulted from top-down attentional influence. Similarly, in a study by Hua et al. (2010), training largely improved perceptual contrast sensitivity of V1 neurons in cats; however, the animals were anesthetized in this study as well. After these controversial results, Adab and Vogels (2011) demonstrated that learning could result in robust plasticity in visual representation areas. In their recent study, they showed that the orientation signals in macaque cortical area changed as a result of practicing in coarse orientation discrimination. Learning effects were most robust when the trained orientation was close to the preferred orientation of the cell, and more importantly, learning-induced plasticity was specific to the orientation of the trained stimuli. Furthermore, this study showed that learning did not occur as an effect of attentional processes, since it was present outside the context of the training task as well implicating that learning was free from top-down attentional modulation.

Learning-dependent brain activity was measured by electrophysiological methods in human visual event related potentials studies providing evidence for changes in V1 electroencephalographic (EEG) responses as a consequence of learning (e.g. Skrandies & Fahle, 1994; Pourtois et al., 2008). Pourtois et al. (2008)

reported that perceptual learning in a texture discrimination task modulated early visual responses, starting at 40 ms after stimulus onset. Since earlier studies suggested that top-down influence arises in V1 after 100 ms, the conclusion is that the observed early influence is related to local changes in V1, induced by learning. Similarly, in an event-related potential study applying sine-wave gratings, Bao et al. (2010) found that perceptual learning could increase early visual area response through local receptive field changes.

Several human imaging studies revealed learning induced changes in specific brain areas. In a 3D positron emission tomography study, Schiltz and colleagues (1999) compared cerebral activation before and after training in an orientation discrimination task, and found changed activation patterns in the striate and extrastriate visual cortices. In functional magnetic resonance imaging (fMRI), neuronal correlates of perceptual learning were studied by mapping brain areas in which the activity level changes as a result of learning. Applying a global-motion direction discrimination task, Vaina et al (1998) showed activation increment in MT (medial temporal area), which was interpreted as a result of learning-induced cortical recruitment. After monocular training in the texture discrimination task, Schwartz and colleagues (2002) found stronger activation in V1 for the trained eye as compared with the untrained eye. Similarly, several other human imaging studies reported changes in the activation of the primary visual cortex after training, e.g., in a contrast detection task (Furmanski et al., 2004) and in a curvature discrimination task (Maertens & Pollmann, 2005); after practicing in a shape identification task, activation changes were found in the lateral occipital complex as well (Sigman et al., 2005).

In a series of experiments, Watanabe and his colleagues (Watanabe et al., 2001, 2002; Seitz and Watanabe, 2003) demonstrated that learning occurs for stimulus features even when those are presented in the lack of awareness or focused attention. Temporal pairing between the presentation of a task-irrelevant motion stimulus and a task-target led to performance enhancement in motion discrimination demonstrating the phenomenon of task irrelevant perceptual learning (TIPL). Furthermore, TIPL studies found specific learning for low-level visual features such as local motion direction (Watanabe et al., 2002), orientation and retinal location (Nishina et al., 2007), eye of exposure (Seitz et al., 2009) and contrast polarity of motion stimuli (Pilly et al., 2010). Moreover, in a TIPL psychophysical and fMRI experiment on motion direction discrimination, Tsushina et al. (2006) found activation in MT+ in those conditions that promote TIPL, while LPFC (lateral prefrontal cortex) remained inactive. Since LPFC is known to subserve high-level functions such as cognitive inhibitory control and decision making, authors suggested that TIPL does not involve higher cognitive functions. However, Seitz and Watanabe (2003) also emphasized that a global reward, triggered by successful task-relevant performance, is necessary for task-irrelevant perceptual learning. Seitz and Watanabe (2005) suggested that task-irrelevant stimuli benefit from the learning signals that are released due to processing of task-relevant stimuli. Sasaki et al. (2010) suggested that it is the reward signal, rather than visual attention, that reinforces learning both in task-relevant and task-irrelevant learning.

I.2.2.2. Evidence for the contribution of higher cortical areas to perceptual learning

Parallel with the concepts of low-level learning in perceptual tasks, theories and models were raised about involvement of higher cortical processes in perceptual

learning. These theories emphasized that learning may arise from changes in connections between the sensory territories and decision units that are located at higher cortical levels (see e.g., Mollon and Danilova, 1996). Similarly, Dosher and Lu (1998) proposed that the improved readout from sensory to decision stages could be accounted for enhanced performance in perceptual tasks. This research group described perceptual learning as 'selective reweighting', where perceptual learning reflects plasticity in the relative activity of different basic visual channels, which give input to higher cortical areas being responsible for abstract representations (Petrov et al., 2005). As Dosher and Lu (2004, p.475) pointed out :„Plasticity based on reweighting has the additional advantage that early visual representations are left unchanged, so that perceptual learning of one task need not impact on another task ...". This theory could be considered as selectionist in a Gibsonian way, since it suggests that the observer learns to discriminate better within the activation patterns of low-level networks.

Animal neurophysiological studies that showed the lack of substantial alterations in early visual cortices with training or practice, could be assumed as indirect evidence for the substantial role for higher cortical areas in VPL. Schoups et al. (2001) have shown a modest effect of practice in the orientation discrimination task in terms of the characteristics of orientation tuning of individual V1 neurons in monkeys, which could not be accounted for the large behavioral enhancement. On the other hand, Ghose and colleagues (2002) reported no significant effect of training in monkeys' V1 and V2, and concluded that observed neuronal changes are insufficient to explain the improvement in behavior. Similarly, in a motion direction discrimination task, practice did not result in changes of neuronal responses in MT (Law & Gold, 2008).

Furthermore, the most prominent feature of perceptual learning, its high level of specificity (i.e. lack of generalization) seems to be challenged by more recent human behavioral studies, questioning the concept of low cortical level learning. By applying a double training method, Xiao et al. (2008) showed complete transfer of perceptual learning to new retinal location. Double-training paradigm is a new method to address perceptual learning; it employs standard feature training at one location, and additional training with an irrelevant feature/task at a second location, either simultaneously or at a different time. In the study by Xiao et al. (2008), additional location training enabled a complete transfer of feature learning to the second location, furthermore double training often produced as much learning as single training. In their very recent work, Harris and colleagues (2012) demonstrated that location specificity in standard texture discrimination paradigm (see e.g., Karni & Sagi, 1991) occurs as a result of sensory adaptation. When they interleaved so called 'dummy' trials (task-irrelevant trials containing texture oriented +/-45° relative to the target's orientation) between target trials to remove adaption, complete generalization of perceptual learning was found to a new location (while transfer was not present e.g. in case of dummy trials contained texture oriented 90° relative to target, since this type of stimulus did not diminish adaptation). Harris et al. suggested that spatial invariance depends on the level of adaptation, since adaptation induces local plasticity in neuronal networks, whereas unadapted low-level networks produce space-invariant responses. By avoiding adaptation during the course of perceptual learning, it becomes possible for learning to generalize from one location to another, while adaptation during training leads to the failure of this transfer of learning.

Yotsumoto and collagues (2008) reported changes in the pattern of brain activation in V1 over the time course of perceptual learning: the initial increased

activation in the sub-region of the human V1 for the trained location disappeared, while the performance enhancement was maintained. The authors suggested that these findings might be explained by synaptic downscaling (Censor et al., 2006; Tononi and Cirelli, 2003) since results are "in accord with the hypothesis that the strength or number of synaptic connections increases in the local network during the initial period. After performance saturation, high performance is maintained by smaller number of synapses that survive overall synaptic downscaling." (Yotsumoto et al., 2008, p.7).

The involvement of attention in perceptual learning has been demonstrated by several psychophysical studies. For example, Shiu and Pashler (1992) found that subjects do not improve if their attention is directed to the brightness feature of the stimulus in an orientation discrimination task. Similarly, learning on orientation of local elements did not generalized for the orientation of the global shape (Ahissar and Hochstein, 1993), and learning to detect a target within a horizontally or vertically elongated array did not transfer to the non-attended feature of the array (the orientation of the array) (Hochstein and Ahissar, 2002). Ahissar and Hochstein (1997) systematically examined the effect of task difficulty on the specificity of learning, and found that the level of specificity in learning depended on the difficulty of the trained conditions. In the easy condition they found learning transfer, which led them to the conclusion that the task was performed and learned at high cortical levels, while the lack of learning transfer in the difficult condition was interpreted to indicate that learning took place at low cortical levels. Ahissar and Hochstein (1997, 2004) postulated the reverse hierarchy theory of visual perceptual learning, suggesting that learning begins at high-level areas of the visual system (high-level cortical representations are ecologically meaningful), and when these are not

sufficient (e.g. because of poor signal-to-noise ratio), there is a gradual access to the more informative input levels with better signal-to-noise ratio. In this theory, learning is thought to be attention driven, since attention chooses the relevant neuronal population by increasing its functional weight, so in this concept, learning is considered as a top-down process. In line with this, Wanning et al. (2011) proposed, the interactions between early brain processing areas (such as V1) and higher order brain regions may contribute to perceptual learning by engaging attentional mechanisms that enhance the perception of hole objects using Gestalt grouping cues.

The evidence, discussed above, are quite controversial: some show that perceptual learning originates in enhancement of early sensory representations (see e.g., Adab & Vogels, 2011), others demonstrate that performance improvement is a result of the contribution of higher cortical areas in visual processing (through selective re-weighting of connections from the sensory representations to specific responses, Dosher & Lu, 2004), while there are theories which enumerate both high and low cognitive levels as important factors in learning (e.g., Ahissar & Hochstein, 2004). The questions, what is learnt during perceptual learning and at what cortical level the changes are manifested, are still open. It is likely, that both low-level and higher-level cortical areas contribute to perceptual learning, and the relevant question might be related to how do these areas work together in learning.

I.2.2.3.The role of sleep in visual perceptual learning

A large body of evidence supports the involvement of sleep dependent mechanisms in visual perceptual learning. The role of sleep has been studied extensively in the texture discrimination paradigm. Behavioral studies demonstrated that improvement in a perceptual tasks was significant only after a night of sleep (e.g., Karni et al., 1994; Stickgold et al., 2000b), while equivalent time of awake did not lead to performance improvement.

In a polisomnographic study, Karni et al. (1994) demonstrated that performance on this task improved after a normal night's sleep and showed that selective disruption of REM, but not NREM sleep, results in a loss of this performance gain. Karni and colleagues suggested that REM sleep might contribute to offline improvements through modulation of cholinergic neurotransmission. Using the same perceptual task, Gais and colleagues (2000) reported evidence for the role of both NREM and REM sleep in perceptual learning. In their study, subjects were selectively deprived of early sleep (normally dominated by NREM slow-wave sleep) or late-night sleep (normally dominated by REM and NREM 2). They concluded that NREM slow wave sleep initiated consolidation enhancements, while REM sleep supported additional improvement. In a further study on perceptual learning in the texture discrimination task, Stickgold et al. (2000a) found positive correlation between sleep-dependent improvements and the amount of slow wave sleep early in the night, as well as the amount of REM sleep late in the night. Based on these findings, Stickgold and colleagues proposed a two-step process of memory consolidation, which requires the sequential contribution of NREM and REM stages. Furthermore, in an additional study (Stickgold et al., 2000b) they found that less than 6 hours of sleep after training did not lead to significant overnight learning, however,

a total first night sleep deprivation resulted in the lack of sleep-dependent improvement even after two subsequent recovery nights of sleep. To investigate further the role of sleep in perceptual learning, Aeschbach and his colleagues (2008) applied an acoustic slow-wave suppression paradigm to reduce slow wave activity in NREM, and found that texture discrimination performance improved after sleep in the control group, but not in the suppression group. Furthermore, they found a correlation between power density in NREM slow wave sleep activity and the amount of behavioral improvement in the task. These findings strengthened the earlier results showing that slow wave activity is an important determinant of sleep-dependent gains in perceptual performance.

Mednick et al. (2003) reported that sleep-dependent learning in a texture discrimination task can be elicited not only by night sleep, but also by a brief (60- 90 min) daytime nap containing both slow-wave sleep and rapid eye movement sleep. They found that improvement could not be achieved when only slow wave sleep is present during the nap. However, a short nap containing only slow wave sleep was useful in preventing performance deterioration that otherwise emerges with repeated task performance during a day of training (Mednick et al., 2002) or within a training session (Mednick et al, 2005).

Applying the texture-discrimination task in a behavioral study, Censor et al. (2006) showed that the intensity of the training, i.e., the number of trials within a training session affects its dependency on sleep. A relatively small number of trials (225) produced equal learning effects with and without sleep (daytime improvement), whereas learning with an increased number of trials (400) was not significant during daytime, learning occurred only after a night of sleep. A further increase in the number of trials (800) blocked learning regardless of presence or

absence of sleep (Censor et al., 2006). This suggests that short training resulted in efficiently consolidated learning, and saturation of the network can be avoided by decreasing the number of trials in perceptual tasks. On the other hand, in case of extremely high number of trials, deterioration of performance might happen due to over-learning, and an over-exposure to the stimuli may invade consolidation. These findings imply that sleep plays a protecting role against interference and over-training (by normalizing synaptic weights to avoid local saturation, without which further training may cause interference), and in strengthening memory (enhancement). Censor et al. (2006) assumed that normalization is carried out during slow wave sleep stages and that enhancement is carried out in the REM stage.

I.2.3. Contour integration and visual perceptual learning

The ability of the visual system to link local, fragmented image features into global, complex forms has been investigated extensively in contour integration (CI) tasks (see Kovács & Julesz, 1993; Field et al., 1993). Contour integration tasks apply contours formed by oriented, disconnected elements, which are embedded in random noise. To measure the visual system's sensitivity and capacity to integrate elements, two types of manipulations are typically introduced in contour integration tasks. In one form of the task, the relative density of noise elements is varied. In this type of CI tasks, the detection of the contour becomes more difficult at higher noise density levels. In another form of the CI task, the contour elements are jittered from the original path of the contour, while the density is kept constant. Increased orientation jitter results in a higher difficulty level of the task. Contour integration tasks may also employ open or close contours as target stimuli. In a series of experiments, Kovács and Julesz (1993) found that the maximum spacing between adjacent elements for detecting closed contours is higher than that for open contours, implying that closed contours are more salient than open contours.

In contour integration tasks, where a contour composed of collinear Gabor elements embedded in a complex background noise of randomly oriented and positioned Gabor elements, the noise forces the observer to carry out local measurements at the scale of the individual Gabor signals to acquire orientation information (Kovács & Julesz, 1993; Hess & Field, 1999). The long-range orientation correlations along the path of the contour could only be detected by the integration of local orientation measurements, and observers have to rely exclusively on long-range interactions between local filters to connect the contour elements. Considering these features of the contour integration tasks, it can be concluded that

these stimuli are appropriate to examine long-range interactions subserving spatial integration and perceptual organization in V1.

At the neuronal level, visual contour integration involves spatial integration and it is mediated by activity within the long-range horizontal connections of orientation selective neurons in the primary visual cortex (e.g., Kovacs & Julesz, 1993; Angelucci et al., 2002; Chisum & Fitzpatrick, 2004). Cortical pyramidal cells have axonal arbors that extend for distances up to 8 mm parallel to the cortical surface, and connect neurons with similar orientation preference with non-overlapping receptive fields (Gilbert & Wiesel, 1979; Rockland & Lund, 1982; Gilbert & Wiesel, 1983). These long-range horizontal connections enable neurons to collect and integrate information over relatively large parts of the visual field, considerably larger than a receptive field size of an orientation selective neuron.

Several studies examining the role of feedback connections in contour integration suggested that feedback connections might also contribute by mediating top-down influences (e.g. Li et al., 2006, 2008). However, Giersch and colleagues (2000) studied a visual agnosic patient with intact V1, and severely damaged occipital areas beyond V1, who showed normal contour integration performance. This indicates the sufficiency of V1 in mediating contour integration. The existence of shape dependent contextual processes was shown at the level of V1 (Kovács & Julesz, 1994; Mathes & Fahle, 2007), and neuronal correlates were explored 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). Li et al. (2006) reported correlation between the responses of neurons in V1 and the perceptual saliency of contours, which neurophysiological finding supports the concept, that V1 has a cardinal role in contour integration.

Kovacs et al. (1999) found significant performance improvement in children between 5 and 14 years in the CI task, suggesting an unexpectedly late development of contour integration abilities in humans. These results are in line with the neuroanatomical finding that the development of horizontal connections in layer II/III of the human primary visual cortex extends well into childhood (Burkhalter et al., 1993). Perceptual learning in CI is specific to stimulus features, such as orientation and color (Kovacs et al., 1999), and this high level of specificity strengthens the concept that the process involves use-dependent changes in connectivity within the orientation selective neuronal network in the primary visual cortex. We have examined the role of sleep in perceptual learning in contour integration, and found that 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 one (Gerván & Kovács, 2010).

I.3. *Williams syndrome*

Among NDDs, I have been extensively studying Williams syndrome (WS). The neuroanatomy and neurophysiology of the WS brain, and the genetic basis of the syndrome is well explored. Moreover, the mild to moderate level of mental retardation in this population, their highly sociable nature and the well-preserved language skills make them an ideal population to work with, since communication barriers, task engagement difficulties or problems with the understanding of instruction rarely occur. The following chapter will discuss the cognitive profile, neuroanatomy, genetics and sleep disorders in Williams syndrome.

I.3.1.Overview of Williams syndrome

Williams syndrome (also called Williams–Beuren syndrome) is a neurodevelopmental disorder caused by a hemizygous microdeletion of cc. 20-30 genes on chromosome 7q11.23, that includes the elastin (ELN) gene (Ewart et al., 1993). Based on the findings that more than 98% of individuals with WS have deletions of the elastin gene (Lowery et al., 1995; Mari et al., 1995), a FISH test (fluorescent in situ hybridization) was developed to probe for the ELN deletion and supply a reliable genetic test for WS (Lowery et al., 1995). The prevalence of WS is estimated 1 per 7,500-20,000 live births (Morris et al., 1988; Strømme et al., 2002), and it is equally prevalent in both sexes and present in all populations throughout the world (Morris et al., 1988). WS individuals tend to have distinct facial characteristic, so called 'elfin' face profile with flat and upturned nose, full lips, wide mouth, heavy orbital ridges (Morris & Mervis, 2000). Growth retardation, short figure, hoarse voice and cardiovascular abnormalities (e.g. supravalvular aortic stenosis) are also

found to be common and prominent features of WS (Morris et al., 1988). During infancy, eating and feeding problems are frequent in this population (Martin et al., 1984), causing vomiting and irritability, leading to failure to thrive. Hyperopia (vertical strabismus) and esotropia (inward strabismus) were found in 78 percent of cases (Kapp et al., 1995) implying that ocular problems are general too. An interesting feature of WS is auditory hyperacusis, an abnormal sensitivity to certain sounds (van Borsel et al., 1997).

Personality characteristics include non-social anxiety, hyperactivity and a tendency to be friendly and sociable towards adults (Bellugi et al., 1999a). Studies usually found large individual differences in the WS population, which is reflected in the fact that some adults with WS are able to live independently or semi-independently, whereas others require significant support (Udwin, 1990).

Increasing knowledge about the neuroanatomy, neurophysiology and genetic basis of WS makes it very promising in terms of genotype-phenotype correlations (e.g. Bellugi et al., 1999b; Meyer-Lindnberg et al., 2006), and WS has definitely been in the focus of neurodevopmental research during the last decades.

I.3.2.Cognitive characteristics

Approximately 95% of WS individuals have mild to moderate learning disabilities and the mean IQ is around the mid-50s to low 60s range (Udwin et al., 1987, Bellugi et al., 2000, Mervis et al., 1999; Atkinson et al., 2003). WS individuals generally have intriguing cognitive profiles associated with poor visuo-spatial abilities compared to fairly intact language skills and facial recognition (Bellugi et al., 1999b,c). Due to these dissociations, the cognitive phenotype of WS became the target of dissociative developmental theories as a particularly interesting potential

evidence for innately specified cognitive modules. The idea, that selectively spared language could justify claims about cognitive modularity, was first introduced by Bellugi and her colleagues in 1988. Furthermore, based on early findings in WS language processing and production, language was claimed to be autonomous of other cognitive processes by Pinker as well (Pinker 1991, 1999 in Thomas et al., in press). Moreover, Pinker declared that WS together with Specific Language Disorder show a double dissociation for language vs. non-verbal cognition impairment. Later studies of the relative strengths and weaknesses in the language profile suggested that language is not as intact as it was suggested earlier (see later in I.3.2.1.), and face processing has been shown to be atypical in WS (see later in I.3.2.3.). Recently, it has been emphasized that it is no longer acceptable to consider WS as evidence for modularity (e.g. Levy & Herman, 2003; Karmiloff-Smith et al., 2003; Lukács, 2005; Brock, 2007).

I.3.2.1.Language in WS

At the first glance, expressive language in WS tends to be grammatically correct, complex and fluent, however cliché's and stereotyped phrases are very common. WS individuals tend to be very chatty, and the social use of language is particularly well developed.

However, language development in WS is not only delayed, but also follows an atypical developmental pathway (Klein & Mervis, 1999). WS subjects typically perform well in assessments of semantic fluency (Jarrold et al., 2000), and have a rich, well-developed vocabulary (Udwin & Yule, 1990; Bellugi et al., 1994), but they show difficulties and/or delays in irregular past tense and plurals (Pléh et al., 2003; Thomas et al., 2001). Johnson & Carey (1998) showed that global semantic

organization remains at the level of young children and never reaches a mature state. Similarly, Vicari et al. (2002) reported lexical-semantic difficulties in a sentence repetition task. Recent studies showed that language abilities in WS are more injured than it was originally claimed, atypical morphology, syntax as well as pragmatics was reported in this population recently (for review see Mervis & Becerra, 2007; Martens et al., 2008), although there is little doubt that language functions are superiors compared to most of the functions in the nonverbal domain.

Spatial language is especially interesting in WS language production, since this syndrome is characterized by a strong visuo-spatial deficit (see later). In a test of spatial preposition, Bellugi et al. (2000) found that the Williams syndrome group made significantly more errors than typically developing controls. WS subjects showed difficulty in a path description task in a study by Landau et al. (2006), however the authors concluded that errors, such as omitting path words, emerged due to problems with spatial memory. Similarly, Lukács et al. (2007) found that WS individuals have more errors than typically developing control subjects in spatial comprehension and completion tasks, but the pattern of errors were similar in the two groups implying that there is no selective deficit of spatial terms within WS language. The performance of WS children on the Test of Relational Concepts (TRC) was compared with TRC raw score matched typically developing controls, and relational vocabularies of WS showed no significant difference (Mervis & Morris, 2007). This led to the conclusion that children with WS have difficulty with relational language and concepts in general, rather than specifically with spatial terms.

I.3.2.2.Visuo-spatial skills in WS

The disturbance of visuo-spatial skills is one of the most prominent features of cognitive characteristics in WS. Several studies reported poor performance in drawing and copying figures, copying the Rey figure, on block design subtests of the WISC and WAIS (Wechsler Intelligence Scale for Children, Wechsler Adult Intelligence Scale), and other visuo-sptaial tasks (e.g., Bellugi et al., 1988; Mervis et al., 1999; Vicari et al., 1996). Other visual abilities, such as orientation matching and discrimination (Bellugi et al., 1988; Wang et al. 1995; Palomares et al., 2009), perceptual grouping (Farran, 2005), mental imagery and rotation (Farran et al., 2001) were also reported to be impaired in WS. Visuo-perceptual performance seems to be superior to visuo-spatial performance. It seems that basic mechanisms of object recognition are spared in WS: object recognition has been shown to be better than in Down syndrome (Wang et al., 1995), and at a similar level to typically developing controls matched on overall mental age (Landau et al., 2006). Similarly, spared or intact biological motion perception was also reported in WS (Jordan et al., 2002; Reiss et al., 2005)

Spatial abilities represent a peculiar area in WS research, and there has been considerable debate regarding the origin and nature of the spatial deficits. Bellugi and colleagues (2000) have proposed that spatial deficits in WS are associated with impaired global visuo-spatial processing, and with difficulties with the integration of local elements into a global form. This suggestion was based on the poor performance shown in free drawings, copying of hierarchical figures and in the block design task (Bihrle et al., 1989; Rossen et al., 1996). However, later studies found no evidence for a local bias in perception of hierarchical figures (Farran et al., 2003),

moreover WS subjects demonstrated normal facilitation of block design performance when the target design was segmented (Farran et al., 2001; Mervis et al., 1999). Farran and Jarrold (2003) suggested that individuals with WS can perceive information at local and global levels as well, but they have difficulty using this information in visuo-spatial construction at the global level. Consequently, their poor performance might be related to inability to use mental imagery rather than a feature processing bias. However, Farran reported atypical holistic processing in WS a few years later, based on their findings of a further study investigating perceptual grouping (Farran, 2005). Another suggested explanation for the local/global processing deficits in WS was offered by Pani and colleagues (1999), who argued that this deficit is a result of a general weakness in planning and organizing information in working memory. The assumption was based on their findings that WS individuals disengaged from global processing in visual search task if the task required local processing for success.

To explain the dissociation between visuo-perceptual and visuo-spatial performances in WS, Atkinson and colleagues (1997) proposed that WS individuals have impaired visual information processing in the dorsal visual pathway, while the ventral pathway is relatively intact. This view is supported by evidence of weak box posting and motion coherence task performance (considered as tests of dorsal stream function), and relatively better performance in box slot orienting and form coherence task (involving the ventral stream) (Atkinson et al., 1997; Atkinson & Bradick 2011).

However, although visual-perceptual performance is probably superior to visuo-spatial performance, it is unlikely that ventral stream functions are intact in WS. Ventral visual areas are considered important for complex visual object recognition (see e.g., Ungerleider & Mishkin, 1982). such as faces (Kanwisher et al.,

1997). As it can be seen in next subchapter, face perception in WS was atypical and weak in terms of configural analysis by several studies.

I.3.2.3.Face processing in WS

Similarly to language abilities, early research exploring face processing suggested good performance and face processing was claimed to be 'intact' or 'spared' (e.g., Bellugi et al., 1999b). Several studies reported performance in the normal range on tests such as the Benton Test of Facial Recognition (see e.g., Bellugi et al., 1992; Wang et al., 1995), furthermore, WS subjects had good performance in identifying emotional expressions as well (e.g. Karmiloff-Smith et al., 1995). However, just like in the case of language, more recent studies have shown a general delay in face perception (e.g., Deruelle et al., 1999), and atypical processing of faces as well. For example, Karmiloff-Smith (1997) reported that WS subjects showed better performance in recognizing faces distinguishable based on a single feature, than in recognizing those that requiring configural analysis, while typically developing subjects showed no such performance dissociation. Using configurally and featurally modified schematic faces Deruelle et al. (1999) found further evidence for the previous findings by Karmiloff-Smith, and showed that WS subjects are biased to process featural over configural information in face perception.

However, even if face processing is a relative strength in WS, a growing body of evidence shows that the underlying processes differ from typical patterns of processing. Mills et al. (2000) found abnormal early ERP components for faces in WS, which were not found in any group of typically developing, brain-injured or other populations with learning disability. Furthermore, the lack of the face inversion effect, which is present in healthy, typically developing adults when processing inverted faces, was shown in magnetoencephalography (MEG) and ERP studies by

Nakamura and colleagues (2006, 2012). Mobbs and colleagues (2004) in an fMRI study also found an atypical manner of face perception, where large activation increase was observed in the right fusiform gyrus and several frontal and temporal regions, while primary and secondary visual cortices showed less activation during face perception compared to controls. The increased anterior activation was considered as a compensatory mechanism for early visual-perceptual deficits.

I.3.2.4.Memory in WS

Similarly to other developmental disorders, WS is characterized by memory deficiencies and learning difficulties. Studies of working memory in WS found dissociation between verbal and visuo-spatial working memory subsytems. It has been demonstrated that WS individuals have a much lower span on the Corsi block test (spatial memory task) than on the digit span task (auditory-verbal memory) (e.g. Jarrold et al., 1998; Wang & Bellugi, 1994; Racsmány et al., 2002). These findings led to the conclusion that the capacity of verbal working memory is comparable to that of the mental age-matched control group, while the capacity of visuo-spatial working memory is seriously impaired (Udwin & Yule, 1991; Vicari et al., 1996; Wang & Bellugi, 1994).

Not surprisingly, the dissociation between the visuo-spatial and visuo-perceptual domain seems to be present in WS memory performance as well. Vicari and colleagues (2003, 2005) found that visual-object memory is intact, while spatial memory is significantly weaker than in controls.

There are mixed results regarding the explicit memory in WS. Vicari found (2001) that explicit memory in both visual and verbal tasks is similar in WS and typically developing mental-age matched controls, while Jarrold et al. (2007) showed poor performance on tests of long-term memory for visual information in the Doors and People test, and Brock et al. (2006) reported poor long-term verbal memory. Vicari and colleagues (1996) described poor episodic retrieval of both verbal and visuo-perceptual stimuli in a group of WS children.

Based on the performance of WS subjects in the Tower of London, Serial Reaction Time and two other implicit learning tasks, Vicari et al. (2001) concluded, that a specific deficit of procedural learning exists in WS. Similarly, Mandolesi and

colleagues (2009) reported a deficit in acquisition of procedural competence in a maze learning study. Procedural learning, both in the motor and perceptual domains, has been investigated by our research group lately. WS subjects practiced a finger-tapping task consisting of a four-element sequence for five consecutive days, and presented reduced initial performance rate along with decreased learning rate (Berencsi & Kovacs, 2009). Correspondingly, perceptual learning in the contour integration task showed high inter-individual variability but overall weak baseline performance and reduced learning capacity in the WS group (Gervan et al., 2012).

I.3.3.Neurological and neuroanatomical profile of WS

Post-mortem and magnetic resonance imaging studies of neuroanatomy showed reduced overall brain size and altered brain shape in WS with structural abnormalities including abnormally increased gyrification and folding abnormalities (e.g., Bellugi et al., 1999c; Galaburda & Bellugi, 2000; Galaburda et al., 1994; Reiss et al., 2000; Van Essen et al., 2006). The volumetric reduction is more prominent in the posterior compared to the frontal regions (Reiss et al., 2000), and suggested to be largely driven by white matter deficiency.

Relatively large loss of gray matter volume in parieto-occipital areas along with relative good preservation of other cortical areas was reported by several studies (e.g. Thompson et al., 2005; Reiss et al., 2004; Chiang et al., 2007). Studies revealed a well-differentiated area V1 in WS; however, the volume of this area is smaller compared to controls (Galaburda et al., 2002, Thompson et al., 2005, Chiang et al., 2007). Besides the volumetric abnormalities, increased cell packing and neuronal size differences were described in this V1 region (Galaburda & Bellugi, 2000; Galaburda et al., 2002). Taking together the findings above, an atypical V1 functioning is implied in WS.

Decreased intra- and occipitoparietal sulcus (Meyer-Lindenberg et al., 2006), and smaller superior parietal lobule gray matter volume (Eckert et al., 2005) were reported. Moreover, in a diffusion tensor imaging study by Hoeft et al. (2007) higher fractional anisotropy in the right superior longitudinal fasciculus of WS subjects was shown. This is in line with the findings on impaired visuo-spatial functioning in WS, since these regions are part of the dorsal visual stream reported to function inadequately in WS (e.g.; Atkinson et al., 1997).

Thompson and colleagues (2005) reported increased cortical gray matter thickness in the superior temporal gyrus and inferior temporal regions in WS subjects, in line with the earlier findings on relative preservation of frontal cortex, superior temporal gyrus and the cerebellum (Reiss et al., 2000). Holinger and colleagues (2005) found well-preserved primary auditory cortex in WS subjects. These findings have been linked with relatively good language abilities, auditory processing, and with strengths in music.

The results with respect to emotion and face processing (such as amygdala, orbital prefrontal cortex and anterior cingulated) are slightly controversial, Reiss et al. (2004) found significant reduction in these areas, while Chiang and colleagues (2007) reported them well preserved. In a functional MRI study by Meyer-Lindenberg and collagues (2005), WS subjects showed hypoactivation in the amygdala in response to threatening socially relevant pictures, and increased activation to socially irrelevant stimuli. Hypoactivation might be the basis of social disinhibition and extreme friendliness observed in Williams syndrome (Meyer-Lindenberg et al., 2005). Furhermore, Avery and colleagues found white matter integrity deficits in prefrontal-amygdala pathways in WS, and it was proposed that

this deficit might underlie the increased amygdala activity and extreme non-social fears in WS (Avery et al., 2012).

It is important to emphasize that these above-mentioned links between neuroanatomy and complex cognitive functions are very promising, but have remained speculative.

I.3.4.Genetic characteristics in WS

The genetic impairment was studied in detail throughout the 1990's, and initially the size of the deletion was estimated to be around 20 genes, spanning a 1.5 megabase chromosomal segment on chromosome 7q11.23 (e.g. Ewart et al., 1993a,b). However, more recent studies showed that the number of suspected deleted genes is around 28 (Meyer-Lindenberg et al., 2006; Eckert et al., 2006).

As it was mentioned earlier, elastin gene deletion was reported in 98% of individuals diagnosed with WS (Lowery et al., 1995), based on that, the clinical diagnosis of WS is established by a probe for elastin (FISH, see above). Nickerson and colleagues (1995) reported four non-ELN–deleted WS patients, who showed nor the typical facial appearance neither cardiac diseases, and led to the conclusion that elastin gene can account for a number of the distinct features of WS, including cardiac abnormalities, facial characteristics, and premature skin ageing. Importantly, three out of four subjects had mental retardation, so seemingly the presence of ELN had no connection with mental abilities. Consequently, Frangiskakis et al. (1996) emphasized that ELN can not be found in the brain, consequently it could not contribute to typical cognitive characteristics in WS.

It has been suggested, that by studying individual genetic profiles and deletion patterns, an opportunity emerges to determine the relevance of particular

genes and establish genotype-phenotype correlations (e.g., Bellugi et al., 1999). However, although the effort and advances have been made over the past decades in linking genotype to phenotype in WS, the contribution of the deletion size, and types of genes from chromosome 7 have remained still vague.

The first gene, which was suggested to have potential contribution to the distinct WS cognitive characteristic, was the gene LIM domain kinase 1 (LIMK1) (Frangiskakis et al., 1996). It was suggested that the spatial construction deficit in WS may be related to the deletion of this gene, and the quantitative reduction in *LIMK1* protein. Frangkrais and collagues (1996) based their hypothesis on previous findings that LIMK1 encodes the protein tyrosine kinase and is expressed in the developing brain showing involvement in intracellular signaling. However, further analysis of other patients who lack this gene, but did not have spatial problems indicated that LIMK1 is either unrelated or not sufficient to explain the cognitive defects in Williams syndrome (Tassebehji et al., 1999).

Stx1A is also thought to be a relevant gene in terms of cognitive features in WS. This gene encodes Syntaxin-1A, a protein that plays a crucial role in synaptic exocytosis of neurotransmitters (Nakayama et al., 1998). Growing evidence supports the role of Stx1A in deficits of learning and memory in WS (Botta et al., 1999a; Gao et al., 2010). However, Tassabehji (2003) noted that although deletion of syntaxin 1A (STX1A) may be important within the deleted region of chromosome 7, it is unlikely to be responsible for the typical cognitive characteristic in this disorder.

Cyln2 is another possible candidate gene contributing to structural–functional abnormalities and impaired plasticity in WS (Hoogenraad et al., 2002). Cyln2 encodes proteins that regulate dynamic aspects of the cytoskeleton of the cells.

Altered regulation might lead to defects during brain development and/or deficits in synaptic plasticity in adulthood (Meyer-Lindenberg et al., 2006).

Hirota and colleagues (2003) examined three WS subjects with atypical deletion patterns, i.e. no deletion of GTF2IRD1 and GTF2I on chromosome 7q11.23, along with other WS subjects with typical deletion. They found that typical WS facial features were absent in case of the three „atypical" subjects and their visual spatial performance in cognitive tests were above that of full deletion WS subjects. In a recent study by Monique and colleagues (2010), the before-mentioned findings were strengthened, and based on a mouse model, they indicated that the hemizygous deletion of the GTF2IRD1 and GTF2I contributes to the neurocognitive and craniofacial aspects of WS.

In conclusion, a number of different deletions combine to create the distinctive profile in WS (Tassabehji et al., 1999; Tassabehji, 2003), but the only unequivocal link so far is between the ELN gene and supravalvular aortic stenosis (e.g., Tassabehji et al., 1999). Most probable, multiple genes may contribute to the cognitive defects, and the exact impact of genetic deletions remains blurred in relation to the WS phenotype (Tassabehji, 2003, Hoogenraad et al., 2002)

With regard to the genetic determination of the cognitive symptoms in WS, it is important to recognize that there is variability in the amount and type of genetic impairment. Studies reported atypical, partial deletions (e.g., Botta et al., 1999b; Ashkenas, 1996) providing a potential explanation for the inhomogeneous behavioral performance in the WS population.

I.3.5.Sleep in WS

Although subjective reports of WS individuals and the parents imply high incidence of sleep difficulties in WS, sleep disorders have been investigated in depth only recently. In a pioneering study by Arens and colleagues (1998), WS parents were questioned in a telephone survey about their children's sleep habits. Data showed no evidence for breathing arousal disorder, but movement arousal disorder was present in 57% of the cases (Arens et al., 1998). Further polysomnographic studies proved difficulties in initiating sleep, fragmented sleep with long wake periods, decreases in sleep time and sleep efficiency (Arens et al., 1998; Mason et al., 2009; Gombos et al., 2011). Arens at el. (1998) found periodic leg movements during sleep (PLMS), but the diagnosis of PLMS was not confirmed by further studies (Goldman et al., 2009; Gombos et al., 2011), however, an increased number of non-periodic leg movements was reported by Gombos et al. (2011) as well. WS subjects also were reported to spend less time in NREM 1 and 2 stages, and more time in stages NREM 3 and 4 than TD participants (Arens et al., 1998). WS participants presented a significantly higher amount of NREM and a decreased amount of REM sleep percentage (Gombos et al., 2011). Sleep disturbance seemed to persist after childhood, wrist actigraphic and and polysomnographic studies reported disturbed sleep in the population of adolescents and young adults with WS as well (Goldman et al., 2009; Gombos et al., 2011).

Gombos and colleagues (2011) also showed increased frontal slow wave activity in NREM sleep, as well as decreased alpha and sigma activity in both NREM and REM sleep of WS subjects. In a spectral profile analyzis of WS polysomnographic data (Bódizs et al., 2012), higher frequency of NREM sleep sigma

activity and higher spectral peak frequencies in the 8-16 Hz range were shown to be a characteristic feature of WS, suggesting an alteration of sleep-dependent thalamocortical activity in this population (Bódizs et al., 2012).

To sum up, disordered sleep was found in the WS population, which has been reflected in alterations and fragmentations in the macro-pattern of sleep, and an atypical micro-pattern and spectral characteristics as well.

II. The aims and synopses of the theses

The main motivation behind this work was to examine the factors underlying impaired plasticity and learning abilities in a genetically determined neurodevelopmental disorder, Williams syndrome. The typical cognitive characteristics of WS consist of poor visuo-spatial abilities as compared to relatively preserved verbal functions. This syndrome is likely to result in specific parieto-occipital cortical reduction and abnormalities, along with a high risk of sleep disorders.

The phenomenon of perceptual learning provides an especially appropriate behavioral research framework to investigate impaired learning abilities. The extensively examined and explored mechanisms and neuronal background offer the possibility of controlled and specified interrogation with respect to determinants affecting learning and plasticity. Furthermore, perceptual learning requires low cognitive load from observers, which is a potential confounding factor in investigations of neurodevelopmental disorders with mental retardation. Applying the contour integration task in visual perceptual learning studies seemed to be a fortunate choice, since the well-defined nature of stimulus processing in CI guarantees that it is a good tool for examining long-range neural interactions in the primary visual cortex. Moreover, it investigates visual functions at a larger scale than usual discrimination tasks (such as orientation or texture discrimination tasks) frequently applied in perceptual learning studies.

Before investigating baseline and perceptual learning capacity in the CI task in Williams Syndrome, we investigated those factors first that determine

performance in the typically developing population. How do age and the functional maturation of V1 influence the baseline in contour integration? Moreover, does age affect learning capacity in contour integration? To answer these questions, we collected data to characterize the typical developmental trend of contour integration and perceptual learning. In addition to that, - considering the findings about the role of sleep in earlier perceptual learning studies - another important question arises: how does sleep contribute to learning in CI? The second goal was to determine the role of sleep in perceptual learning in CI.

After the exploration of the factors determining performance in a large typically developing population, investigation of perceptual learning in the contour integration task might be considered as a standardized and controlled method for detecting factors influencing baseline performance and learning capacity in an atypically developing population. Our previous findings in the typically developing population allowed us to make assumptions with respect to the causes of impaired function.

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

***[1]**

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

[1] The topic of typical developmental trend of contour integration and perceptual learning is discussed in Study I. and in Stuy III as well.

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 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 is WS (learning in CI is sleep dependent, see Thesis II.).

III. Studies

Study I.

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.

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Vision First? The Development of Primary Visual Cortical Networks Is More Rapid Than the Development of Primary Motor Networks in Humans

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Abstract

The development of cortical functions and the capacity of the mature brain to learn are largely determined by the establishment and maintenance of neocortical networks. Here we address the human development of long-range connectivity in primary visual and motor cortices, using well-established behavioral measures - a Contour Integration test and a Finger-tapping task - that have been shown to be related to these specific primary areas, and the long-range neural connectivity within those. Possible confounding factors, such as different task requirements (complexity, cognitive load) are eliminated by using these tasks in a learning paradigm. We find that there is a temporal lag between the developmental timing of primary sensory vs. motor areas with an advantage of visual development; we also confirm that human development is very slow in both cases, and that there is a retained capacity for practice induced plastic changes in adults. This pattern of results seems to point to human-specific development of the "canonical circuits" of primary sensory and motor cortices, probably reflecting the ecological requirements of human life.

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Introduction

The development of cortical functions and the capacity of the mature brain to learn are largely determined by the establishment and maintenance of neocortical networks. The specification of long-range connectivity within larger inter-areal and more local intra-areal networks is a basic architectural requirement of cortical processing. Long-range lateral intralaminar connections between pyramidal cells (Figure 1A) seem to be a ubiquitous feature of the superficial cortical layers in, e.g., cats [1–3]; tree shrews [4]; and monkeys [4–5]. It has been suggested that these long axonal projections shape the neocortex into "canonical circuits" serving spatiotemporal integration within the functional maps [6–7]. The specificity of long-range connections has been extensively studied in primary sensory and motor cortices of different mammalian species. With respect to the primary visual cortex (V1 or Brodmann area 17, see Figure 1A), it has been shown that clusters of layer II/III long-range horizontal connections connect neuronal columns with similar orientation specificity in cats and monkeys [8–9], assumedly mediating object-related processing and visual perceptual learning in humans as well [10–11].

With respect to the primary motor cortex (M1; Brodmann area 4, see Figure 1A), pyramidal cells with same or similar output properties are accumulated in columns, forming elementary movement representations [12–14]. Collaterals of the pyramidal cells in layer II/III project horizontally as far as 3 mm long and terminate in columns with similar output to that of the original column [5]. These intrinsic connections are thought to be important in the selection and coordination of different movement representations [13,15], in the control of different muscles around a given joint [16–17], or neighboring joints of the same extremity [18]. It has been proposed that the intrinsic long-range connections also mediate motor map plasticity and the learning of new motor skills in rats [19–21], cats [22] and primates [23].

Rough clusters of horizontal connections in V1 are present in cats and ferrets before eye opening, become refined soon thereafter [24–25], and the adult pattern of connections is there at birth in primates [26]. With respect to movement representation in M1, it seems to develop after the somatosensory representations and corticospinal terminations develop mature topography in cats [22], however, information is lacking with respect to the postnatal development of horizontal connectivity.

Is it a possible scenario that these "canonical circuits," mediating basic perceptual and motor function and learning, develop similarly in different mammals, including humans? Or, alternatively, based on the obviously increased demand for human learning capacity, shall we assume that this type of long-range cortical connectivity has a human-specific developmental trend? The development of horizontal connections in layer II/III of the primary visual cortex of humans has been indicated to extend into childhood [27], corresponding to behavioral findings on the late maturation of V1-related contour integration abilities, improving until the teenage years [28–29]. Although little is known about the characteristics of the M1 motor representation in infants and

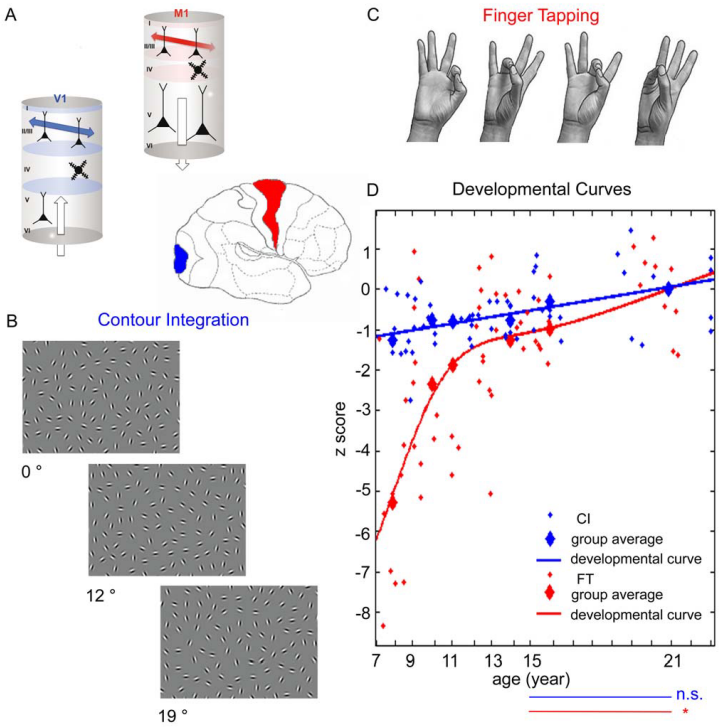

Figure 1. Summary of the methods and results. (A) Sideview of the human brain with the primary visual cortex (V1, Br 17) in blue, and the primary motor cortex (M1 or Br 4) in red. The cerebral cortex is generally divided into six functionally distinct layers, and the principal source of long-range lateral intralaminar connections is layer II and III, as shown in the insets corresponding to V1 and M1. (B) Contour Integration (CI) stimuli, addressing long-range connections in the primary visual cortex. The collinear chain of oriented elements forming a horizontally placed egg-shape is hidden in the background of randomly positioned and oriented elements. The panels show three levels of difficulty in the CI task. Practice and development leads to improved performance. (C) Movement-sequence in the Finger-tapping (FT) task addressing long-range connectivity of the primary motor cortex. Accuracy and speed of carrying out this sequence improves following practice and during the course of development. (D) Developmental curves in CI (blue) and in FT (red). Day 2 performance of each age-group was normalized to that of the adult performance in each task. Small symbols: individual data; large symbols: age-group average. Curve fitting was done on the age-group average values. The horizontal lines at the bottom connect two age-groups (15 and 21 y), and significance levels of the difference in performance in the two tasks, respectively, are denoted.
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young children, there are studies investigating the postnatal development of motor responses induced by transcranial magnetic stimulation (TMS). Motor-evoked potentials produced by TMS occur only at maximal currents in 2-year-old humans, and stimulation thresholds decrease until the age of 15 [30–31]. These suggest a protracted development of both sensory and motor long-range intra-areal connectivity, with the possibility of M1 'wiring' taking a longer time than V1 'wiring.' However, to tackle the functional development of long-range lateral intralaminar connections in humans is an intricate issue, considering the necessity to apply non-invasive measurements, and the fact that even the finest brain imaging techniques are orders of magnitude below the spatial resolution needed for such estimations.

Here we address the human development of long-range connectivity in primary visual and motor cortices, using well-established behavioral measures that have been shown to be related to these specific primary areas, and the long-range neural connectivity within those. The visual paradigm is a Contour Integration task (CI, see Figure 1B), and the motor paradigm is a sequential finger-tapping task (FT, see Figure 1C). CI has originally been developed to test the spatial integration properties of neurons with conjoint orientation preference in the primary visual cortex [32–33]. The presence of global, shape-dependent contextual processes at this early cortical level has been demonstrated [32,34–36], indicating that long-range connectivity might contribute to object related processing, and that even primary visual processing is well beyond local feature analysis. Neural correlates, involving the correspondence between neuronal and behavioral responses in monkeys [35], direct architectural data in monkeys [9], optical imaging of contextual interactions in monkeys [37], human neuropsychology [38] and human fMRI [39–40] indicate the relevance of low-level visual areas integrating

the contour-in-noise stimulus. Based on these studies, the possible candidate for assembling local orientation information in CI is the plexus of long-range horizontal connections in V1. The well-defined nature of stimulus processing in CI guarantees that it is a good tool to probe the development of long-range neural interactions in V1. FT is a motor coordination paradigm, where participants touch the thumb with the other fingers in a given order as quickly and precisely as possible. Combined with imaging and electrophysiological techniques, it has been an important tool to study motor learning in the last two decades. Training in FT leads to experience specific changes in M1, revealed by fMRI [41–42], TMS [43] and electrophysiology [44] in humans. M1 subregions contain multiple overlapping motor representations that are functionally connected through an extensive horizontal network [16–17,45–46]. Suggested mechanisms for functional reorganization involve activity-driven synaptic strength changes in these networks [45,47]. It is important to mention that FT performance is affected by conduction velocity of the corticospinal tract due to myelination (see the Results section). To eliminate the effect of age-related corticospinal tract conduction velocity changes, we measured maximum finger tapping speed and subtracted it from the FT data. This procedure ensured that the corrected results reflect cortical plasticity.

In addition to finding the suitable behavioral paradigms to establish maturational trajectories, comparison between the two domains requires particular consideration. Even in well-established behavioral tasks (such as CI and FT) clearly addressing long-range connectivity within primary visual and motor areas, performance might depend on a number of factors that are irrelevant in terms of the comparison of developmental rates across the two modalities. It would be precarious to directly contrast performance of different age-groups in CI and FT as there might be differences in terms of task difficulty and a potentially different impact of both subcortical mechanisms and higher level cognitive processes across modalities and across different age-groups. In order to deal with latent confounding factors we relied on a training-based design in both tasks. All observers practiced over the course of five days, allowing us to establish learning curves for each studied age-group. It has been indicated that both in CI [48] and in FT [42,49,50], there is an initial fast phase of learning that might be less specific in terms of its transfer properties, and involve higher level cognitive processes. Our rationale is to find the beginning of the second, more specific phase of learning where the initial familiarization with the task is finished, and learning mostly relies on activity and plasticity in the primary cortices. Comparison of performance levels (normalized to that of the adult performance) at the beginning of this second phase of learning in CI and FT should provide us with comparable maturational trajectories of long-range connectivity within primary visual and motor areas.

We find that there is a temporal lag between the developmental timing of primary sensory vs. motor areas; we confirm that human development is very slow in both cases, and that there is a retained capacity for practice induced plastic changes in adults.

Materials and Methods

Participants

Subjects were recruited from kindergartens, primary schools and universities in Budapest, Hungary. Relevant features of the subject pools in CI and FT are summarized in Table 1. Those with a history of neurological or psychiatric illness were excluded. All observers in the CI task had normal or corrected to normal vision, and those who had skeletal disorders or were professional musicians were excluded from the FT task. Written informed consent was obtained from adult subjects and the parents of participating children. Subjects were not paid for their participation. During the course of the experiment, participants were asked to report the amount of their night sleep. Those with less than 6 hours of sleep on a particular night, or those with sleep-wake cycle disruptions were also excluded from the study.

Table 1. Age groups of participants in the CI and FT tasks.

Age-group	CI task			FT task			
	Age (mo)	M	F	Age (mo)	M	F	R/L handed
7 years	89,4	5	5	84,9	6	4	9/1
9 years	103,6	4	6	100,8	4	5	7/2
11 years	132,5	5	5	132,6	5	5	9/1
13 years	153,6	6	4	150,5	5	5	9/1
15 years	176,1	5	5	173,2	4	5	7/2
21 years	249,6	5	5	246,5	5	5	9/1
		30	**30**		**29**	**29**	**50/8**

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Ethics statement

This study was approved by the Social Sciences Ethical review Board of the Budapest University of Technology and Economics. Written informed consent was obtained from adult subjects and the parents of participating children.

Contour Integration Task

Stimuli. The contour integration paradigm was originally introduced and presented in greater detail by Kovacs & Julesz [32]. In this altered version of the task (see also [51]) images were composed of collinear chains of Gabor elements forming a horizontally positioned egg shape (target) on a background of randomly positioned and oriented Gabor patches (noise). The carrier spatial frequency of the Gabor patches was 5 c/deg and their contrast was 95%. The spacing between the contour elements was kept constant (8λ; where λ is the wavelength of the Gabor stimulus) as was the average spacing between the background elements. The signal-to-noise ratio as defined by a D parameter (D = average background spacing/contour spacing) of each image was 0.9. By keeping D at a constant level, the orientation jitter of the contour elements was varied between 0° to 24° across six difficulty levels (0°, 8°, 12°,16°, 20°, 24°, see examples in Figure 1B). A set of 40 images was presented at each of the six difficulty levels, a new shape and background were generated for each stimulus, but all of the contours had the same general size and egg-like shape.

Procedure. Each participant was trained in the contour integration task over five days, with an approximately twenty-four hour shift between the practice sessions. The images were presented in blocks of 10 trials, 40 stimuli at each of the six difficulty levels, in an increasing order of orientation jitter. One session lasted about 20–30 minutes. In a two-alternative forced-choice (2AFC) procedure, subjects had to indicate which direction the narrower part of the egg pointed to. Stimulus onset was 2000 milliseconds, with a fixation cross between stimuli (500 ms, or shorter if the subject responded faster). Subjects were tested binocularly, and were seated at about 0.7 m away from a 17 in. HP monitor in a normally lit testing room. Monitor resolution was

set to 1280×1024. Images subtended 19.93° of visual angle vertically and 26.57° of visual angle horizontally from the testing distance. The mean luminance of the monitor was 21.5 cd/m^2.

Psychometric functions for each subject were plotted using mean scores for each of the six levels of jitter, and threshold performance was calculated by fitting a Weibull function on the data points. Threshold was defined by orientation jitter at 75% correct performance.

Finger-tapping Task

In the Finger-tapping task (FT) participants were asked to touch the thumb with the other fingers in a given order as quickly and precisely as possible. They were instructed not to correct errors and continue with the task without pause as smoothly as possible. Participants were asked to close their eyes, thus visual feedback was not allowed. Data acquisition started when participants were able to produce three correct sequences successively, with eyes closed. The beginning and the end of a practice block was signaled by a 'beep' sound from the computer The practice sequence was a four element sequence of 1-3-2-4 (1: index finger; 2: middle finger; 3: ring finger; 4: little finger). Ten blocks of 16 sequences were performed each day, with self-paced rest periods between them. The practice sessions were conducted approximately at the same time of the day through five consecutive days. On the fifth day, transfer of the practice sequence to the dominant hand (Transfer 1), and transfer to a new sequence (4-2-3-1) in both hands were also tested (Transfer 2 and Transfer 3). The three transfer tests were randomly ordered. Transfer tests are very relevant to carry out in FT in order to see whether prolonged or multisession learning involves use-dependent changes in connectivity within the neuronal populations in the primary motor cortex, in which case, lateralized motor representation results that is specific to task parameters with little or no transfer to the non-trained hemisphere or for a novel task involving the same movement elements [41–42,50]. We introduced three transfer tests in order to see whether lateralized, task-specific representations have developed in M1.

A maximum motor speed task was also carried out with a new sample of participants of the same age-groups by a non-serial finger-tapping task (n = 60). In this task subjects had to touch the thumb with the index finger of the non-dominant hand as fast as possible. Blocks of 64 index finger taps were repeated three times with an at least two-minutes rest between them. Maximum motor speed was defined as the number of index finger taps/s.

Data acquisition. Finger-tapping data were obtained in an improved version of the original finger-tapping paradigm. Since subjects in different age-groups might have considerably varying motor abilities, we developed a data acquisition method that enables precise and automated measurement of performance without using external equipments, such as a computer keyboard. A custom-made 'data glove,' consisting of metal rings was placed on the participants' fingertips. Each metal ring electrode corresponded to a given finger and was connected to a laptop computer through a USB-Serial converter. The 'data glove' enabled participants to use their hands freely, and to close their eyes during the task. A task sequence was identified from the first element of the sequence to the next first element. For example, when a sequence of 1-3-2-4 was the task, sequences are identified and separated as follows: 1-3-2-4 – 1-3-2-4 – 1-3-2-2-4 – 1-3 – 1-3-2-4 – 1-3-2-4). Motor performance of groups with different motor abilities can only be compared by taking the speed/accuracy trade-off into account. A combined measure of speed and accuracy parameters might bring a diplomatic balance into this trade-off. Inconsistent performance also alters the length of the FT sequences, so it may vary from trial to trial, e.g., an incorrect sequence can be either two- or eight-element long. It has influence on speed and accuracy measures. Therefore, instead of using sequence based performance measures such as number of sequences in a given time, we introduced performance measures based on finger taps. In order to eliminate the speed-accuracy trade-off in the raw data, a combined index of performance rate (PR) was calculated. It is defined as the product of speed and accuracy, where speed is defined as the number of finger taps in a second (taps/s) and accuracy is defined as the ratio of the number of finger taps in correct sequences and the number of finger taps in all sequences.

When comparing perceptual and motor data, we wanted to eliminate the influence of corticospinal tract myelination level on motor speed at different ages. Corticospinal myelination level shows close correlation with maximum motor speed (see the Results section). Therefore, PR was corrected by maximum motor speed in the following way: first, we calculated FT intertap interval as 1/PR (ms); after that we subtracted the minimum intertap interval gained as 1/maximum motor speed (ms). Thus, we gained a corrected intertap interval index that is corrected both for the speed-accuracy trade-off and for the myelination effect of the corticospinal tract. These corrections led to a more precise measure of motor cortex related changes during motor learning.

Data analysis

Developmental data in CI and FT. We determined perceptual and motor development based on 2nd day performance in the two tasks in order to avoid confounding cognitive effects (see the section on "Finding comparable regions in the learning curves in CI and FT" in the results section). Performance of each age-group was normalized to that of the adult performance level within each task (z score) and two-way ANOVA (learning condition×age) was performed on the records. Multiple comparisons were performed by LSD. We also conducted independent-t tests on the developmental data to compare the average performances of the age-groups.

Practice induced learning in CI and FT. We analyzed the learning rates in four periods (1: from Day 1 to Day 2; 2: from Day 2 to Day 3; 3: from Day 3 to Day 4; 4: from Day 4 to Day 5) in the two learning conditions. Day 1 performance was considered 100%, and performance on subsequent days was expressed relative to that. Three-way mixed ANOVA (learning condition×age×learning period) was performed on the learning data. Multiple comparisons were performed by LSD. Significance level was set at $p<0.05$.

Results

Developmental and practice-induced learning curves are presented in the joint-spaces of Figure 2A and 2B for vision and movement, respectively. The data in Figure 2A represent the assessment of both perceptual learning capacity and developmental trajectories in CI in a sample of 60 subjects (7 to 21 years of age, 5 days of practice; see Methods). Visual CI performance increases both as a function of age (ANOVA $F(5,54) = 5.41$, $p<0.01$) and practice-days (ANOVA $F(4,216) = 156.43$, $p<0.01$). These data confirm that contour integration has a slow developmental course as it has been indicated earlier [28]. It is also confirmed that practice leads to enhanced performance levels even in adults (see also 48, 51). Although the interaction between age and practice was not significant (ANOVA $F(20,216) = 1.53$, $p<0.1$), further analysis revealed a significant main effect of age for days 1 and 2 ($p<0.01$), indicating that there is a faster progression of learning in the younger age-groups at the beginning of practice. However, in the later phases of training, all age-groups learn at the same rate.

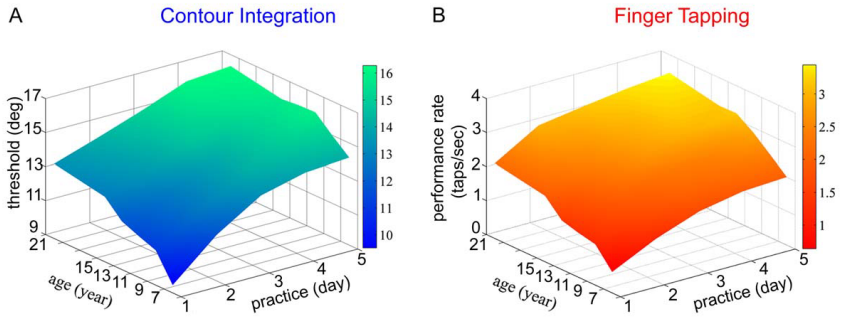

Figure 2. Developmental-learning surfaces. (A) Developmental-learning surface in CI. Performance threshold of each age-group is expressed in degrees of orientation jitter along the contour as a function of age and practice. Performance in CI increases as a function of age, suggesting that contour integration has a slow developmental course. Performance also increases as a function of practice, with a faster progression of learning in the younger age-groups at the beginning of practice. However, in the later phases of training, all age-groups learn at the same rate. (B) Developmental-learning surface in FT. Performance rate (number of taps/second) is expressed as a function of age and practice. Performance in FT increases both as a function of age and practice, similarly to CI.
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Developmental and practice induced improvements of motor performance in the FT task are shown in Figure 2B (n = 58; 7 to 21 years of age, 5 days of practice; see Methods). FT performance rate (as measured in terms of the correct taps per second) increases both as a function of age (ANOVA $F(5,52) = 10.76$, $p<0.01$) and practice (ANOVA $F(4,208) = 248.05$, $p<0.01$). These results are in accordance with previous findings, where a developmental a trajectory was found in FT learning between the ages of 9 and 17 years [52]. While earlier studies indicated that the capacity to improve is preserved in adults [41,42], the extremely slow developmental curve from childhood to adulthood in FT is reported here for the first time. We found a superior learning capacity in the younger age-groups across all 5 days of practice, as it is shown by the significant interaction between age and practice (ANOVA $F(20,208) = 1.81$, $p<0.05$).

This pattern of results indicates that both visual (CI) and motor (FT) performance improves throughout an extended developmental period in humans, and that practice induced improvements of performance are significant in all studied age-groups in both tasks. However, as indicated above, a direct comparison between the two surfaces of Figure 2 will not provide a clear view on the comparative maturational trajectories of visual and motor cortices.

As discussed in the introduction, neural correlates indicate the role of lower level visual areas in integrating the contour-in-noise stimulus a [39,38,40,53,54], in addition to its specific design that addresses the primary visual cortex. The design of the motor task allows less control over the involved cortical areas than the design of the visual task. One of the important factors affecting performance in FT is maximum finger tapping speed (FTS) that is determined by conduction velocity of the corticospinal tract due to myelination [55]. Maximum FTS shows a lifespan trajectory reaching a peak around the age of 40 years ([52,55–56] see Figure 3A). Consequently, it is likely that maximum FTS has an effect on motor performance throughout the age range of the present study in a serial FT task as well. To eliminate the effect of age-related corticospinal tract conduction velocity changes, we measured FTS within the same age range as in the learning task (Figure 3A). Then we subtracted FTS from the developmental learning surface (see Methods), ensuring that such a corrected developmental-learning surface reflects cortical plasticity (Figure 3B). The role of M1 in FT was also tested by the transfer tests (the same task carried out by the non-trained hand (Transfer 1); a novel task carried out by the trained (Transfer 2) and the non-trained (Transfer 3) hand, Figure 3C). Transfer performance did not exceed Day 2 performance in any of the groups ($p<0.05$). The lack of learning-transfer clearly indicates that processing and learning involve use-dependent changes in connectivity within the neuronal populations in the primary motor area.

The comparability of the two tasks is a challenging issue, especially in terms of task complexity and potential cognitive load. In order to reveal differences in these, we employed learning paradigms. It has been suggested in both cases [42,48–50] that the initial faster and less specific phase of learning might be related to task familiarization and higher-level cognitive processes, while in the second, slower and more specific phase, performance and improvements might be more related to primary sensory or motor cortices. In order to discern these two phases and find the second phase that would serve our perceptual and motor comparison better, here we calculate and compare session-by-session learning speed in the two tasks for all age-groups. While Figure 2 presents developmental and practice-induced learning curves in CI and FT in separate graphs, we plot learning speeds (Learning rate) within the same graph in Figure 4. As it is clearly shown in Figure 4, the two tasks are different in terms of the initial speed of learning. There is a much faster improvement from the first to the second session in FT than in CI across all age-groups (7y: $t = -4{,}18$, $df = 17$, $p<0{,}01$; 9y: $t = -4{,}17$, $df = 17$, $p<0{,}01$; 11y: $t = -7{,}2$ $df = 17$, $p<0{,}01$; 13y: $t = -5{,}24$, $df = 17$, $p<0{,}01$; 15y: $t = -4{,}41$, $df = 17$, $p<0{,}01$; 21,5y $t = -6{,}06$, $df = 17$, $p<0{,}01$). However, this large difference seems to diminish and disappear later. Improvement from the second to the third session is the same in FT and in CI, except for some relatively small differences in 9–11 year olds (9y: $t = -2{,}29$, $df = 17$, $p<0{,}05$; 11y: $t = -2{,}78$, $df = 17$, $p<0{,}05$). Learning rates become nearly equivalent in the two tasks across all ages from the third session. Different initial learning speeds can be interpreted as a difference in task complexity and/or cognitive load, while similar speeds in the later phase indicate a higher degree of comparability between task performances. Since learning rates are reasonably similar from the second day on, we propose that second day performance in CI and FT is the most

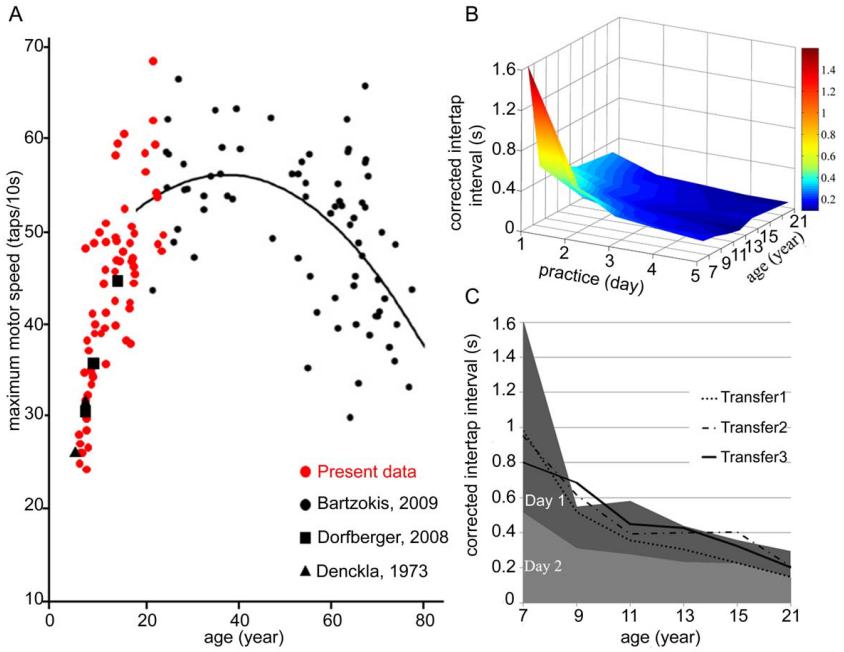

Figure 3. Correction of Finger-tapping data. (A) Variation of maximum finger tapping speed (FTS = finger taps/s) as a function of age. Maximum FTS is affected by corticospinal tract conduction velocity due to myelination [55] and likely has impact on developmental motor performance. (B) Developmental learning surface corrected by maximum FTS. Data are expressed as the interval between finger taps (s) in correct sequences in the serial FT task after subtraction of maximum FTS. Correction with maximum motor speed ensures that the developmental-learning surface reflects cortical plasticity with no effect of corticospinal myelinization on performance. After correction, there is a marked initial improvement at the age of 7 with no significant learning effect after the 3rd day in any age-group ($p<0.05$). (C) Performance in transfer tests compared to Day 1 and Day 2 performance in the learning task. Transfer 1 refers to practice effects with the non-trained hand. Transfer 2 is a new task performed with the trained, and Transfer 3 with the non-trained hand. Transfer performance did not exceed Day2 performance in any of the groups ($p<0.05$). The lack of learning-transfer clearly indicates that processing and learning involve use-dependent changes in connectivity within the neuronal populations in the primary motor area.
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advantageous for the comparison between the maturational trajectories of primary visual and motor areas using behavioral measures. Second day performance seems to satisfy both relevant conditions: (1) the second phase of learning has begun; and (2) we are still assessing maturational trajectories which are not confounded by the capacity to learn at different ages.

Comparing Developmental trajectories of V1 and M1

In order to compare the developmental curves in FT and CI we expressed Day 2 performance of the participants in z score (Figure 1D). Performance of younger age-groups was standardized to that of the adult group. Two-way mixed ANOVA (age×learning condition) showed significant main effect for both age ($F_{1,5} = 14.74$, $p<0.01$) and learning condition ($F_{5,108} = 30.45$, $p<0.01$) with significant age×learning condition interaction ($F_{5,108} = 6.13$, $p<0.05$). We found significant differences between CI and FT performance at age 7 (CI z-score = −1,264, FT z-score = −5,2852, t = −5,150, df = 18, $p<0.01$), at age 9 (CI z-score = −0.767, FT z-score = −2,360, t = −2,3515, df = 18, $p<0.05$) and at age 15 (CI z-score = −0.2998 FT z-score = −0.9728, t = −2.09, df = 17, p = 0.052). In order to see whether there is a difference in the performance of adults and 15-year-old children, we employed an independent t-test. There was no significant difference in CI (t = −0,775, df = 18, p = 0,449), however 15-year-old children performed significantly below the adult level in FT (t = −2,415, df = 17, p = 0,027). These results imply that fine motor functions are not operating at the adult level in terms of speed and accuracy at the age of 15, while contour integration reaches the adult level at this age. Since CI and FT both address long-range connectivity in primary visual and primary motor cortices, respectively, we suggest that the functional development of long-range lateral intralaminar connections in humans is slower in the primary motor cortex than in the primary visual cortex.

Discussion

We employed behavioral paradigms, a Contour Integration test and a Finger-tapping task, to assess the functional maturity of long range horizontal cortico-cortical connections in primary visual and primary motor areas. Several earlier studies revealed that these tasks require long-range integration within the primary cortices. In

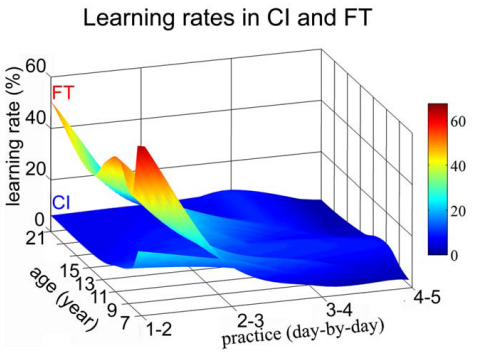

Figure 4. Comparison of learning rates in Contour Integration and Finger-tapping. Day 1 performance is considered 100%, and performance in subsequent days is expressed relative to that. Improvements are calculated by taking the difference between thresholds in consecutive days of practice (such as, Day 1–Day 2, Day 2–Day 3, Day 3–Day 4, Day 4–Day 5). There is a larger improvement from Day 1 to Day 2 in FT than in CI across all age-groups. This difference vanishes from Day 2 to Day 3, and learning rates become nearly equivalent in the two tasks after Day 3.
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addition to applying these well-established methods, we carefully eliminated possible confounding factors, such as different task requirements (complexity, cognitive load) by using these tasks in a learning paradigm. We have shown that initial performance levels might not be appropriate for comparisons since the rate of performance improvement is significantly different from the first to the second practice session (Day 1 to Day 2) across tasks and across age-groups. However, this first, and highly variable phase of learning, probably involving higher level cognitive processes, seems to be over by the second session (Day 2), and performance improvement proceeds at the same rate in both tasks and all age-groups. Therefore, it appeared reasonable to use Day 2 data in deriving and comparing the two developmental curves. In the case of the Finger-tapping task, the impact of myelination and age-related changes in corticospinal tract conduction had to be considered as well. To this end, we registered the maximal speed in a single finger-tapping task (determined mainly by corticospinal tract conduction velocity) in each age-group, and deduced it from the sequential finger-tapping data. The resulting values are believed to reflect cortical network functioning.

Following the above mentioned corrections, our results show that the developmental curves in the perceptual (CI) and in the motor (FT) tasks are not overlapping. Although both curves are demonstrating protracted development, extending well into the teenage years, motor development, as measured by the FT task, is relatively more delayed: fine motor coordination is not reaching adult levels in terms of speed and accuracy by age 15, while perceptual integration is adult like at this age.

Greater capacity to cortical plasticity in M1 may stem from the more distributed organization of M1. While M1 consists of distinct representations of larger body parts (e.g., the hands), within these functional subregions, a widely distributed and overlapping representation system exists, involving horizontal connections [46]. It has been suggested that such an organization is more advantageous to provide greater capacity for storage and to contribute to flexibility [17,46]. Flexibility is crucial in generating a wide repertoire of movements, including ones not performed previously. Maintaining this repertoire requires the ability to have access to a large number of combinations of muscle contractions. Similarly, during the acquisition of new skills this aforementioned distributed type of network in M1 could be reorganized to represent new combinations more rapidly, while a discrete somatotopic representation would limit this capacity [45–46]. The extremely extended temporal window, during which experience can shape the fine functional connections, might be explained by the fact that the size of various body parts and the proportion of body parts are exposed to enormous alterations. Furthermore, daily motor performance in our continuously changing physical environment puts a permanent constraint on the motor system. To adjust to these constraints, the system has to continuously create novel movements. The prolonged time course of the maturation of the primary motor connections might be necessary to maintain a higher capacity of the system to meet these requirements mentioned above.

Our behavioral data, suggesting that the functional maturation of long-range lateral intralaminar connections and the refinement of these neocortical networks in primary motor cortex are slower than that of the primary visual cortex in humans, are in line with histological (e.g. pruning or GABAergic network properties [57–58]), and psychophysiological (e.g. synchronized oscillations [59]) accounts indicating that changes incidental to development occur earlier in the primary visual than in the primary motor region. Studies of developing horizontal connections often emphasize that collateral pruning and selective synapse elimination are important for achieving functional maturity (e.g. [60]). Synapse production continues postnatally, and after an initial overproduction, synaptic density reaches its peak in infancy [61]. Following this peak, there is a prolonged selective elimination of the connections, resulting in a structural and functional alteration in neuronal circuits. Synaptic density decreases to adult values during late childhood and early adolescence, however, synaptic elimination and network refinement occurs in a hierarchical pattern in the human cortex: primary sensory areas develop first, followed by the maturation of the motor and association cortices, while the prefrontal cortex develops last [57]. Synaptic density in V1 decreases to adult levels by 10 years of age [57]. With respect to M1, synaptic density remains elevated until the age of 10 and decreases to adult values in late childhood and early adolescence [62].

The development and maturation of cortical networks strongly depends on neuronal activity, whereby synchronized oscillations play an important role in the stabilization and pruning of connections. There are significant oscillations during childhood and adolescence, e.g. there is a reduction in the amplitude of oscillations that is predominantly pronounced for delta and theta activity [63]. This developmental change occurs more rapidly in posterior than in frontal regions [59], and takes place earlier in the primary visual than in the primary motor area.

In addition to the number of connections, the types of connections are equally important in the functioning of cortical networks. An appropriate balance between excitatory and inhibitory synaptic inputs appears to be necessary. GABAergic interneurons play a pivotal role in establishing neural synchrony in local circuits. It was demonstrated that a single GABAergic neuron might be sufficient to synchronize the firing of a large population of pyramidal neurons [64]. In the human visual cortex, studies on the developmental changes in GABAergic mechanisms in postmortem tissues have shown that the relevant changes start to occur between the ages of 10 and 13 years of age [58]. Although there are no postmortem studies on GABAergic mechanisms in the motor cortex, it has been shown that both N-methyl-

Daspartate receptor activation and GABAergic inhibition play a crucial role in use-dependent plasticity in the human motor cortex [65]. Furthermore, in a TMS study it was confirmed that the GABAergic interneuron system does not function at an adult level even in adolescence in the motor cortex [66].

In conclusion, we confirm that human development is very slow both in the primary visual and motor domains, and we find a retained capacity for practice induced plastic changes in adults. Based on the temporal lag between the developmental timing of primary sensory vs. motor functions, we suggest that the ontogenetic maturational rate of the intracortical horizontal connections in the primary motor cortex is slower than that of the primary visual cortex, providing a wider temporal window for experience-dependent plasticity in the motor system. Our results seem to be in strong correlation with anatomical and physiological data on the developmental order of different cortical areas. This pattern of results also raises the possibility of human-specific development of the "canonical circuits" of primary sensory and motor cortices, perhaps reflecting the ecological requirements of human life.

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Author Contributions

Conceived and designed the experiments: PG AB IK. Performed the experiments: PG AB. Analyzed the data: PG AB. Contributed reagents/materials/analysis tools: IK. Wrote the paper: PG AB IK.

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Study II.

Gervan, P. & Kovacs, I. (2010). Two phases of offline learning in contour integration. *Journal of Vision*, 10(6), 24, 1-7..

Two phases of offline learning in contour integration

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We demonstrate daytime and overnight offline modulations of perceptual learning in a visual integration task. We employed a contour integration task, which requires longer range spatial integration than the more commonly used texture discrimination task, yet, still addresses the earliest cortical processing levels. In order to dissociate the effect of daytime and overnight offline modulations on perceptual learning, we introduced a 12-h shift between the practice times of two groups of subjects. Throughout the five practice sessions, the 12-h shift resulted in stepwise modulation of a typical learning curve, with a phase shift between the two groups. Between sessions (offline) improvement during the day was relatively small and only occurred in the first few sessions, while it was always significant after a night of sleep. Our results extend the body of evidence on the potential role of sleep in perceptual learning and generalize it to integrative visual processes. We have clearly distinguished two phases of learning: both daytime and overnight improvements in the initial phase, and only overnight improvements in the later phase.

Keywords: sleep, learning, perceptual learning, visual integration, contour integration

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Introduction

Repeated exposure to sensory experience results in enhanced performance in perceptual tasks and plastic reorganization even in the adult brain (e.g., Karni & Sagi, 1991; Schwartz, Maquet, & Frith, 2002). With respect to visual perceptual learning, sleep dependence has been studied extensively in a texture discrimination paradigm (Gais, Plihal, Wagner, & Born, 2000; Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000) and, more recently, with respect to orientation discrimination (Matarazzo, Frankó, Maquet, & Vogels, 2008). Visual contour integration involves spatial integration at a longer range than texture or orientation discrimination; however, it still relies on early visual processes such as long-range interactions between orientation-selective neurons in the primary visual cortex (e.g., Giersch, Humphreys, Boucart, & Kovács, 2000; Kovács, 1996; Kovács & Julesz, 1993; for neural correlates, see, e.g., Altmann, Bulthoff, & Kourtzi, 2003; Kourtzi, Tolias, Altmann, Augath, & Logothetis, 2003; with respect to the low-level nature of this task, also see the first paragraph of the Discussion section). Perceptual learning has been demonstrated earlier in contour integration (Kovács, Kozma, Fehér, & Benedek, 1999; Kozma, Kovács, & Fehér, 2002), and it was found to be specific to stimulus features (Kovács et al., 1999). Cue independence of learning indicates that it is related to early visual processing, possibly involving use-dependent changes in connectivity within the orientation-selective neuronal populations in the primary visual area. The well-defined nature of learning in the contour integration task promises that it might become a good model of memory consolidation in more general terms and motivates the question whether—similarly to improvements in texture or orientation discrimination—it is sleep-dependent or not. Our aim here is to clarify the modulatory role of both daytime and nighttime offline learning in contour integration.

In terms of methodology, sleep deprivation is a standard behavioral method to confirm the role of sleep in perceptual learning (Karni et al., 1994; Stickgold, James, & Hobson, 2000). However, it is equivocal whether the deterioration in performance is purely due to the lack of sleep (or certain sleep phases) or to other confounding factors such as fatigue, reduced attention, etc. The daytime nap paradigm has been introduced by Mednick, Nakayama, and Stickgold (2003) to control for many confounds of sleep studies. Another approach is to vary the time distribution of training sessions: for example, one group of subjects practices within the same day, while the practice sessions of the other group are distributed into two or

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more consecutive days (Kozma et al., 2002). The flaw in this design is that it does not allow for the distinction between time- vs. sleep-dependent learning. In order to avoid the above-mentioned confounding factors, we employ a 12-h shift design (see Figure 1b and the Methods section) that was developed earlier to test motor skill learning by Walker, Brakefield, Morgan, Hobson, and Stickgold (2002) and introduced to visual learning by Mednick, Drummond, Boynton, Awh, and Serences (2008) and Matarazzo et al. (2008) more recently. By applying a larger number of sessions, this design is useful not only in terms of investigating the sleep dependency of learning, but it might help isolate purely sleep-dependent performance enhancement from other more mixed stages of perceptual learning, such as an initial phase, where higher level cognitive and attentional factors play a role. In the 12-h shift design, we expect that the typical learning curve (Figure 1a) will be modulated by alternating phases of practice, where only every second practice session is followed by a night (Figure 1b). However, as sleep is not the sole determining factor of learning, we expect that the typically continuous learning curve, shown in Figure 1a, will be modulated by the step functions shown in Figure 1b with a phase shift. Introducing a 12-h shift between the first sessions of the two tested groups allows us to clarify whether daytime and nighttime offline learning modulates performance similarly or not.

Methods

Forty university students (22 males, 18 females; mean age = 20.8 years) participated in this study. All observers

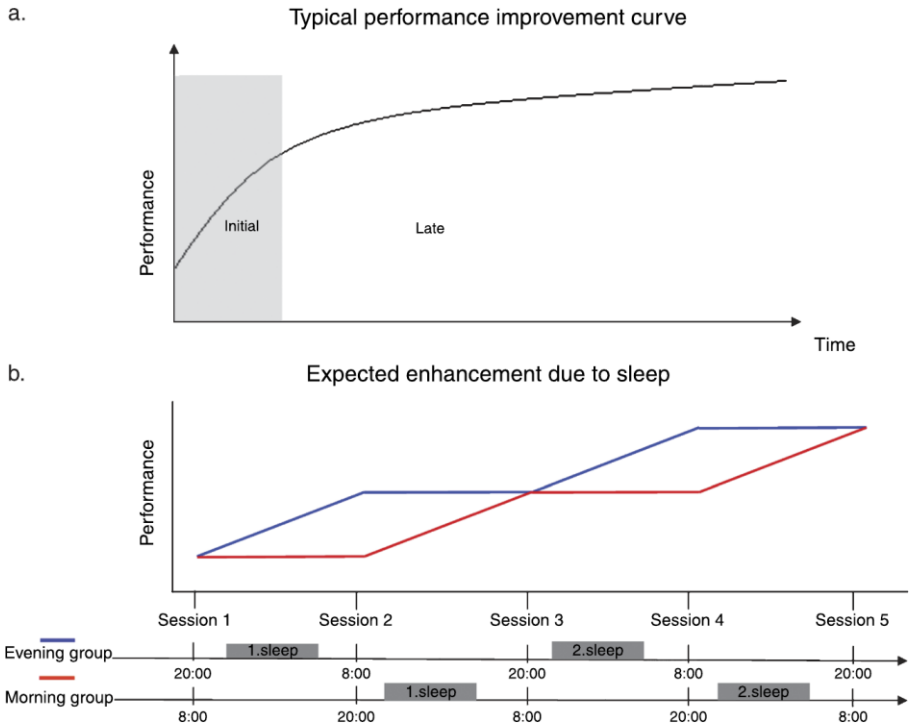

Figure 1. Expected learning curves in the 12-h shift design. (a) The initial phase of learning is usually faster in perceptual learning, resulting in the steeper part of the curve (after Karni & Sagi, 1993). (b) Sessions are shifted by 12 h in the two tested groups (MG: Morning Group, starting at 8:00 AM; EG: Evening Group, starting at 20:00 PM). Both groups are tested every 12 h. By the 2nd and 4th sessions, the EG group has one more night of sleep than the MG group. The blue (EG) and red (MG) curves represent the anticipated performance improvement due to sleep.

had normal or corrected-to-normal vision and had no history of neurological illness or sleep disturbance. Participants were randomly assigned to two groups (Morning Group (MG), n = 20, 11 males, 9 females; mean age = 21.7 years; or Evening Group (EG), n = 20, 11 males, 9 females; mean age = 20.7 years; see later) and were naive to the purpose of the study. In order to rule out the confounding effects of chronic sleep restriction, and possible daytime sleep, we asked our subjects to report the amount of both night- and daytime sleep preceding every training session. Less than 6 h nighttime sleep or a reported daytime nap of any length were excluding factors even if the subject completed a number of training sessions already. During the course of the experiment, we excluded 7 subjects because of less than 6 h sleep, and 2 subjects because they reported a daytime nap. We replaced the excluded subjects with new subjects in order to keep 20 subjects in each experimental group.

Stimuli were composed of closed contours against noisy backgrounds (see, e.g., Kovács & Julesz, 1993; Kozma-Wiebe et al., 2006). The target was a collinear chain of Gabor elements forming a horizontally oriented egg shape with its narrower part pointing either to the right or to the left. The egg-shaped contour was embedded in a background of randomly positioned and oriented Gabor patches. The carrier spatial frequency of the Gabor patches was 5 c/deg and their contrast was 95%. The spacing between the contour elements was kept constant (8λ; where λ is the wavelength of the Gabor stimulus). The signal-to-noise ratio as defined by a D parameter (D = average background spacing/contour spacing) of each image was 0.9. By keeping D at a constant level below 1.0 (D = 0.9), subjects' performance is a function of the adequacy of long-range interactions between orientation-selective neurons in the primary visual cortex (see, e.g., Kovács, 1996). The orientation jitter of the contour elements was varied between 0° and 24° across six difficulty levels (0°, 8°, 12°, 16°, 20°, 24°, see Figure 2). A set of 40 images was presented in 4 blocks of 10 trials at each of the six difficulty levels in each session. One session of 240 trials lasted about 20 min. A new shape and background were generated for each stimulus, but all of the contours had the same general size and egg-like shape.

The blocks of images were presented in a two-alternative forced-choice (2AFC) procedure, in an increasing order of difficulty, starting with the easiest (0° orientation jitter) level, and followed by more and more difficult (8°, 12°, 16°, 20°, 24° orientation jitter) levels. Stimulus duration was 2 s, with a fixation cross between stimuli (0.5 s, or until the subject responded). Subjects had to indicate which side of the screen the narrower part of the egg was pointing to. Subjects were tested binocularly and were seated at about 0.4 m away from a 17-in. HP monitor in a normally lit testing room. Monitor resolution was set to 1280 × 1024. Images subtended 19.93° of visual angle vertically and 26.57° of visual angle horizontally from the testing distance. The mean luminance of the monitor was 21.5 cd/m^2.

Psychometric functions for each subject were plotted using mean scores for each of the six levels of jitter, and threshold performance was calculated by fitting a Weibull function on the data points. Threshold was defined by orientation jitter at 75% correct performance.

We introduced a 12-h shift between the two groups of subjects. Each participant practiced in the contour integration task five times within 2 and a half days. MG subjects

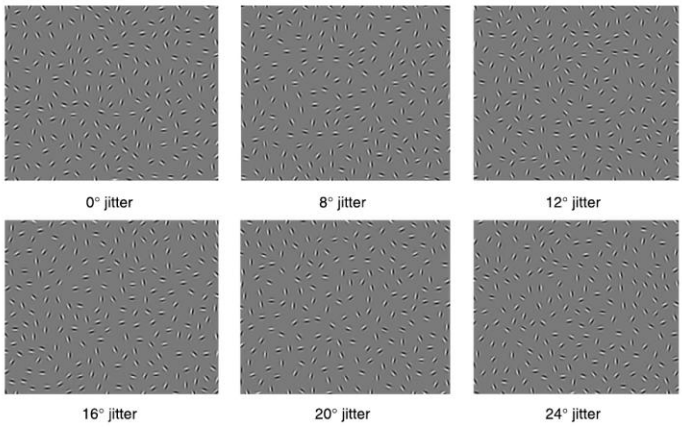

Figure 2. Stimuli. There is a collinear chain of Gabor elements forming a horizontally placed egg shape on a background of randomly positioned and oriented Gabor patches within each panel. The orientation of contour elements was jittered from the original path of the contour allowing for six difficulty levels, as shown in the individual panels.

started the first session at 8:00 AM, while EG subjects started at 20:00 PM on the same day (see Figure 1b). By the second and fourth sessions, the groups had different amounts of night sleep, but other factors (number of trials, time between sessions, etc.) were equivalent.

It is relevant to mention that, compared to earlier studies, here we increase the number of sessions. That might augment the offline effects of sleep in the later sessions where those are not confounded by the initial boost of performance observed both in perceptual and motor learning (Hotermans, Peigneux, Maertens de Noordhout, Moonen, & Maquet, 2006; Karni et al, 1994).

Results

Evening group

Between Session 1 and Session 2, EG showed significant performance enhancement (1.44°; paired t-test: $t = -6.94$, $df = 19$, $p < 0.001$). Statistically significant but smaller improvement (0.6°; paired sample t-test: $t = -2.46$, $df = 19$, $p = 0.023$) was present between Session 2 and Session 3. Between Session 3 and Session 4, the group continued to improve significantly (1.9°; paired sample t-test: $t = -6.82$, $df = 19$, $p < 0.001$). EG performance did not change between Session 4 and Session 5 (paired sample t-test: $t = 1.15$, $df = 19$, $p = 0.263$; see Figure 3).

Morning group

Between Session 1 and Session 2, MG improved significantly (0.7°; paired t-test: $t = -3.52$, $df = 19$, $p = 0.002$). A more substantial enhancement was found between Session 2 and Session 3 (1.3°, paired sample t-test: $t = -8.46$, $df = 19$, $p < 0.001$). MG presented no enhancement between Session 3 and Session 4 (paired t-test: $t = -0.04$, $df = 19$, $p = 0.963$) but improved significantly between Session 4 and Session 5 (1.7°, paired sample t-test: $t = -7.34$, $df = 19$, $p < 0.001$).

Intergroup differences

Initial (Session 1) performance was the same in the two groups (EG = 13.4°, $SD = 0.71$; MG = 13.46°, $SD = 0.96$; independent-groups t-test: $t = -0.237$, $df = 38$, $p = 0.812$). However, in Session 2, EG performed significantly better than MG (EG = 14.84°, $SD = 0.87$; MG = 14.13°, $SD = 1.2$, independent-groups t-test: $t = 2.12$, $df = 38$, $p = 0.04$). Performance was very similar in the two groups in Session 3 again (EG = 15.47°, $SD = 1.7$ and MG = 15.44°, $SD = 1.36$;

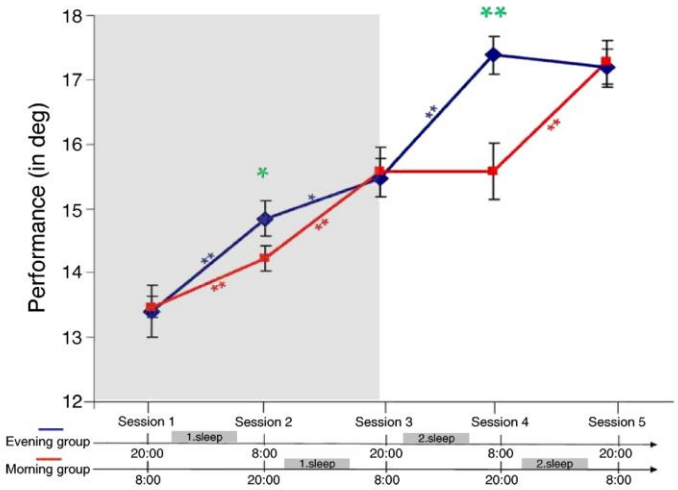

Figure 3. Learning curves in the 12-h shift design (red: MG, blue: EG). Performance of each group in the five practice sessions (horizontal axis) is presented as the maximal orientation jitter at threshold (vertical axis) in the contour integration task. The 12-h shift resulted in a stepwise modulation of the typical learning curve (as predicted in Figure 1a), with a phase shift between the two groups, clearly indicating a strong modulatory effect of nighttime offline learning. Daytime learning is only observed in the first few sessions (shaded box), while overnight learning is more pronounced in the later ones.

independent t-test: $t = -0.168$, $df = 38$, $p = 0.78$). In Session 4, EG performed significantly better (EG = 17.37°, $SD = 1.93$; MG = 15.45°, $SD = 36$; independent t-test, $t = 3.62$, $df = 38$, $p = 0.001$), and the difference between the two groups was more remarkable than in Session 2. Final performance in Session 5 was very similar again (EG = 17.18°, $SD = 1.56$; MG = 17.16°, $SD = 1.33$; independent t-test: $t = 0.038$, df = 38, $p = 0.97$).

Note that significant intergroup difference was present only in Session 2 and Session 4, where the groups had a different amount of sleep. In case of all the other sessions, the groups had the same amount of sleep and there was no significant difference in their performance.

A repeated-measures two-way ANOVA compared the performance of the two groups (MG/EG) in the five sessions. The effect of group was not significant ($F(1, 38) = 2.47$, n.s), in other words, overall performance, and improvement of the two groups, disregarding the 12-h shift, was the same. The effect of session was significant ($F(1, 38) = 98.77$, $p < 0.01$), a consistent session by session improvement was present. Group by session interactions were revealed by a post hoc analysis and were significant in Session 2 ($F(1, 38) = 4.5$, $p < 0.05$) and Session 4 ($F(1, 38) = 13.14$, $p < 0.05$), as the green asterisks also indicate that in Figure 3, based on the results of the paired t-tests.

A three-way repeated-measures ANOVA tested for the effects of group (MG/EG), learning phase (*initial phase*: improvements between Session 1 and 2, and Session 2 and 3; *late phase*: improvements between Session 3 and 4, and Session 4 and 5; the initial phase is indicated by the shaded box in Figure 3), and the effect of sleep (sleep vs. no sleep improvements). The effect of sleep was significant ($F(1, 38) = 110.21$, $p < 0.01$) whereas the effect of group ($F(1, 38) = 0.03$, n.s.) and the effect of learning phase ($F(1, 38) = 1.32$, n.s.) were not. Further analysis revealed that sleep by learning phase interaction was significant ($F(1, 38) = 7.02$, $p < 0.05$), implying that sleep affected performance differently in the two learning phases. The effect of consolidation phase was significant for no sleep improvements ($F(1, 38) = 7.35$, $p < 0.05$), while it had no effect for improvements preceded by sleep ($F(1, 38) = 0.77$, n.s.). In other words, the effect of sleep was always significant, while daytime improvements only occurred in the initial phase (as shown by the results of the paired t-tests in Figure 3 as well).

Discussion

We used a contour integration task to study the effects of sleep and time in perceptual learning. The contour integration task has been developed earlier in order to test the integration properties of neurons with conjoint orientation preference in the primary visual cortex in a behavioral paradigm (Field, Hayes, & Hess, 1993; Kovács & Julesz, 1993). These stimuli have been designed to specifically address processing in the primary visual cortex. Neural correlates, found more recently, seem to indicate the role of lower level visual areas in integrating the contour-in-noise stimulus as well (Altmann et al., 2003; Giersch et al., 2000; Kourtzi et al., 2003). A possible candidate for assembling local orientation information already within the primary visual cortex is the plexus of long-range horizontal connections (see, e.g., Gilbert & Wiesel, 1992). Cue-specific perceptual learning in the task has been demonstrated earlier. It has been shown that practicing with color- vs. orientation-defined contour stimuli does not transfer across these attributes (Kovács et al., 1999). This cue-specific improvement indicates that learning takes place at an early cortical level, not involving high level, or feedback processes. In this respect, the contour integration task is similar to the frequently used texture discrimination task (Karni & Sagi, 1991) and the more recently developed coarse orientation discrimination task (Matarazzo et al., 2008) that are both employed in studies on sleep-dependent learning. However, the contour integration task requires integration across a large area in the visual field, while performance in the texture and coarse orientation discrimination tasks is based on the output of local filters. The specific type of contour integration stimulus employed in our experiment is also different from the generally used version, where a relatively short, straight, or slightly curved line is embedded in a constant amount of noise (Field et al., 1993; Hess & Field, 1999). Our paradigm allows for adjusting the amount of noise and the shape of the contour. Both of these parameters are important in demonstrating that closed contours are easier to detect in this task than non-closed ones, and that shape-dependent contextual effects are already present at this level of processing (Kovács & Julesz, 1993, 1994; Mathes & Fahle, 2007). The current study, employing the latter type of visual stimuli, addresses the question whether these more global shape-dependent processes are enhanced by offline learning during sleep.

Perceptual learning in the 12-h shift paradigm followed a typical learning curve (Figure 1a) with a stepwise modulation (Figures 1b and 3). The stepwise modulation appeared with a phase shift in the two experimental groups, and it was more enhanced in the last few sessions. The pattern of results unequivocally indicates that night sleep results in the enhancement of performance in the lack of further stimulation or practice, which is consistent with earlier findings in perceptual learning (e.g., Karni & Sagi, 1991; Stickgold, James et al., 2000). Improvement might be a result of use-dependent changes in connectivity within the orientation-selective neuronal populations in the primary visual area.

The 12-h shift paradigm with 5 sessions and 2 experimental groups also provided for a clear distinction between two phases of offline learning. Our results indicate that there is an initial phase of learning, including the first few

sessions, in which relatively smaller but significant daytime improvements also occur in addition to sleep-dependent learning. In the second phase of learning, we only observed overnight improvements. Significant daytime improvements were also observed in texture discrimination, depending on the number of trials in a single session (e.g., Censor, Karni, & Sagi, 2006) and during the acquisition of skilled motor performance (e.g., Karni et al., 1998; Korman, Raz, Flash, & Karni, 2003; Walker et al., 2003). Such a clear distinction between the "mixed" and "sleep-dependent" phases has not been demonstrated before. There is a possibility that the initial phase involves higher level cognitive and attentional processes, and the second phase is more specific to low-level cortical changes. In future studies, cue specificity of these two phases might clarify this issue.

An alternative scenario is that the two observed phases of learning are different in terms of the level of sensory adaptation present in the low-level visual system. Censor and Sagi (2008, 2009) recently put forward a saturation hypothesis with respect to perceptual learning in texture discrimination. In this framework, overexposure to the stimulus saturates the processing network and results in less efficient processing by strengthening task-irrelevant synapses. They have shown that both daytime and overnight improvements depend on the number of practice trials. In our experiment, there is a possibility that improved performance by Session 3 results in a larger number of visible contours compared to that of Session 1. Theoretically, the "extra" (approximately 40) visible contours might have resulted in a saturation effect, thereby eliminating daytime improvement. Practically, however, such a change in the adaptation state of the network has been induced in the earlier studies (Censor & Sagi, 2008, 2009) by hundreds of "extra" trials. Therefore, we suggest that the difference between the first and second phases of learning is valid in terms of mixed daytime and overnight versus only overnight improvement.

The role of different sleep stages in the two distinguishable phases of perceptual learning of visual integration shall be a topic of further polysomnographic studies.

Conclusions

We distinguished two phases of offline perceptual learning in a visual integration task using a 12-h shift design: both daytime and overnight improvements in the first phase, and only overnight improvements in the second phase.

Acknowledgments

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Study III.

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Perceptual Learning in Williams Syndrome: Looking Beyond Averages

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Abstract

Williams Syndrome is a genetically determined neurodevelopmental disorder characterized by an uneven cognitive profile and surprisingly large neurobehavioral differences among individuals. Previous studies have already shown different forms of memory deficiencies and learning difficulties in WS. Here we studied the capacity of WS subjects to improve their performance in a basic visual task. We employed a contour integration paradigm that addresses occipital visual function, and analyzed the initial (i.e. baseline) and after-learning performance of WS individuals. 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 of similar age. This approach helped us to reveal information about the possible origins of poor performance of WS subjects in contour integration. Although the majority of WS individuals showed both reduced baseline and reduced learning performance, individual analysis also revealed a dissociation between baseline and learning capacity in several WS subjects. In spite of impaired initial contour integration performance, some WS individuals presented learning capacity comparable to learning in the typically developing population, and vice versa, poor learning was also observed in subjects with high initial performance levels. These data indicate a dissociation between factors determining initial performance and perceptual learning.

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Introduction

Genetically determined neurodevelopmental disorders (GNDs) involve impairment in the growth and development of the central nervous system and refer to a variety of disorders of brain functions, which can affect social behavior, emotions, learning ability and memory. Reduced learning capacity is a main feature of GNDs, e.g. Williams-, Rett-, fragile X- and Down syndrome [1].

Variations and anomalies in the structural and neurocomputational features of neurodevelopmentally disordered systems are extensive, and it is these altered features that determine the limits of plasticity and learning capacity. Pennington [2] suggests three groups of genetic effects on brain development that are possibly disrupted in neurodevelopmental disorders. Genetically driven alterations might be detected (i) in brain size, by altering the number of neurons or synapses; (ii) in the pattern of neuronal migration, occasionally in a regionally specific manner; and (iii) in the features of neurotransmission, either in terms of changed neurotransmitter levels or altered binding properties of receptor proteins.

In addition to genetically determined structural abnormalities [3–11] and altered features of neurotransmission [12–14], the characteristic difficulty to learn may occur because of disruption in terms of classic 'epigenetic factors,' such as sleep [15–21].

Our aim was to assess the ability to learn in a simple visual task in a group of subjects living with a GND, and to compare their initial and after-learning performance to that of a group of typically developing subjects. Perceptual learning is exceptionally helpful when assessing learning abilities in GNDs, since it requires relatively low cognitive load. Another advantage of employing a perceptual learning paradigm is that perceptual learning has been extensively studied and its neural background has been clarified (e.g. [22–24]). Because of the relatively small genetic deletion, and the well-defined functional and structural impairments of the visual system, we have decided to study perceptual learning in Williams syndrome (WS). WS is a genetic disorder caused by a hemizygous microdeletion of cc. 20–30 genes on chromosome 7q11.2, and it causes –among other problems - mild to moderate mental retardation and is associated with poor visuo-spatial abilities [25–26]. Earlier studies reported impaired short-term visuo-spatial memory deficits (e.g. [27–28]), relatively poor performance on tests of visual and verbal long-term memory [29] and poor episodic retrieval of both verbal and visuo-perceptual stimuli [28]. Reduced learning rate was found in procedural tasks [30–31] in groups of WS children; however, perceptual learning has not yet been studied in this population.

We employed a Contour Integration paradigm (CI) that was originally developed by Kovacs and Julesz [32] to study low-level visual integration processes. CI images are composed of collinear chains of Gabor elements forming a horizontally placed egg shape on a background of randomly positioned and oriented Gabor patches (Figure 1A). At the neuronal level, visual contour integration involves spatial integration and it is thought to be mediated by the long-range horizontal connections of orientation

selective neurons in the primary visual cortex (e.g. [32–34]). Behavioral studies found an unexpectedly late development of contour integration abilities, improving until the early teen-age years [35–36].These results are in line with the neuroanatomical findings on the prolonged development of horizontal connections in layer II/III of the human primary visual cortex, which extends well into childhood [37]. Perceptual learning in CI is specific to stimulus features, such as orientation and color [35,38], indicating that the process involves use-dependent changes in connectivity within the orientation selective neuronal network in the primary visual cortex. More recently, it has been demonstrated that after an initial acquisition phase, significant performance increase in this task occurs only after a night of sleep, indicating that learning in CI is sleep dependent [39].

It is especially challenging to evaluate the different aspects of behavior, perception and cognition in GNDs, and well-controlled comparisons across subject groups are difficult. GND populations are frequently studied as groups, and individual variability is not always taken into account. Large individual differences have been shown to exist in GND populations (e.g. in Down Syndrome (DS): [40]; in WS: [41]), therefore, averaging across subjects leads to significant information loss. It has also been suggested that group matching can be misleading in GND research when only the equivalency of means across groups is monitored routinely, and the homogeneity of their variances or the shapes of their distributions are not [42]. It is extremely common to choose a control group by matching for IQ or using IQ as a covariate in group-matching studies [43]. Generally, GNDs result in significant disparity between chronological and mental age, so researchers have the options to either appoint chronologically younger typically developing (TD) persons with similar mental

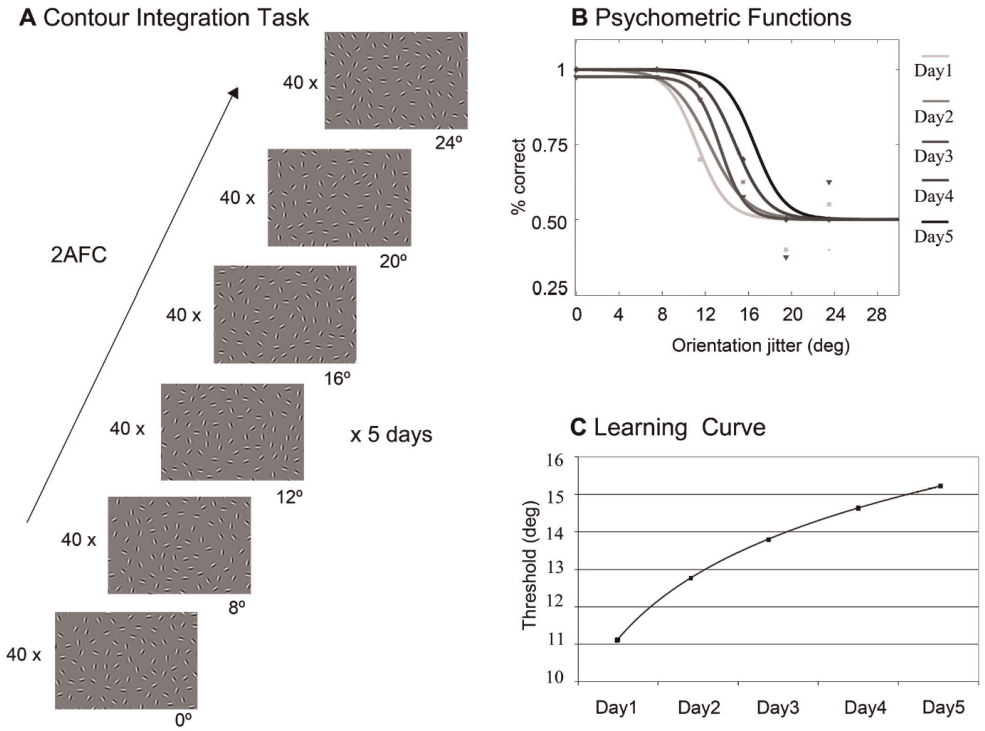

Figure 1. Procedure. (A) Contour Integration task. The visual stimulus consists of a collinear chain of Gabor elements forming a horizontally placed egg shape embedded in random noise. The contour elements were jittered from the original path of the contour in an increasing order of difficulty, between 0° to 24,° across six difficulty levels. Observers were presented with forty stimuli at each difficulty level and had to decide in a 2AFC procedure which direction the narrower part of the egg points to. Subjects practiced on five consecutive days. (B) Calculating perceptual threshold. This panel shows an example of how the perceptual threshold was calculated for every subject during the five-day training. Percentage of correct responses (on the y axis) was recorded at each of the six difficulty levels (on the x axis). Individual marks (triangles, squares etc.) are the measured data points. Perceptual threshold was calculated by fitting a logistic psychometric function on the data points. Threshold was defined by orientation jitter at 75% correct performance. Threshold increased (i.e. performance increased and this resulted in shifting of the fitted curves to the right) during the five-day-long training as a consequence of perceptual learning. (C) Example of a learning curve. The learning curve shows how the perceptual threshold increases through a five-day long training as a result of perceptual learning. These curves were drawn for each TD age-group by plotting the perceptual thresholds of the groups across the five practice days (see Figure 2B).
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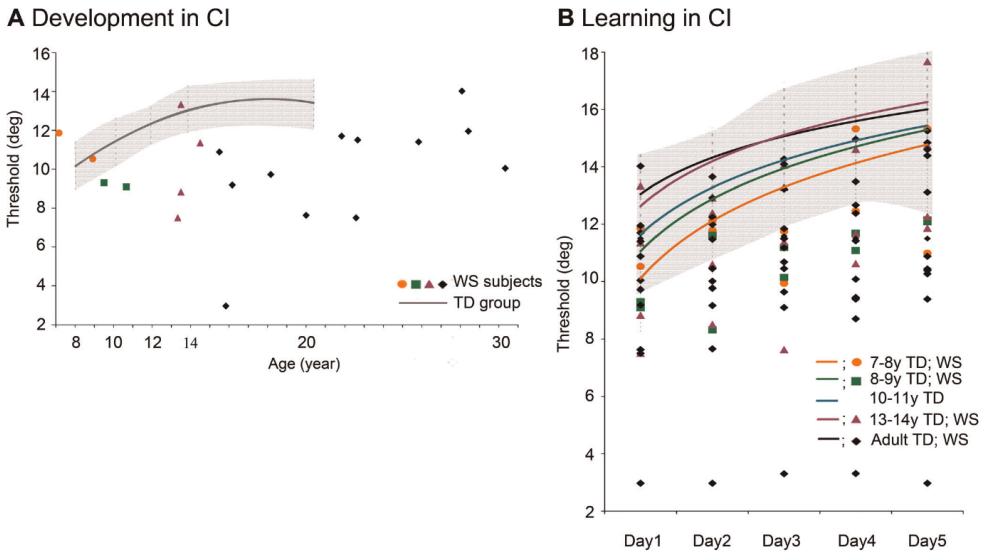

Figure 2. Development and learning in CI. (A) Development in CI. The developmental curve of the TD group was fitted on the baseline averages of the six age-groups (goodness of fit: R = 0,9162*), the shaded area designates standard deviation. Visual CI performance increases as a function of age showing a slow developmental course of contour integration, reaching the adult level by 13–14 years of age. Colored symbols stand for individual WS subjects. Colors correspond to the appropriate age-groups shown in Fig. 2B. Performance of WS subjects has an extremely high variability and only a few subjects are within the TD range. (B) Learning in CI. Colored lines represent learning curves of each TD age-group (standard deviation is shown by light-grey shading). Younger TD subjects seem to learn at a greater speed. Colored symbols stand for individual WS subjects. Colors correspond to the appropriate age-groups. WS subjects vary a great deal in terms of learning capacity, and only a few subjects are in the TD range.
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age as a control group, or select a control population with a different disorder and similar mental and chronological age. In the case of selecting TD controls, maturational and experience-related concerns arise as younger controls will be at a more immature neural level, and a shorter amount of time will be available for them for perceptual, social and cognitive experiences. On the other hand, choosing atypically developing controls brings on the problem of uneven cognitive profiles, which is fairly common in GNDs (e.g. in DS: [44]; in WS: [41]). Similar overall IQ scores can arise from entirely different response profiles, i.e. from dissimilar cognitive profiles, in different GNDs [45]. Moreover, it has been suggested that IQ is not sufficient as a covariate in cognitive studies, and using IQ as a matching variable or covariate has resulted in over-corrected, inconsistent, and counterintuitive findings about neurocognitive functions [43]. Here we attempt to overcome the above mentioned difficulties arising in the classical matched-control design, and strive to obtain more informative and reliable evaluation of WS individuals. According to this effort, we analyzed individual WS data as compared to the data of typically developing subject groups of corresponding ages in a perceptual learning paradigm.

We assume typically low initial (baseline) performance, and, at the same time, relatively high individual variability both in the initial contour integration performance and in learning capacity within the WS population. We assume that initial performance and learning capacity might be dissociated: low initial performance may not be linked with reduced learning capacity, and, vice versa, reduced learning may not be coupled with low initial performance.

Materials and Methods

Participants

Williams syndrome subjects. 19 individuals (7 males, 12 females, age range: 7 to 30 years) with WS took part in the experiment. Detailed demographic data of the WS group is described in Table 1. In case of each WS subject, the genetic diagnosis was established using fluorescent in situ hybridization (FISH) probes for elastin. All participants had normal or corrected to normal vision.

Typically developing (TD) subjects. The TD control children and adults were recruited from primary schools and universities in Budapest. The TD population consisted of eighty children in four age-groups (40 females, 40 males; age range: 7–14 years) and twenty adults (10 males, 10 females; age range: 18–23 years). Further details of the TD population are summarized in Table 2. Those with a history of neurological or psychiatric illnesses were excluded. All observers had normal or corrected to normal vision. During the course of the experiment participants were asked about the amount of night sleep. Those who did not have at least seven hours of sleep were also excluded from the study.

Table 1. Demographic data of participating WS subjects.

WS code	Age (years)	Gender
WS1	7	Male
WS2	9	Female
WS3	10	Male
WS4	11	Female
WS5	13	Female
WS6	14	Male
WS7	14	Female
WS8	15	Male
WS9	16	Female
WS10	16	Male
WS11	18	Female
WS12	20	Female
WS13	22	Female
WS14	23	Male
WS15	16	Female
WS16	26	Male
WS17	28	Female
WS18	28	Female
WS19	30	Female

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Ethics

Written informed consent was obtained from adult subjects and the parents of participating children. Subjects participated voluntarily and were unpaid. Ethical approval was granted by the Social Sciences Ethical Review Board of the Budapest University of Technology and Economics.

Procedure

In this altered version of the CI task, orientation jitter was introduced along the contour (see also in [46]). Orientation jitter of the contour elements was varied between 0° to 24° across six difficulty levels (0°, 8°, 12°,16°, 20°, 24°, see Figure 1A). The carrier spatial frequency of the Gabor patches was 5 c/deg and their contrast was 95%. The spacing between the contour elements was kept constant (8 λ; where λ is the wavelength of the Gabor stimulus) at the average spacing value between the background elements. The signal-to-noise ratio as defined by a D parameter (D = average background spacing/contour spacing) of each image was 0.9. The stimulus onset time was maximum 2000 milliseconds (or until the subject responded), with a fixation cross between stimuli (500 milliseconds). Observers had to determine which direction the egg shaped contour pointed to. A set of 40 images was presented at each of the six difficulty levels in four blocks of 10 trials, which means 240 trials/session. Stimuli were presented in the order of increasing difficulty levels. The experiment took a maximum of 20 minutes to complete. The percentage of correct responses was recorded at each difficulty level. Threshold was determined by a psychometric function at 75% correct performance. Observers practiced in the CI task through five consecutive days in the same design. Thresholds were calculated for each day (see example in Figure 1B), and these thresholds outlined a learning curve for the five-day-long training period (see example in Figure 1C). Day1 performance was considered as baseline and we measured perceptual improvement by Day5. No feedback was provided to the participants.

Table 2. Age-groups of TD participants.

Group	Age(months)	SD	Male (n)	Female(n)
7–8 years	95,3	7,6	10	10
9–10 years	120,5	8,2	9	11
11–12 years	142,3	7,3	9	11
13–14 years	165,5	7,4	10	10
Adults	243,9	20	10	10

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Results

Typically Developing Subjects

Adults vs. children. Table 3 presents the baseline and learning data of TD age-groups. Independent t-test revealed significant differences in baseline performance between Adults and Group 7–8y, Group 9–10y, Group 11–12y (Adults vs. Group 7–8y: $t = -6.244$, $df = 38$, $p<0.01$; Adults vs. Group 9–10y: $t = -4.653$, $df = 38$, $p<0.01$; Adults vs. Group 11–12y: $t = -2.836$, $df = 38$, $p<0.01$).

In order to determine the learning capacity of the different age-groups, a learning rate was calculated by subtracting Day1 threshold from Day 5 threshold. Independent t-test showed significantly lower learning rate in Adults than in Group 7–8y, Group 9–10y, Group 11–12y (Adults vs. Group 7–8y: $t = 2.959$, $df = 38$, $p<0.01$; Adults vs. Group 9–10y: $t = 2.931$, $df = 38$, $p<0.01$; Adults vs. Group 11–12y: $t = 2.246$, $df = 38$, $p<0.05$).

No significant differences were found between Adults and Group 13–14y in baseline (independent t-test; $t = -0.808$, $df = 38$, $p = 0.424$) or in learning rate (independent t-test; $t = 1.602$, $df = 38$, $p = 0.118$).

Differences between age-groups of children. Independent t-test revealed significant differences in baseline performance between Group 7–8y and all the other child groups (Group 9–10y: $t = -2.534$, $df = 33.798$, $p<0,05$; Group 11–12y: $t = -4.395$, $df = 31.605$, $p<0.01$, Group 13–14y: $t = -5.321$, $df = 38$, $p<0.01$). Group 9–10y's baseline performance was significantly lower than that of Group 11–12y and Group 13–14y (independent t-test: Group 11–12y: $t = -2.246$, $df = 38$, $p<0.05$; Group 13–14y: $t = -3.580$, $df = 38$, $p<0,01$). Independent t-tests showed no significant differences in the learning rate of the different groups of children.

Williams Syndrome Subjects

Normalization and correction of the TD and WS data. As Figure 2 demonstrates, there are enormous individual differences among WS subjects. Some subjects are within the typically developing performance range, while some are far below the average TD performance. Since evaluating WS subjects as a group would have lead to loss of information, we analyzed the performance of WS subjects individually. In order to perform normalization on the TD population data we converted individual baseline values (Day1 perceptual threshold in jitter) and learning rate (the improvement by Day5 expressed in jitter; i.e. subtracting Day1 threshold from Day5 threshold) into z-scores. Baseline performance and learning rate of the TD individuals were normalized with respect to the age-group they belonged to. Baseline performance and learning rate of WS individuals were

Table 3. TD baseline and learning data.

Group	Baseline group means and SE (in degree)	Learning group means and SE (in degree)
7 – 8 years	10,02 (0,4)	4,46 (0,44)
9 – 10 years	11,24 (0,29)	4,15 (0,3)
11 – 12 years	12,07 (0,33)	3,87 (0,32)
13 – 14 years	12,91 (0,38)	3,57 (0,27)
Adults	13,22 (0,36)	2,81 (0,34)

The raw baseline and learning data of the TD age-groups. The table shows mean baseline data (threshold on Day1) and the average learning data (improvement from Day1 to Day5 expressed in degree) of the TD participants.
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normalized with respect to their TD age-group as well, calculating z-scores for WS individuals from the mean and standard deviation of the corresponding TD age-group. Although previous studies have shown age-related performance reduction in contour integration, this was only found well beyond the age of 30 [47–48]. Therefore, it is safe to compare our older WS subjects to the younger TD adult group.

Figure 3A presents the relationship between the baseline and learning z-score values. There is a significant negative correlation ($r = -0.372$, $p<0.0001$) between the baseline and learning z-score values of the TD population. The lower the baseline, the greater the improvement is during the five-day learning course. Regression analysis showed linear connection between learning and baseline z-score values (regression coefficient = −0.372; $R^2 = 0.1384$; $F = 15.7373$; $p<0,0001$; error variance = 0.8353). Most WS subjects have poor baseline z-score values, thus the amount of their improvement does not represent adequately their learning abilities compared to the TD population, who start from a higher baseline value. In order to eliminate the baseline effect and to create an improvement measure that is comparable across TD and WS populations, we corrected the learning z-score values of every subject. Correction was performed by subtracting the baseline value multiplied by the regression coefficient from the learning z-score values, thereby subtracting the regression line value at the baseline z-score value from the learning z-score value (see Figure 3B).

TD subjects flock together around zero, while WS subjects are typically outside of the TD range both with respect to baseline and corrected learning z-score. However, they also show large individual differences. After the correction of the learning z-score values, mean of the baseline and the corrected learning z-score values of the TD population were 0 with a standard deviation of 0.9796 and 0.9093, respectively. The range of one and two standard deviations around the mean of the baseline z-score (shaded and colored vertical strips in Figure 3B) and the corrected learning z-score (shaded and colored horizontal strips in Figure 3B) of the TD population were calculated respectively. Table 4 shows the individual baseline and corrected learning z-score data of the WS subjects.

Discussion

According to Figure 3B and Table 4, WS subjects' performances show 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. We would like to draw attention to the fact that (2) and (3) are particularly interesting with respect to the potential dissociation between the factors determining initial (baseline) performance and learning. According to the current state of knowledge (see references below), these factors might be related to genetically determined structural brain damage (in the case of initial performance); and genetically determined changes in the morphology, altered features of neurotransmission or epigenetic factors (learning).

The observer is assumed to rely on the horizontal connections of the orientation selective neurons in V1 while carrying out the CI task [32,49], therefore, baseline performance in CI might be considered as an indicator of V1 function, and poor performance suggests structural and/or functional damage in V1. Brain imaging and anatomical studies found an overall smaller brain volume in WS with structural abnormalities, including abnormally increased gyrification and a relatively large loss of gray matter volume in parieto-occipital areas (e.g. [50–53]). Studies identified a well-differentiated area V1 in WS; however, the volume of this area is smaller compared to controls [50,52]. Besides the volumetric abnormalities, increased cell packing and neuronal size differences were described in this region [52–53]. The above mentioned findings imply atypical V1 functioning in WS. However, in order to directly demonstrate the connection between the behavioral scores in CI (baseline performance) and V1 structural abnormality at the level of WS individuals, further imaging and anatomical studies are needed.

There might be a number of different factors behind reduced learning capacity in WS. Functional, morphological or cell–cell interaction- and connection abnormalities are likely to be involved. Genetically determined changes in the morphology, shape and number of dendritic spines, or alterations of synaptic transmission and subsequent impairment of synaptic function will likely underlie learning and memory deficits. One of the genes commonly missing in WS is Limk1 [54]. Limk1 is thought to be involved in regulating dendritic spine size [55]. Dendritic spines are localized at the postsynaptic sites of excitatory synapses, and as sites of axonal-dendritic contacts, they are potential mediators of the connective plasticity underlying learning, memory, and cognition [56]. In addition to Limk1, Cyln2 [57] is another possible candidate gene contributing structural–functional abnormalities and impaired plasticity in WS. Cyln2 encodes proteins that regulate dynamic aspects of the cytoskeleton of the cells. Altered regulation might lead to defects during brain development and/or deficits in synaptic plasticity in adulthood [58]. Stx1a is also mentioned as a relevant gene in terms of cognitive features in WS. This gene encodes Syntaxin-1A, a protein that plays a crucial role in synaptic exocytosis of neurotransmitters from neuronal cells [59]. Growing evidence support the role of Stx1a in deficits of

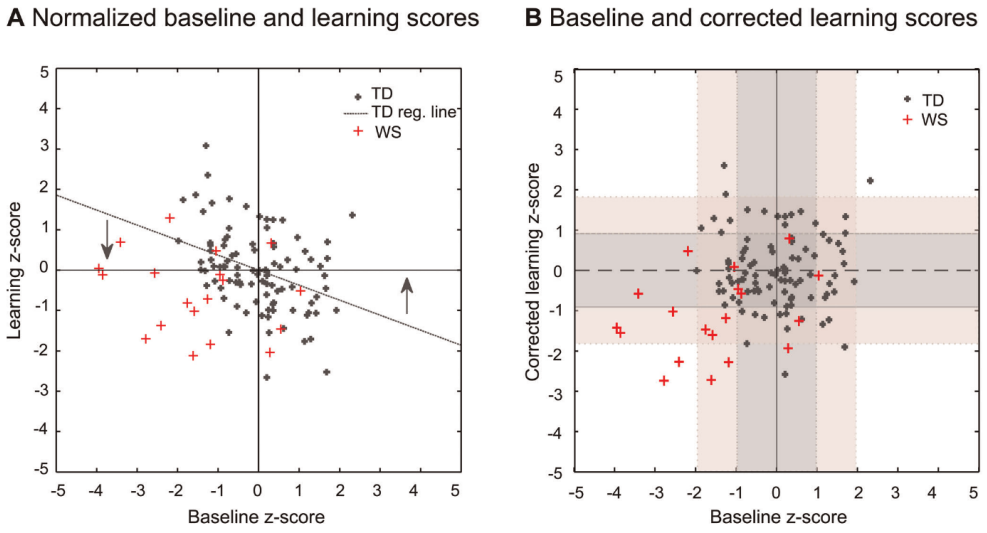

Figure 3. Normalized and corrected scores in CI. (A). Normalized baseline and learning scores. The scatter-plot shows individual baseline (threshold on Day1) and learning (Day5 threshold - Day1 threshold) z-score of individual TD (dark grey cross) and WS (red cross) subjects. Average performance on both axes is at zero. The dotted grey line represents the linear regression line fitted on the TD data set. There is a significant negative correlation between baseline performance and the amount of learning in the task ($r = -0{,}372$, $p < 0{,}0001$): the lower the baseline is the greater the improvement will be by the fifth day. (B). Baseline and corrected learning scores. In order to eliminate the effect of the baseline on improvement we corrected the learning data. Corrected learning z-scores were obtained by subtracting baseline values multiplied by the regression coefficient from the learning z-scores. The scatter plot represents individual baseline z-scores and corrected learning z-scores of the TD (dark grey cross) and WS (red cross) participants. Light grey and light pink zones show the range of one and two standard deviations around the mean of the baseline z-score (vertical strip) and the corrected learning z-score (horizontal strip) of the TD population, respectively.
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learning and memory in WS [60–61]. In spite of the genetic determination of the cognitive symptoms in WS, it is important to recognize that there is also variability in the amount and type of genetic impairment. Studies reported atypical, partial deletions [62–63], providing a potential explanation for the inhomogeneous behavioral performance in the WS population.

In addition to the genetically determined morphological, functional, neurotransmission related alterations, another possible factor determining reduced learning capacity is disturbed sleep in WS. Polysomnographic studies report decreased sleep time, fragmented sleep, atypical limb movements, increased slow wave sleep, decreased REM sleep and irregular sleep cycles in WS [64–66]. In the spectral analysis of the polysomnographic recordings Gombos and colleagues [65] also showed increased frontal slow wave activity in NREM sleep as well as decreased alpha and sigma activity in both NREM and REM sleep of WS subjects. The higher frequency of NREM sleep EEG sigma activity was shown to be a characteristic feature of WS suggesting an alteration of sleep-dependent thalamocortical activity in this population [66]. Normal baseline CI performance associated with poor learning in some of our WS subjects might suggest that impaired sleep might be the culprit. However, this hypothesis needs confirmation from polysomnographic sleep studies.

In addition to gaining further insight about the learning abilities of WS subjects, we also intended to highlight variability in this atypically developing group. Individual differences are amplified even during typical development as a consequence of interactive effects of genetic and epigenetic factors. These emerging differences are greater in atypical development. Several difficulties may arise with respect to group-matching studies, involving loss of information about individual differences, missing the link between behavioral phenotypes and genes, and also between altered cognition and abnormal structural organization of the neural system. And finally, merging individual data in atypically developing groups might prevent the development of optimal treatment strategies. Effective treatment requires that exact determination of factors underlying cognitive/behavioral symptoms. Here we compared the individual results of WS subjects to that of the typically developing age-groups in order to avoid the above mentioned drawbacks.

We studied initial performance and perceptual learning capacity of Williams Syndrome and typically developing subjects in a basic visual task involving the Contour Integration paradigm. In order to avoid the usual drawbacks arising in group-matching studies, we compared WS individuals to typically developing populations in a novel way. 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 of similar age. We have chosen the contour integration task since we wanted to study an assumed dissociation between measured baseline performance and learning capacity in a given task. We assumed that the majority of the WS subjects would have difficulty and lower than TD level performance in this task. This choice allowed us to highlight and emphasize that structural/functional impairments would not necessarily lead to reduced/impaired

Table 4. Individual data of the WS individuals.

WS subject code	Raw Baseline Data (in deg)	Raw Learning data (in deg)	Baseline (B) z-score	Corrected Learning (CL) z-score	Deviation from average B	Deviation from average CL
WS1	11,86	3,46	1,0344	−0,1283	+	N
WS7	13,3292	4,3382	0,313	0,79	n	N
WS8	11,349	3,3856	−0,9527	−0,465	n	N
WS18	11,9511	2,4351	−0,8777	−0,5768	n	N
WS2	10,5258	0,4629	0,2823	−1,9329	n	– –
WS17	14,02	0,58	0,5479	−1,2563	n	–
WS13	11,7	3,55	−1,0508	0,0858	–	n
WS19	10,0418	4,7975	−2,1934	0,4743	– –	n
WS5	7,5	4,357	−3,413	−0,5806	– –	n
WS3	9,29973	2,78907	−1,587	−1,6059	–	–
WS4	9,09	3,06	−1,7578	−1,4682	–	–
WS16	11,3988	1,7173	−1,2583	−1,1865	–	–
WS15	11,5	0,0004	−1,6158	−2,7197	–	– –
WS9	10,88	−0,43	−1,6158	−2,7197	–	– –
WS12	7,63	2,638	−3,8553	−1,5521	– –	–
WS14	7,5	2,887	−3,9449	−1,4231	– –	–
WS6	8,82892	3,43368	−2,5636	−1,0246	– –	–
WS10	9,18383	0,21007	−2,7846	−2,7371	– –	– –
WS11	9,72214	0,71536	−2,4136	−2,2696	– –	– –

Note:
+: z-scores above one standard deviation.
n: z-scores within one standard deviation.
-: z-scores below one standard deviation.
- -: z-scores below two standard deviations.
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learning capacity. Some of those who gave very low baseline level performance presented learning capacity within the normal range, and vice versa. The detailed analysis we offer might affect treatment strategies at the level of the individual. Exploring individual differences and looking at each subject individually with a goal-oriented and comprehensive approach shall enable substantial advancement in the field of neurorehabilitation in the future.

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Author Contributions

Conceived and designed the experiments: PG IK. Performed the experiments: PG. Analyzed the data: PG FG. Contributed reagents/materials/analysis tools: PG IK FG. Wrote the paper: PG IK FG.

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IV. General discussion and further aims

I investigated the cortical structural and functional factors underlying visual perceptual learning in typically developing children and young adults, and in people living with Williams syndrome. The contour integration task is an optimal tool for these investigations, since it specially addresses V1 horizontal connections, and the fundamental mechanisms and the neuronal background are well explored.

First, I plotted the developmental trend of contour integration and perceptual learning based on the results of a large typically developing population (n=100, 7-23 years). The behavioral data demonstrated protracted development of contour integration suggesting slow functional maturation of long-range lateral intralaminar connections in the primary visual cortex. This finding is consistent with earlier behavioral results (Kovács et al., 1999) and evidence from anatomical and cellular studies. Burkhalter et al. (1993) reported that the development of horizontal connections in layer II/III of the human primary visual cortex extends well into childhood. Furthermore, studies of developing horizontal connections often emphasize that collateral pruning and selective synapse elimination are important for achieving functional maturity (White & Fitzpatrick, 2007). After the early childhood overproduction of synapses, synaptic density decreases during childhood and early adolescence as a result of prolonged selective elimination of the connections (Huttenlocher & Dabholkar, 1997). In addition to the number of connections, the types of connections are equally important in the functioning of cortical networks. An appropriate balance between excitatory and inhibitory (mainly GABAergic)

synaptic inputs appears to be essential. In the human visual cortex, studies on the developmental changes in GABAergic mechanisms in postmortem tissues have shown that the relevant changes start to occur between the ages of 10 and 13 (Pinto et al., 2010). We also found, that learning performance was affected by age in the typically developing population, younger age-groups showed a larger capacity to learn in contour integration. These results are consistent with the general idea that the developing brain is more responsive to experience than the adult brain (see e.g., Kolb et al., 2011).

In a further investigation, we identified two phases of perceptual learning in contour integration and determined the role of sleep in these phases. We found that there is a fast, initial acquisition phase, where sleep is not crucial for performance enhancement, followed by a later phase where significant improvement occurs only after a night of sleep. We showed that learning in contour integration is determined by sleep in the typically developing population. There is a possibility that the initial phase involves higher level cognitive and attentional processes, and the second phase is more specific to low-level cortical changes. Additionally, the extra amount of visible contours in the later sessions of training as a result of learning might be an alternative explanation for the observed difference between two phases. It has been suggested that daytime and overnight improvements depend on the number of practice trials in the texture discrimination task (Censor et al., 2006; Censor & Sagi, 2008), since overexposure to the stimulus saturates the processing network and this saturation could be eliminated by sleep. However, in our design, only an average of 40 extra stimuli were visible in the later phase, which is unlikely to lead to saturation.

After specifying factors underlying performance in the contour integration task, we employed it in a Williams syndrome population to determine the spatial

integration and perceptual learning capacities in WS. 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 on an individual basis. The assumptions were based on our findings with respect to the factors influencing baseline performance and learning capacity in the typically developing population. This might be considered as a novel approach within the research field of neurodevelopmental disorders, since most of the studies apply group comparisons.

In group-matching studies, it is extremely common to choose a control group by matching for IQ or using IQ as a covariate (Dennis et al., 2009). Applying typically developing controls, the experimenter faces maturational concerns as younger controls have a less mature nervous system and limited perceptual, social, cognitive experience. On the other hand, choosing atypically developing controls brings on the problem of uneven cognitive profiles, in various NDDs: it is likely that similar overall IQ scores arise from entirely different response profiles, i.e. dissimilar cognitive profiles (Spitz, 1982). In a comprehensive work, Dennis and her colleagues (2009) discussed that IQ is not sufficient as a covariate in cognitive studies, and using IQ as a matching variable or covariate had resulted in overcorrected, inconsistent, and counterintuitive findings about neurocognitive functions. Furthermore, by grouping and averaging inhomogeneous individuals together, one would diminish the individual differences, which would lead to information loss. Facon and his colleagues (2011) in their review showed how group matching could misconstrue in developmental disability studies, when only the equivalency of means across groups was routinely monitored, but not the homogeneity of their variances or the shapes of their distributions. At last but not least, another counter indication of

group-matching studies is that by losing the individual differences, we miss the opportunity to link varying behavioral phenotypes to genes, and/or the possibility to associate altered cognition with abnormal functional, structural organization of the neural system.

The main motivation behind this research was to overcome the above-mentioned challenges in analyzing and evaluating the performance of people with neurodevelopmental difficulties. Studying WS individual performance, we were able to obtain more information about the possible origin of poor performance than in a classical matched-control design study. This approach appeared to be fruitful, as it has led to dissociable behavioral markers of learning disability, and to testable hypotheses with respect to their origins. One of our suggestions is that 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 be behind the ability to find the contour in the noise. There might be more than one factor behind reduced learning capacity in WS. On one hand, it is the potential lack of genes (e.g. Linkk1, Stx1, Cyln2) determining dendritic spine growth and synaptic transmission that underlies impaired learning. On the other hand, disturbed sleep pattern might be a possible factor determining reduced learning capacity in WS.

In our future work, we will attempt to directly demonstrate the connections between genes and behavior, sleep and learning capacity, and 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 perceptual learning data of WS subjects were analyzed together. The pilot results showed enhanced left hemispheric Beta activity in individuals with higher learning capacity (compared to

those who showed reduced learning capacity). To get more reliable and detailed results and correlations, the analysis of further WS data is in progress. Finding connection between sleep architectural impairments and cognitive/behavioral symptoms might be helpful to develop effective treatment for learning difficulties in WS.

Furthermore, in our future work it would be essential to clarify the possible contributing role of higher-level processes to learning in the CI task, since it would be very important to know whether the learning capacity missing in WS is related to reduced plasticity in early cortical areas, in regions beyond these, or in both. The fact that we found normal learning capacity in subjects with low baseline performance (which indicates impaired V1 processing) could possible lead to the assumption that well functioning higher-level mechanisms made it possible to overcome the original poor performance as a result of practice, i.e. learning. Certainly, these assumptions should only be made after a systematic study of the potential modulatory role of higher cortical processes on learning in CI.

Identifying the factors underlying the impaired performance hopefully will contribute to the development of optimal and individual rehabilitation techniques in neurodevelopmental disorders, such as Williams syndrome.

Epigenetic factors should be considered as potential causes of significant heterogeneity in phenotype expression within the WS population as well. Individual differences are amplified even during typical development as a consequence of interactive effects of genetic and epigenetic factors. In atypical development, these emerging differences are more enormous, and might be related to non-genetic as well as genetic variations. Consequently, significant individual differences in WS performance are probably related to variations in the experience, life-style, and education of the subjects as well. Although, these are factors that can not be easily

controlled in studies, they need to be considered as a potential contributor to performance variation.

Besides identifying determining factors of impaired learning performance in WS, another important aspect of these investigations should also be emphasized. WS subjects in the typical performance range might be considered as particularly interesting cases. In NDD, brain development deviates from typical brain development starting as early as neurogenesis. It is possible, that a behavioral pattern, which appears normal, is not a result of a well-preserved function, but an outcome of compensatory mechanisms in the brain (see e.g., Thomas & Karmiloff-Smith, 2002). If it is so, it can be considered as a special case of neuronal plasticity. From the point view of prevention, treatment and rehabilitation in NDD, it is very relevant to clarify these compensatory mechanisms.

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