FINE MOTOR DEVELOPMENT AND LEARNING

IN TYPICAL DEVELOPMENT

AND IN WILLIAMS SYNDROME

PhD Thesis

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Glossary of abbreviations

FT – finger tapping

PR – performance rate

WS – Williams syndrome

TD – typical development

TMS – transcranial magnetic stimulation

REM – rapid eye movement

NREM – non-rapid eye movement

EEG – electroencephalography

PSG – polysomnography

fMRI – functional magnetic resonance imaging

PET – positron emission tomography

SRT – serial reaction time

aSRT – alternating serial reaction time task

M1 – primary motor cortex

SMA – supplementary motor area

PMC – premotor cortex

CMA – cingulate motor area

CS – corticospinal

BG – basal ganglia
Abstract

The aim of the present thesis was to map developmental aspects of fine motor performance and learning in typical development. A further aim was to examine motor performance and learning characteristics through the window of a neurodevelopmental disorder, Williams syndrome. This syndrome is characterized by fine motor problems and atypical sleep (Annaz, Hill, Ashworth, Holley, & Karmiloff-Smith, 2011).

First, developmental trajectories of repetitive and sequential finger movements were characterized (Study I.) in a large sample of TD children, adolescents and adults (n=80) between 6-30 years of age. Baseline performance had a prolonged development until adulthood in both tasks. Speed increased until 30 years of age in the sequential finger tapping task. This is in accordance with the cortical developmental trajectory of grey matter structures (Giedd, Shaw, Wallace, Gogtay, & Lenroot, 2006) and the prolonged myelination of the CS tract that results in increasing motor speed (Bartzokis et al., 2010) both in repetitive and sequential tasks. While did not reach statistical significance, the developmental trajectory showed an unexpected peak at early puberty with respect to baseline performance in different age groups (Study I.). This motivated our further study, the systematic investigation of gender and age effect on the baseline of fine finger task performance in puberty (Study III. and Study V.). Our results showed that behavioral results paralleled sexually dimorphic maturational changes in the central nervous system: there was a female advantage in sequential tasks until adolescence, then performance levelled off at the age of 14 in females. On the other hand, males showed superior performance in repetitive tasks that increased beyond puberty. This may be related to continuing myelination related to increased testosterone levels in males (Raznahan et al., 2010). After correction of the CS tract myelination effect on speed, we found that the motor developmental trajectory still showed earlier maturation in females than in males. Since the motor cortex plays a crucial role in coding and learning independent finger movements, the developmental pattern in this sequential task may correspond to earlier cortical maturation in females.
Motor learning is the sum of processes related to practice and experience, which causes changes in motor abilities and also includes the formation of new series of muscle contractions and the rebuilding of existing ones. Age dependent plasticity in the motor system continued until adulthood (Study I.). The rate of learning was the highest in the early phase of learning reaching peak in childhood and early puberty and learning capacity was extended into adult age (Study I.). It parallels the maturation of the motor cortex where the selective elimination of synapses occurs around the age of twelve years (Huttenlocher, 2002). Horizontal connections in this area are implicated in the selection and coordination of motor representations (Donoghue, Leibovic, & Sanes, 1992). In adulthood, plasticity may subserve lifelong adaptation in the motor system and based not only on horizontal connections in the grey matter but may also be associated with myelination (McKenzie et al., 2014).

In a neurodevelopmental disorder, the Williams syndrome, we examined fine motor performance characteristics and studied whether altered sleep is related to motor learning impairment. In WS motor performance differed from TD both in baseline and in learning capacity (Study II.). The baseline was below TD both in accuracy and speed and had great individual variability between participants. First day learning showed that the improvement in online performance was comparable across TD and WS groups. On the other hand, sleep dependent offline improvement was impaired in WS (Study II., IV.). After a period of five days of learning, improvement in accuracy and speed dissociated in WS. While there was improvement in accuracy, speed reached a plateau in the sequential task. It was not dependent on decreased CS tract conduction velocity, but showed a behavioral pattern observable in basal ganglia disorder. Since WS is associated with sleep alteration in the sigma frequency band in NREM sleep (Bódizs et al. 2012; 2014), it raised a question whether the decreased amount of learning in this sleep dependent learning task is related to alteration in sigma band activity (Study IV.). Baseline, first day online and offline learning performance were correlated with sigma band activity in WS. Improvement in accuracy was comparable both online and offline in this first phase of learning. Offline improvement in accuracy was related to higher 11-13.5 Hz z-transformed power, while higher oscillatory peak frequency in sigma band was associated with
decreased learning performance. In other words, sigma frequency band characteristics closer to TD resulted in superior learning in WS. These results support the role of sigma band activity in motor learning.
**Kivonat**

Jelen tanulmány célja, hogy a finommozgások fejlődési és tanulási sajátosságait feltárja a gyermekkortól a felnőttkorig. Ezen túl egy genetikai eredetű fejlődési rendellenességen, a Williams szindrómán keresztül a finommozgásos teljesítmény és tanulás jellegzetességeit, és alvással való összefüggését vizsgálja.

A tanulmányban az egyszerű ismétlődő és szeriális újimozgások fejlődési görbéit vizsgáltam egy 80 fős mintán 6 és 30 éves kor között. Mindkét mozgás esetén a kiindulási teljesítmény nőtt az életkor előrehaladával, s egy elnyújtott fejlődési trended mutatott felnőttkorig. A mozgás pontossága a felnőttkorra jellemző szintet 20 éves korban érte el, míg a mozgás sebessége 30 éves korig folyamatosan emelkedett (Study I.). Ezek az eredmények párhuzamba állíthatók a nagyagykérgi szürkeállomány fejlődéssel bekövetkező változásaival (Shaw et al., 2006), a sebességben való elnyújtott javulás pedig további összefüggést mutat a kortikospinális pályarendszer elnyújtott érésével (Bartzokis et al., 2010). Ugyanakkor a fejlődési görbe nem volt egyenletes, a serdülőkor környékén több csúcsot is találtunk a kiindulási teljesítményben. Ez felvetette a szükségességét az életkor és a nemi különbségek további vizsgálatának a serdülőkorra fókuszálva (Study III. and Study V.). Az eredmények azt mutatták, hogy a viselkedéses eredmények a központi idegrendszer érésének nemi különbségeivel együtt járnak számos ponton: serdülőkorig a nők teljesítménye két évvel megelőzte a férfiakét a szeriális feladatban, majd 14 éves kor után nem javult tovább. A férfiak viszont az egyszerű, ismétlődő feladatban mutattak magasabb teljesítményt, amely a serdülőkor után tovább fokozódott. Ez utóbbi eredmény a magasabb teszoszteron szinttel járó fokozott myelinizációhoz köthető (Raznahan et al., 2010). A kortikospinális pályarendszer myelinizációjával járó sebességbeli különbségeket korrigálva, ugyanakkor, a nők kb. két évvel korábbi érése változatlanul megtalálható a teljesítményben (Study III.). Mivel a motoros kéreg alapvető fontosságú ezen szeriális mozgások szabályozásában, a korrigált eredményben már megjelennek a kérgi motoros területek érésében bekövetkező nemi különbségek.
A mozgástanulás gyakorláshoz vagy tapasztalathoz kapcsolódó folyamatok összessége, amely változást okoz a mozgásos képességeben és magába foglalja új izommozgás sorok kialakítását valamint a meglévők újraépítését. A motoros rendszert a felnőttkorig ivelő plaszticitás jellemezte (Study I.). A teljesítménybeli változás a tanulás korai szakaszában volt a legnagyobb, a csúcsát gyermekkorban és kora serdülőkorban érte el. Ez megfeleltethető a motoros kéreg érésének, mely során a szinapszisok szelektív eliminációja kb. 12 éves korra tehető (Huttenlocher, 2002). Ezekben a mozgatókéregbeli horizontális kapcsolatokban zajlik a motoros reprezentációk kiválasztása és összehangolása (Donoghue et al., 1992). A felnőttkorban is fennmaradó plaszticitás a mozgatórendszerben hozzájárul az élethosszig tartó adaptációs készséghez, azonban feltehetően nem csak a kérgi szürkeállomány, hanem a fehérállomány éréséhez is köthető a myelinizáció által (McKenzie et al., 2014).

A Williams szindróma (WS) egy genetikai eredetű fejlődési rendellenesség, amelyben a finommotoros képességek mellett azt is vizsgáltuk, hogy a motoros tanulás összefüggést mutat-e a megváltozott alvásjellemzőkkel. WS-ban mind a kiindulási teljesítmény, mind a tanulási teljesítmény elmaradt a tipikus fejlődésüket képest (Study II.). A kiindulási teljesítmény elmaradt mind pontosságát mind a sebességét tekintve, valamint nagyfokú egyéni variabilitás volt jellemző. Az első napi gyakorlás során a WS-val születettek online teljesítménye nem maradt el a TD-hez képest, az alvás alatti konszolidáció azonban elmaradt a teljesítmény egészét tekintve (Study II., IV.). Öt napos gyakorlást követően a teljesítményjavulás szétvált a pontosság és a sebesség tekintetében. Míg pontosság tekintetében javulás volt látható, a sebességben plafon hatás mutatkozott. E plafon hatás hátterében azonban nem a kortikospinális pályarendszer érintettsége feltételezhető, a viselkedéses jellemzők sokkal inkább a törzsducok sérülése során bekövetkező mintázatot mutattak. Mivel a WS gyakran társul alvásszavarhoz, és a szindrómára jellemző alvásmintázatot is leírtak (Bódizs et al., 2012; 2014), felmerült a kérdés vajon ebben az alvásfüggő tanulás típusban van-e összefüggés a teljesítménybeli elmaradás és a WS-ben leírt szigma frekvenciasáv változásai között (Study IV.). A kiindulási teljesítmény, a gyakorlás alatti (online) és a gyakorlást követő (offline) teljesítményváltozást vetettük össze a szigma frekvenciasávbeli teljesítménnyel NREM-ben. A pontosságból való nagyobb mértékű
offline teljesítményjavulás a 11-13.5 Hz frekvenciatartománybeli magasabb teljesítménnyel járt együtt. Emellett a magasabb szigma tartománybeli csúcsfrekvenciák (mint jellemző WS-beli tulajdonság) csökkent tanulásbeli teljesítménnyel jártak együtt WS-val születetteknél. Tehát, a tanulási teljesítmény azokban az esetekben volt a legmagasabb, amelyekben a szigma frekvenciasáv jellemzői a tipikus fejlődésükekéhez a leginkább közelítettek.
I. Introduction

Motion is an inevitable part of human existence. For the majority of human beings the acquisition of a new movement is a natural process, which becomes integrated into the process of motor development and turns into a response to the constant adaptive challenges of the environment. Fine movements of the hand are human specific features. They involve precision grasp and manipulation that in turn require independent finger movements, opposition of the thumb with the other fingers and haptic perception (Naumer & Kaiser, 2010). They are supported by postural control of the trunk and proximal parts of the upper extremity (Noronha, Bundy, & Groll, 1989). Fine movements of the hand require complex sensory and motor integration, which take place at different levels of the central nervous system from the spinal cord to cortical control (Johansson, 1996). An important feature of independent hand and finger movements is that they heavily depend on cortical motor control (Leonard, 1998). Therefore, development and plasticity related to such behavior may be applied as an approach to studying the motor cortical function.

In this dissertation, I will discuss the developmental characteristics and the neural bases of fine motor development from childhood to adulthood. I would like to unravel the question how baseline performance measured as initial performance in a task changes with age and if there are gender based differences in development. I will cover the features of motor learning, its underlying neural structures and influencing factors to see if motor system plasticity changes with age in typical development. Furthermore, I will discuss Williams syndrome as a unique window to explore the relationship between motor performance and learning capacity and the influencing factors such as sleep in a neurodevelopmental disorder.

I.1. Motor control of fine motor function of the hand

Motor cortices of the frontal lobe are the primary motor cortex (M1), the premotor cortex (PMC), the presupplementary motor area (preSMA), supplementary motor area (SMA) and cingulate motor area (CMA) (Fig.1.light blue). These cortical areas show somatotopic organization where greater representational area is associated with more fine movements of the
given body part. Somatotopy, on the other hand is not point to point as in sensory cortices (Barbay, Zoubina, & Nudo, 2005; Schieber, 2001). This organization may subserve coding of complex movement patterns or ethologically relevant motor behavior (Graziano, 2016). Cortical motor areas play a role in the preparation (PMC, preSMA, SMA) and initiation (M1) of voluntary movements. Motor cortices give output to subcortical motor areas and to the spinal cord through the corticobulbar and corticospinal tracts (Rouiller, 1996). Huttenlocher (2002) showed that synaptic density in layer V in the motor cortex is lower compared to other cortical areas. Large pyramidal cell and giant Betz-cell bodies are necessary for the quick long-distance conduction of electrical signals. The limited plasticity of motor cortical areas may be due to such structural differences. Synaptic density is the highest at the age of 5-6 months and decreases to adult levels around early puberty (Huttenlocher, 2002). According to Armand et al. (1996) long axons of the layer V pyramidal cells from M1, premotor areas, CMA and in part the somatosensory cortex (S1) form the corticospinal tract and directly on spinal cord motoneurons and interneurons. 90% of corticospinal tract neurons descend contralaterally after crossing in brainstem and play a role in the control of distal parts. This fast conducting tract with direct/indirect connection to motor neurons innervating muscles of the hand enables fast and independent finger movements (Armand et al., 1996). Premotor areas have interconnections with the sensory and association areas of the parietal lobe that contribute to the preparation of hand movements based on somatosensory, visual and vestibular information (Cavada & Goldman-Rakic, 1989; Wise, Boussaoud, Johnson, & Caminiti, 1997).
The basal ganglia (BG) form a subcortical structure in the forebrain consisting five nuclei: caudate nucleus, putamen (the two shaping the striatum), globus pallidus, subthalamic nucleus and substantia nigra. The BG have complex networks both internally and externally. One of the main inputs to the BG is from the cerebral cortex to the striatum. Frontal cortical sites give input to the areas closest to them in the striatum (frontostriatal loop). That is, the prefrontal cortex wires the caudate nucleus and middle part of the putamen while premotor and motor cortices wire more frontal parts of the putamen (Selemon & Goldman-Rakic, 1985). The main output of the BG is through the pallidum and substantia nigra that send projections to the prefrontal and motor cortices via the subthalamic nucleus (Fig. 1., loop indicated with green) (Dasgupta et al., 2014). The roles of BG in motor control are diverse, including, but not limited to the following aspects: The BG works as a dam in the selection of motor patterns while inhibiting others; plays an important role in shifting between tasks or motor sequences; and have a role in the control of muscle tone of both agonist and antagonist muscles (Groenewegen, 2003; Nagano-Saito, Martinu, & Monchi, 2014). Furthermore, frontostriatal loops also play role in accurate and fast motor performance (Shabbott et al., 2013), initiation of movements, and found active during both active and passive movements of a body part (Alexander, DeLong, & Strick, 1986).

Figure 1. Motor loops in the brain (cortico-striatal loop-green; cortico-cerebellar loop-blue). MA-motor areas in the frontal cortex, SN-substantia nigra, IO-inferior olive.
Used under Creative Commons Attribution Licence after Dasgupta et al., (2014)
The cerebellum receives rich motor and sensory inputs to cerebellar nuclei and the cerebellar cortex (Ito, 1968). It gives output through cerebellar nuclei to the thalamus and motor and premotor cortices. In addition, it projects to brainstem structures and spinal cord tracts. The cerebellar cortex influences motor control and learning by inhibition or releasing inhibition. The vestibulocerebellum plays a part in the control of equilibrium, eye and head movements. The spinocerebellum is involved in online motor control/adaptation by comparing planned movements with feedback on ongoing and executed movements e.g., during goal directed hand and finger movements. The cerebrocerebellum is interconnected with the cerebral cortex (Fig.1., loop shown in blue) and is concerned with e.g., movement planning, sequencing, initiation, online control and termination of movement (Houk, Buckingham, & Barto, 1996; Ito, 2013) for a recent review see (Manto et al., 2012).

I.2. Age related changes in hand movements

I.2.1. General characteristics

Hand and finger movement including sequential movements mature later compared to other movements. The majority of overall speed improvement in hand movements occurs until the age of 10 years, reaching 70-80% of the performance at 18 years of age (Gasser, Rousson, Caflisch, & Jenni, 2010). Denckla (1973) reported progress in motor speed in children aged 5 to 10 years, with more progress at younger ages.
The developmental curve of simple repetitive finger movements e.g. tapping a key with the index finger as fast as possible (index finger tapping\(^1\)) shows a U shaped distribution with a peak at around 38 years (Fig.2.) (Bartzokis et al., 2010), the greatest improvement occurring during the first 10 years of life (Gasser et al., 2010) and there is a decline between early and late adulthood (Sivagnanasunderam et al., 2014). There is a continuous improvement in index FT speed in adolescence (Dorfberger, Adi-Japha, & Karni, 2009). Tapping rate decreases and performance variability increases with increasing FT task complexity (Hausmann, Kirk, & Corballis, 2004). More complex hand and finger movements such as alternating and sequential movements mature later, around 20-21 years (Gasser et al., 2010).

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\(^1\) Finger tapping task has several variations. In detail see I.4.3.
I.2.2. Gender differences

According to Dorfberger et al. (2009), repetitive finger tapping was significantly faster in 17-year-old males compared to females on both dominant and non-dominant hand. In the sequential finger tapping task where a predetermined sequence of finger movement is performed, no initial gender difference in speed and accuracy was found between 9-17 years, but improvement during a single practice session showed superior performance in 17-year-old males. Error rate do not differ between age groups and sexes. In handwriting, female advantage was found at 12 years that diminished in one practice session with no further difference at 17 years (Dorfberger et al., 2009). In adults, male advantage in simple tasks was found regarding speed especially at older ages (7-22 years vs. 16-70 years) (Ruff & Parker, 1993). However, in more complex hand movements (handwriting, pegboard task) results are contradictory, female advantage is often reported (Ruff & Parker, 1993). According to a meta-analysis, repetitive finger tapping does not show gender effect until the age of 10, when males became significantly faster with a peak at 12 years of age (Thomas & French, 1985) and there is no difference between males and females and hands in older ages (Sivagnanasunderam et al., 2014). Handedness may also have an influence on gender differences in fine motor performance (Carlier, Dumont, Beau, & Michel, 1993). The above studies suggest that there is a tendency for male advantage in simple repetitive tasks with age from adolescence to elderly ages. However, this advantage seems to diminish in more complex and sequential tasks with some studies suggesting female advantage in childhood. Since a systematic, step by step exploration of age groups with different gender is lacking in the field of fine motor control and learning, it motivated our study on the topic (Study I., Study II. and Study V.).

I.2.3. Laterality

Developmental changes in motor asymmetry also seem to be task dependent. Laterality of speed show task specific effects. Greatest lateralization is demonstrated in simple repetitive tasks, while complex sequential movements show the least effect (Gasser et al., 2010; Hausmann et al., 2004). Laterality effects in finger tapping do not change but asymmetries in other tasks may increase (e.g., pegboards) or decrease (e.g., Annett task) with age (Sivagnanasunderam et al.,
2014). Left-handers appear less lateralized than right-handers (Carlier et al., 1993). Laterality in the means of performance speed may be associated not only with corticospinal tract but also with hemispheric lateralization (Gasser et al., 2010). These developmental and gender specific features in hand function are related to the development of both the nervous system and the musculoskeletal system.

I. 2.4. Developmental factors underlying fine motor hand function

I. 2.4.1. Musculoskeletal system

The development of the musculoskeletal system continues until early adulthood. Regarding hand function, continuous change of shape, size and articular surfaces of bones in wrist and the joint of the hand lead to continuous change in biomechanical characteristics that affect hand function (Cech & Martin, 2012b). The development of hand bones show correlation with the Risser index (Dimeglio, 2001; Dimeglio & Canavese, 2013), a commonly used indicator of skeletal maturation. By the end of puberty, when skeletal maturation is complete, the hand gradually reaches its mature shape. Skeletal maturation occurs two years earlier in girls than boys, growth spurt starting at age 12 on average (Eveleth & Tanner, 1990). Higher estrogen level in girls leads to earlier fusion of the bone epiphyses. Boys have a later and a more prolonged skeletal maturation resulting in higher stature (Cech & Martin, 2012a). The muscular system follows the growth of the skeletal system and increased levels of testosterone result in increased amount of muscle tissue and fast twitch muscles in boys. In the lower extremity, the vastus lateralis muscle show similar fiber type distribution in males tending to have larger fast-twitch fiber size and proportionally less slow-twitch (Type I) fibers than in females (Staron, 1997; Staron et al., 2000).
I.2.4.2. Central nervous system maturation related to motor function

The cerebral cortex matures the earliest in primary sensory and motor regions. It is followed by areas of spatial and language processing and in late adolescence the prefrontal cortex which is involved in executive function (Heilman & Valenstein, 2003; Toga, Thompson, & Sowell, 2006). Brain volume in men is larger than in women (Fig.3.) (Ruigrok et al., 2014; Wierenga et al., 2014). Cortical grey matter volume follows an inverted U-shape curve between 4-22 years with a different timescale in different lobes reaching its peak 1-2 years earlier in females than in males (Giedd et al., 2006; Raznahan et al., 2010), and decreases with age in both sexes (Sowell, Thompson, Holmes, Jernigan, & Toga, 1999). The volume of subcortical grey matter structures shows differential patterns with age between 7-24 years. The volume of the caudate nucleus, putamen, and accumbens show a decreasing pattern. On the other hand, an inverted U-shaped developmental trajectory is present in the hippocampus, amygdala, pallidum and cerebellum (Wierenga et al., 2014). The volume of caudate nucleus decreases with age between 4-22 years (Giedd et al., 2006), the peak volume being two years ahead in females than in males (Raznahan et al., 2010). The striatum surface area increases from 6-20 years in males but remains unchanged in females (Raznahan et al., 2010). The volume of amygdala increases in males while the volume of the hippocampus increases in females. Gender difference may be caused by the higher amount of androgen hormones in the amygdala, and in the case of the hippocampus by the higher amount of estrogen receptors (Giedd et al., 2006). Regarding the cerebellum, the total volume is increased in males, with an increasing gap between genders between 7-22 years (Tiemeier et al., 2010). Furthermore, the development of cerebellum has “a sexually dimorphic” trajectory. In males, cerebellar grey matter volume shows a U shaped trajectory with a peak at about 16-17 years. Females are characterized by a continuous decrease in this age range (Fig.3.) (Wierenga et al., 2014). Developmental changes in motor-related grey matter structures suggest age-dependent changes in motor skills (see Thesis I. and Study I. page 55). Furthermore, developmental trajectories have gender based differences that assume differences in the motor developmental trajectories (see Thesis I. and Study III. page 79, and Study V. page 104.)
Figure 3. Developmental curves of gray matter volumes in males and females. Vertical axis shows gray matter volume (cm$^3$). Horizontal axis shows age (years). Male data is indicated by blue and female data indicated by red.

(after Wierenga et al., 2014; with permission from Elsevier)

Not only the development of grey matter, but also the development of white matter structures is related to motor performance. Human nervous system development involves axonal changes including axonal density, caliber, and myelin characteristics. Myelination of white matter tracts in humans is prolonged compared to other species. Myelination of white matter tracts can continue into adulthood (Miller et al., 2012). White matter volume shows a sexually dimorphic curve with continuous linear improvement between 4-22 years in females but a more accelerated improvement in males (Giedd et al., 2006).

The corticospinal tract is demyelinated at birth (Kubis & Catala, 2003) and its myelination continues beyond puberty (Miller et al., 2012). “Maximum motor speed is determined by central conduction time that depends on the maturation of corticospinal tract” (Muller & Homberg, 1992) and is in correlation with finger tapping performance (Bartzokis et al., 2010). Conduction velocities of central motor fibers along the spinal cord are around 10 m/sec in newborns, 38 m/sec at the age of 4 years and 48-60 m/sec in adult men. Adult values are approximated around the age of 8 (Khater-Boidin & Duron, 1991). While school-age TD children already have a fast conducting CS pathway with access to spinal motoneurons (Fietzek et al., 2000), and this conduction time is correlated with motor speed, complex fine motor performance is not
available at this age. It seems that CS tract conduction velocity matures earlier than motor performance, at least in school age (Fietzek et al., 2000; Heinen et al., 1998). Differential myelination pattern of both the intracerebral white matter and the corticospinal tract would suggest differential development of motor speed in males and females from late childhood (see Thesis I. and Studies I. page 55 and V. page 104). Furthermore, it should be taken into account when motor performance is compared across different ages and gender (see I.4.4.3. page 41).

I.2.4.3. Developmental changes in the peripheral nervous system

The majority of conduction time maturation in peripheral nerves of the upper extremity occurs in the first five years of life (Garcia, Calleja, Antolin, & Berciano, 2000) but may increase further between 3-19 years of age both in sensory and motor nerves (Lang et al., 1985). Gender is not a major influencing factor in axonal thresholds in motor nerves (Casanova, Diaz, Pinto, & de Carvalho, 2014), and conduction time may show gender difference in sensory but not in motor nerves (Tan & Tan, 1995; Tobimatsu, Sun, Fukui, & Kato, 1998).

The above studies suggest that both central and peripheral nervous system maturation are related to motor performance until puberty. Nevertheless, the maturation of the central nervous system shows a more prolonged development. Both gray matter structures such as motor cortices, basal ganglia, cerebellum and hippocampus and white matter structures e.g. the CS tract show differential developmental trajectories and marked gender differences that may influence fine motor performance and learning after early development into adulthood (see Thesis I. page 50 and Thesis II. page 51).

I.3. Motor Learning

Motor learning is the sum of processes related to practice and experience, which causes changes in motor abilities and also includes the formation of new series of muscle contractions and the rebuilding of existing ones. Motor skill learning is a type of procedural learning (Seel, 2012). In the following chapter, I am going to deal with the phases of motor skill learning, the
neurological structures that play a role in the learning process, and the factors that influence performance and learning. I will also discuss the question of how these phenomena can be studied.

I.3.1. Stages of motor learning


The first, cognitive stage is when the performer understands task requirements: what and how to perform and how the performance is evaluated. This phase requires cognitive activity to sustain attention and to find an effective strategy to execute the task. Appropriate strategies are kept and inappropriate ones are discarded in this process. As a consequence, performance is very inconsistent. Accuracy and speed may be decreased and variability increased in this phase. However, improvement in performance is the highest. Improvement is rather characterized by meeting task requirements and not by the refinement of motor strategies. The cognitive phase has an important verbal component, and task requirements may be kept in the verbal store for reinforcement during task execution. Therefore, the role of instruction and feedback techniques is the greatest in this phase.

The second, associative phase starts when the performer finds an effective execution strategy and only fine modifications are implemented. In this phase, performance is more consistent and improvement is gradual. It is thought that the verbal aspect of the task tends to disappear or be less influential in this phase. The emphasis is on “how to perform” instead of “what to perform.” The first and second phases of learning are the most widely studied experimentally.

Third, the automatic phase is the result of prolonged practice of weeks to years depending on task difficulty. Now the attention requirements decrease and there is less interference during dual task performance. Improvement is moderate but continuous. Controlled studies are difficult to carry out for such a prolonged period. Therefore, this phase is often examined among expert performers such as professional musicians and athletes (Watson, 2006). For further review on
behavioral, computational, and biological interpretations of controlled and automatic processing see Schneider and Chein (2003).

Subsequent models of motor learning distinguish two main phases of learning: a fast experience-dependent phase that is followed by a slow phase in improvements lasting from weeks to months (Karni et al., 1998; Korman, Raz, Flash, & Karni, 2003). A study of Korman et al. (2003) found that in a sequential finger tapping task, there is a significant improvement in terms of speed and accuracy by the end of the first practice day (practice dependent improvement). Performance achieved on the first practice day further improved for the next day with no further practice (between-session improvement), with improvement being specific to the learned sequence. Therefore, this improvement was a function of time and not that of additional exercise. It led to a conclusion that motor memory formation continues beyond training sessions. Further long-term practice lasting for weeks led to additional practice-dependent (also called online) and between-session (also called offline) gains in performance that was specific both to the trained hand and sequence. That is, transfer of the learned sequence to the other hand or to a new sequence remains on a low level. In other words, a task and effector specific representation was formed as a result of the slow phase of learning (Korman et al., 2003).

I.3.2. The role of sleep in motor learning

Based on the above results, in the early 2000s several research groups raised that not only time but also the brain state the learner spends time in may have an impact on long term motor learning (Laureys, Peigneux, Perrin, & Maquet, 2002; Laureys et al., 2001; Maquet et al., 2003; Walker, Brakefield, Hobson, & Stickgold, 2003; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). Emphasizing the role of brain states/sleep in memory formation and further dividing behavioral stages, Walker and colleagues proposed a three-stage model (Walker, 2005; Walker, Brakefield, Seidman, et al., 2003; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). During acquisition, motor performance improves but motor memory is vulnerable. It is supported by the fact that practicing a new sequence 10 minutes after the original one results in
retained speed but decreased improvement in accuracy. On the other hand, learning the two motor sequences with a six-hour difference resulted in no interference between sequences. Not only speed but also accuracy improved in the case of both sequences. Walker and colleagues suggested that a stabilization phase occurs within six hours after acquisition. This first phase of motor memory consolidation as reflected by resistance to interference does not lead to performance improvement compared to the end of acquisition but leads to a resistance to interference with other tasks. It was found that the stabilization phase does not depend on sleep or wake state.

In the second phase of consolidation, called consolidation based enhancement, performance improves without any further practice: speed and accuracy of the learned motor sequence increases. A criterion for the enhancement in speed and accuracy is that a practice session should be followed by a daytime nap or a night of sleep (Fischer, Hallschmid, Elsner, & Born, 2002; Korman et al., 2007; Kuriyama, Stickgold, & Walker, 2004; Walker, Brakefield, Hobson, et al., 2003; Walker et al., 2002; Walker, Brakefield, Seidman, et al., 2003). Sleep deprivation following practice results in the lack of performance improvement. On the other hand, sleep, subsequent to deprivation results in further increases in motor performance, even after 72 hours. The majority of sleep-dependent (offline) improvement takes place during the first sleep after acquisition followed by moderate changes (Walker, Brakefield, Hobson, et al., 2003). Similar to the Karni and Korman model, this enhancement was specific to the learned sequence (Fischer et al., 2002) with more complex tasks and task components benefiting more from sleep (Kuriyama et al., 2004). Dissociation of practice dependent (online) improvement and sleep-dependent (offline) improvement was described both in TD and in clinical populations. That is, the amount of online improvement did not correlate with the amount of offline enhancement. The double amount of practice did not decrease or increase the magnitude of performance enhancement after sleep in TD adults (Walker, Brakefield, Hobson, et al., 2003). Moreover, in conditions with disrupted sleep, e.g. in schizophrenia (Manoach et al., 2004; Manoach et al., 2010), in sleep apnea patients (Landry, Anderson, Andrewartha, Sasse, & Conduit, 2014) and in older adults (Fogel et al., 2014) practice dependent learning is not different from healthy controls,
however, sleep-dependent off-line improvement is not present. Practice-dependent learning and overnight improvement are not correlated in TD and schizophrenia patients (Manoach et al., 2004; Manoach et al., 2010).

I.3.3. Correlation with sleep parameters

Performance improvement during and after acquisition shows interrelation with certain sleep parameters during motor learning. Macrostructural features, such as sleep efficiency or time spent in given sleep stages, characteristics of the power/amplitude spectrum or sleep oscillations such as sleep spindles and K-complexes may be related to learning variables (Diekelmann & Born, 2010; S. Fogel & Smith, 2006). These relationships may be explored by comparing sleep parameters of the night following learning to sleep parameters of an indifferent night. This comparison can be extended to the examination of clinical populations, superior/inferior learners and the effect of age or gender (King et al., 2016; Manoach et al., 2004). Recent studies also focus on the effects of sleep prior to acquisition on subsequent learning results (Appleman, Albouy, Doyon, Cronin-Golomb, & King, 2016). Brain activity in sleep is monitored by EEG during polysomnographic recording. Most recent approaches combine EEG recordings and brain imaging techniques (Fogel et al., 2017). Actigraphy is also a possible and affordable method to estimate certain sleep/wake characteristics during sleep (Sniecinska-Cooper et al., 2015).

An early study, investigating gross motor learning found positive correlation between learning ability and the length of the sleep cycle, REM and slow wave sleep (Buchegger & Meier-Koll, 1988). Early reports showed a role of REM stage in skill consolidation. During learning a perceptuo-motor task, SRT², influence of experience in the wake state was found on brain activity during sleep. PET was used to show the reactivation of brain areas active during learning the task in REM sleep that suggested a role of REM sleep in memory processing (Maquet, 2000). Blocking cholinergic activity during REM resulted in the lack of sleep-

² In detail see I.4.3.
dependent improvement in a motor task, but not in a declarative memory task (Rasch, Gais, & Born, 2009). Furthermore, a recent animal study showed that REM sleep plays a role in the selective pruning of newly formed postsynaptic dendrit spikes in the mouse motor cortex during learning and development (Li, Ma, Yang, & Gan, 2017).

The vast majority of studies, regarding the relationship between skill learning and sleep, focused on the role of NREM sleep in motor memory consolidation. In a visuomotor adaptation task that involves right parietal cortex for motor control task specific local changes in SWS were found after practice in this region (Huber, Ghilardi, Massimini, & Tononi, 2004). Alteration in 1-4.5 Hz oscillatory activity was more explicit in children than in adolescents and adults and was also correlated with brain maturation assessed by gray matter volume in this area. It was suggested that changes in SWS activity after practice (1-4.5Hz) could be used as a marker of experience-driven cortical plasticity (Wilhelm et al., 2014).

Sleep spindles are bursts of waxing and waning oscillatory activity in the sigma band (Hz). They show topographic distribution: slow spindles (11-13 Hz) dominate the superior frontal areas and fast spindles (13-15 Hz) dominate the sensorimotor areas, the mesial frontal cortex, and the hippocampus (Schabus et al., 2007). Apart from their role in sleep maintenance through the gating of sensory stimuli, the above results show their role in offline motor memory consolidation in NREM sleep (Fogel & Smith, 2006). Following motor task acquisition, the length of Stage 2 NREM and the amount of sleep spindles increased during sleep (Fogel & Smith, 2006) and offline improvement positively correlated with the amount of sleep in Stage 2 NREM sleep in the second half of the night (Walker et al., 2002). Following motor sequence learning, but not after non-specific motor activity, an increased number and duration of sleep spindles and an increase in sigma (13Hz) and beta (18-20Hz) activity were found (Morin et al., 2008). Specific sleep parameters, such as sleep spindles and spontaneous delta and fast-sigma oscillations in the SMA contralateral to the trained hand, especially during slow-wave sleep, have been shown to correlate with post-sleep improvement (Barakat et al., 2013; Barakat et al., 2011; Tamaki et al., 2013). This area specific effect may be related to the fact that SMA
pyramidal neurons are involved in the formation of the corticospinal tract that conveys information directly to the spinal cord interneurons, and motor neurons innervating hand muscles. SMA is also involved in the preparation of motor sequences and motor imagery training (Sharma & Baron, 2013; Zapparoli et al., 2013) that is sleep dependent (Debarnot, Creveaux, Collet, Doyon, & Guillot, 2009). The above effects are not independent from the age of the performer. In children, improvement in accuracy in a FT task was sleep-dependent while improvement in speed was not. Less slow spindles, more fast spindles and faster slow waves were associated with better performance. Children with lower initial performance but more slow spindles and slower slow waves improved in accuracy more overnight (Astill et al., 2014). Older adults showed practice dependent improvement but did not show sleep dependent improvement in a FT task. Striatal activity in older participants was decreased during the retention session and was also accompanied with decreased sleep spindle activity. There are results that suggest that the deficit in sleep-dependent motor memory consolidation in elderly individuals is related to a reduction in sleep spindle oscillations and to an associated decrease of activity in the cortico-striatal network (Fogel et al., 2014).

Animal study using single unit recording in motor cortex showed that offline improvement was associated with replay during sleep and temporal shift but only at the early learning phase until movement kinematics are established (Ramanathan, Gulati, & Ganguly, 2015). SWS and REM sleep are thought to have differential but complementary roles in memory consolidation. During SWS sleep hippocampus-dependent processes are reactivated including the neocortex. On the other hand, subsequent REM sleep plays role in local synaptic consolidation (Diekelmann & Born, 2010).

Sleep is demonstrated to be a major contributor of motor memory consolidation, with different sleep stages contributing to distinct memory processing. It raises the question that how motor learning is affected in disorders where sleep alteration is present.
I.3.4. Effect of atypical development or disease on sleep dependent motor learning

If motor learning has a sleep-dependent phase, it is expected to be altered in disorders that are accompanied with atypical sleep pattern. That is, alteration in neural activity during sleep may result in altered/decreased sleep-dependent learning. It is probable especially where changes in delta and sigma band activity in NREM sleep and changes in REM characteristics have been found, the stages involved in consolidation in TD. Alteration in certain sleep stages with failure of motor memory consolidation has been proved in disorders such as ADHD and major depression (Nishida, Nakashima, & Nishikawa, 2016; Saletin, Coon, & Carskadon, 2016). A common feature of these two disorders is the alteration in sigma band activity (12.4–16.4 Hz) that reflects sleep spindle activity as also seen in Williams syndrome (see I.5.4., page 44.) (Saletin et al., 2016) found that when individuals with attention-deficit hyperactivity disorder (ADHD) are trained on a sequential FT task, within-session improvement in speed is similar to that of healthy controls, and delayed gains are expressed at 24 hours and 2 weeks retention. On the other hand, there is no such improvement in accuracy. In ADHD, sleep is characterized by decreased power in the frequency band related to sleep spindles (12.4–16.4 Hz) in NREM2 sleep in the low spindle band (12–13.5 Hz), and more specifically in the fast spindle band (13.5–15 Hz). ADHD was associated with lower baseline performance but it reached TD performance after sleep. Greater offline improvement during the night was associated with higher relative power in the frequency band related to slow sleep spindles (13.5–15 Hz). That is, sigma band power closer to TD resulted in superior learning (number of finger taps in correct sequences in 30s is called as accuracy) among individuals with ADHD. Low sleep spindle activity and offline learning performance showed correlation only in ADHD but not in TD (Saletin et al., 2016).

In a study on patients with major depression, overnight learning was associated with slow frequency spindle activity both in TD and in depression, and alteration of slow frequency spindle activity (10.5-12.5 Hz) influenced motor sequence learning in medicated major depression (Nishida et al., 2016). Decreased learning improvement was found in schizophrenia
and major depression, but a combined fMRI and PSG method revealed a differential activity pattern based on disease.

The above studies suggest that alteration of NREM sigma band activity may be accompanied with impairment of offline memory consolidation in the motor domain, but the underlying patophysiological mechanisms may differ depending on disease.

While there is a robust literature supporting the role of sleep in motor memory formation in the last two decades, this question is still debated. Some studies question the presence of offline gains and attribute them to methodological factors such as inappropriate averaging of performance at certain points of the learning curve or reactive inhibition/fatigue (Brawn, Fenn, Nusbaum, & Margoliash, 2010; Pan & Rickard, 2015; Rickard, Cai, Rieth, Jones, & Ard, 2008). These problems are further addressed in section I.4.6. Exploration of the role of sleep in motor memory formation poses further difficulties by the wide variety of experimental paradigms used under the umbrella term „motor learning”. These paradigms may differ in cognitive load, spatial processing, and motor control requirements, e.g., sequential finger tapping tasks vs. motor adaptation tasks e.g., adaptation to a different external forces during task execution (Korman et al., 2003; Mantua, Baran, & Spencer, 2016); or in their implicit vs. explicit nature, e.g., finger tapping task vs. SRT, aSRT tasks (Kemény & Lukács, 2016; Németh et al., 2010; Rieth, Cai, McDevitt, & Mednick, 2010; Song, Howard, & Howard, 2007; Walker et al., 2005).

The last few years brought a new endeavor to map the impact of sleep along the above listed factors (Albouy et al., 2013; Kuriyama et al., 2004; Németh et al., 2010; Rieth et al., 2010; Song et al., 2007). There is also a new focus on the poorly understood effect of age and gender on sleep dependent motor learning (Dorfberger et al., 2009). Different task requirements lead to the involvement of different brain areas with different weighting across tasks even within upper limb movements (Doyon, Penhune, & Ungerleider, 2003). Therefore, task specific areas should be considered when local sleep-dependent changes are mapped during learning.
I.3.5. Brain imaging correlates of motor learning

The above learning stages are hallmarked not only by behavioral differences but also by the accompanying changes in the neural system. These changes are usually followed up by imaging techniques (PET, fMRI) and electrophysiological methods (EEG, single-cell recording, TMS) (Barbay et al., 2005).

The first studies using imaging techniques (PET) investigated how brain activity changes from the cognitive to the automatic stage of learning. Jenkins et al. (1994) and Jeuptner et al. (1997a; 1997b) found that at the beginning of learning with the non-dominant left hand, brain activity was widespread in the cerebral cortex including the anterior cingulate, premotor and supplementary motor cortex and certain parietal areas (Brodmann. 7, 40) bilaterally, accompanied with the contralateral activity in insula and primary motor cortex. Regarding the subcortical areas, the right caudate nucleus, putamen and globus pallidus in BG showed increased activity on both sides, accompanied by activity in the right insula and the motor cortex. Bilateral thalamic and cerebellar cortical activity come along with ipsilateral activity in the vermis and the cerebellar nuclei. That is, more widespread and more anterior cerebral cortical activity is characteristic when task demands are increased, e.g. attention and preparation for the next motor response is needed and decisions are made (Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; 1997; Jueptner, Stephan, et al., 1997).

When task execution becomes more automatic, activity patterns show a less widespread picture. Activity in the prefrontal cortex and anterior cingulate is decreased. Activity is shifted towards the motor cortices and parietal cortex. Such a posterior shift can also be observed in BG: the posterior part of putamen becomes active instead of the caudate nucleus and the putamen. Correspondingly, improvement in manual tasks was accompanied with reduced coherence across the motor network when measured with MEG or EEG (Mary et al., 2016; Serrien, 2009). In the following section I would like to review learning related changes in the three main sites of motor learning with an emphasis on motor cortical areas that are involved in motor control and learning of finger sequences (Jueptner, Stephan, et al., 1997).
I.3.5.1. Motor cortices

In the last three decades it became clear that M1 plays a role not only in movement initiation and execution but also in motor learning. Karni and colleagues (1998) were the first who studied performance related changes in M1 during learning a fine motor task. During learning a finger tapping sequence, M1 showed widespread activity at the beginning of the practice session that gradually decreased during practice. Activity changes were accompanied with improvement in speed and accuracy, followed by further improvement for the next day. Prolonged practice of three weeks resulted in a distinguished and increased activity pattern related to the learned sequence. The increased activity was present weeks after completing acquisition, and motor performance was not decreased even after a year. It was proposed that long term learning leads to a more specific and widespread activity in the motor cortex. It was consistent with the suggestion of Nudo et al. (1996) that motor learning results in the recruitment of M1 units into local networks that is specific to the learned sequence. That is, M1 is capable of coding complex motor patterns including those learned in adulthood. Two possible mechanisms were suggested to play a role in cortical plasticity in M1. The first is the disinhibition of the silent synapses in lateral connections that may subserve fast improvements in a short range. The second, the formation of new lateral connections between neurons is a slower process that may underlie developmental plasticity and the reorganization of cortical sites following injury.

The effect of long term learning has been studied in professional musicians because they usually start practicing on a daily basis in early childhood. An important part of musical training is motor learning that is accompanied by structural and functional changes in motor and sensory cortices, in the cerebellum and callosal system (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Gaser & Schlaug, 2003; Lee, Chen, & Schlaug, 2003; Schlaug, Jancke, Huang, Staiger, & Steinmetz, 1995). Furthermore, the length and shape of the precentral gyrus differs between musicians and non-musicians (Amunts et al., 1997; Bangert et al., 2006). Measured by diffusion tensor imaging, structural changes occur after four weeks (Wang, Casadio, Weber, Mussa-Ivaldi, & Parrish, 2014) but not two weeks (Kwon, Nam, & Park, 2012) of practice the corpus
callosum and the right hemisphere after training. Studies of musicians underlie the results of Jueptner et al. (1997; 1997) that show decreased activity outside M1 and increased activity within M1 when performance approaches a more automatic level (Lotze, Scheler, Tan, Braun, & Birbaumer, 2003). These results suggest that M1 codes longer complex motor sequences as a result of prolonged practice (Watson, 2006).

I.3.5.2. Basal ganglia

The basal ganglia nuclei show differential activity depending on task expertise. It was suggested that their peak activity may reflect the involvement of different frontostriatal loops and may be related to functional changes in the cerebral cortex. For example, the caudate nucleus shows strong activity when learning a novel motor task but not in automatic tasks (Doyon et al., 2009). It is proposed that this activity is related to mental rehearsal or to motor preparatory processing. Another role may be the reinforcement of motor output during learning (Jueptner, Frith, et al., 1997; Jueptner, Stephan, et al., 1997). The caudate nucleus is involved not only in motor but other serial tasks such as SRT or aSRT. The role of BG are also important in selecting and shifting between possible motor outputs. Successful motor execution results in dopamine release in the striatum that influences BG input and output by increasing the likelihood of choosing the “rewarded” movement (Gazzaniga, 2000). Blocking the anterior parts (associative region) of the striatum by the GABA antagonist muscimol leads to alteration in learning new motor patterns, whereas blocking the posterior (motor) parts results in difficulties when recalling already learned movements (Miyachi, Hikosaka, Miyashita, Karadi, & Rand, 1997). Furthermore, frontostriatal loops show differential activation as learning progresses: motor performance improvement is accompanied with decreasing dopamine release in the sensorimotor part of the globus pallidus and with increasing dopamine release in the interconnected preSMA. Although the role of such reciprocal function is not fully understood up to date, it supports the interaction of BG and frontal cortical areas during motor learning (Garraux, Peigneux, Carson, & Hallett, 2007). Other studies found somewhat contradictory results: the focal lesion of the BG due to stroke led to overall difficulty in performing RT tasks
regardless of its serial or non-serial nature but did not result in decreased learning ability. When BG lesion in stroke patients is accompanied with decreased preSMA and cerebellar volume, there exists a negative correlation with learning performance. It was suggested that BG function relates to overall procedural performance but may not impair learning capacity (Exner, Koschack, & Irle, 2002). While its role is still a subject of debate, it can be concluded that BG has a candidate role in motor performance and learning (Albouy et al., 2015; Doyon, 2008).

I.3.5.3. Cerebellum

There have been a number of models proposed regarding the role of cerebellum in motor control and learning since Marr (1969) and Albus (1971), using partly their theories. In pursuing the model of how the Purkinje-cells in the cerebellum learn, Kawato and colleagues (1992) proposed that the cerebellum takes part in the preparation of motor trajectories based on sensory information. While sending this information to M1, the cerebellum has an “efference copy” (parallel fibers) that is compared to sensory feedback from the executed movement. The difference between the planned and the executed movement gives an error that is signaled by climbing fibers, “teaching” Purkinje cells to minimize errors by inhibition. In humans and primates, cerebellar activity is more widespread at the beginning of learning and then gradually decreases (Jueptner, Frith, et al., 1997; Jueptner, Stephan, et al., 1997). Moreover, primate and cat studies show differential activity in the cerebellar cortex depending on whether the trial was correct or erroneous (Ojakangas & Ebner, 1992; Yanagihara & Udo, 1994). While motor learning is disturbed in cerebellar lesion, visuomotor learning or spatial memory tasks may not be influenced (Nixon & Passingham, 2000). At the same time, the blockade of the dorsal part of the dentate nucleus, which provides input to M1, caused problems in the reproduction of already learned movements but not in learning new movements (Lu, Hikosaka, & Miyachi, 1998).

Walker et al. (2005) measured brain activity following sequential motor task acquisition with the non-dominant left hand. 12 hours later, fMRI showed increased activity in the right M1, in medial prefrontal areas, the ventral part of the striatum and the hippocampus. Left cerebellar cortex activity was also increased in those who slept after practice compared to those who did
Activity was in turn decreased in the left insular cortex, the parietal lobe, and the fronto-polar and temporal areas after sleep. These changes may reflect decreased spatial monitoring and emotional load. They are also in line with previous results by Jenkins (1994), Jeuptner (1997; 1997) and Karni (1998) regarding brain activity alterations with the progression of the learning process with a link to the role of sleep in this process.

### I.3.6. Factors influencing motor performance during learning

Motor performance can be altered by a number of factors during acquisition, retention and transfer tests. One of these questions is that of schedule. It includes the planning and determination of the task to be learned, the amount and distribution of practice. When choosing a motor task, the aim of the study and the physical and cognitive characteristics of the population included should be taken into consideration. Difficulty should be adjusted in order to enable learning but avoid the ceiling/floor effect. Regarding distribution, massed practice (when the given amount of practice is not or less distributed but done in one/only few long session) may lead to performance decrements during practice (Schmidt & Lee, 2011). Fatigue or reactive inhibition may appear at the end of a practice block or training session and influence learning measures (Rickard et al., 2008). Another important factor is the type and frequency of feedback about the movement. Information of mechanoreceptors (muscles, tendons, skin, vestibular system) are naturally complemented by visual and auditory information. These sources of information can be augmented in several ways during acquisition depending on the goal and nature of the task. Type, presence or absence, and frequency of feedback fundamentally affect performance in motor tasks. These circumstances should be considered when different learning paradigms are compared against each other. Other factors that may influence motor performance or the appearance of learning effect and therefore should be taken into account are the following:

- Reactive inhibition: decay in performance due to fatigue during sustained practice. When practice is spaced (e.g., by 5-minute-breaks during practice) or training block are shorter this effect may diminish (Brawn et al., 2010). Recent models on the elimination of the effect of
reactive inhibition e.g. during statistical sequence learning provide promising opportunities for a more exact measurement of learning effect in the field (Torok, Janacsek, Nagy, Orban, & Németh, 2017).

– Time of testing: a circadian effect (time of the day) and homeostatic sleep drive (time since sleep) may influence sleep-dependent learning. E.g., performance in retention tests during early afternoon seems to be higher than in the evening (Pan & Rickard, 2015).

– Age: e.g., in the elderly, warm up is longer and the shape of the learning curve may be different. Therefore, we should consider what part of the learning curve to be compared (Pan & Rickard, 2015).

When considering training duration, we have to be aware of the power law of learning (improvement during learning follows a logarithmic function) when comparing improvement at different learning phases. When performance during early training is involved in baseline calculation, it reduces baseline values and promotes the appearance of the learning effect (Rickard et al., 2008).

I.4. Measurement of behavioral data during motor learning

The process of motor learning and motor memory formation is most often inferred from motor behavior. The approach of motor performance and motor learning differs in a sense that the study of learning focuses on the changes in performance as a function of practice/time (Schmidt & Lee, 2011). Motor learning is hallmarked by more accurate and fast motor execution as the learning progresses. At the same time, there should be no trade-off between speed and accuracy (Fitts, 1954) functions. It is a sign of learning if the execution of a movement becomes more precise or/and faster and the improvement of one function is not accompanied with the deterioration of the other (Dayan & Cohen, 2011).

I.4.1. Learning curves
The most widespread way of studying motor learning is the analysis of learning curves. They indicate performance changes as a function of practice or time (Dayan & Cohen, 2011). Performance measure is selected based on task e.g., accuracy/error, variability, speed, timing etc. Instead of analyzing performance trial by trial, averaging of individual or group data is often used to divide learning stages into major parts. Averaged data, however, do not necessarily reflect the shift in execution strategies and individual variability (Schmidt & Lee, 1999). Skill learning can be characterized by learning curves showing logarithmic function. While learning is continuous, the rate of learning decreases with a given amount of practice resulting in less and less performance gains (Murre & Chessa, 2011).

I.4.2. Retention and transfer

The ability to preserve the performance level reached during acquisition is called retention. It is measured by the so called retention test: performing the learned task under the same condition as in acquisition following the learning phase. It usually consists of more than one trial and the first trial may be of particular interest in some paradigms. Results may be expressed in absolute values or compared to the performance level reached by the end of acquisition.

Transfer is the effect of a learned task on the performance or learning of a new task. It can be negative, positive or indifferent. Transfer can be measured by performing a novel task or by analyzing the learning curve of a new task (Schmidt & Lee, 2011). In daily practice, positive transfer effect is desirable in e.g., rehabilitation settings. On the other hand, acquiring a task at a high level results in little or no transfer effect (Korman et al., 2003). The learned skills are often specific to basic parameters of the training e.g., limb position or motor trajectories. Such specificity of learning suggests that a limited number of neurons that are involved in task specific processing go through learning related changes. Therefore, the transfer test is also used to express the specificity of learning. Task specific representation in explicit sequential tasks is primarily thought to be related to motor cortices (e.g., M1, SMA, preSMA, PMC) and basal ganglia networks, accompanied with specific changes in the activation pattern in these areas (Debas et al., 2014; Debas et al., 2010; Karni et al., 1998; Lehericy et al., 2005; Muellbacher,
Ziemann, Boroojerdi, Cohen, & Hallett, 2001; Muellbacher et al., 2002; Nitsche et al., 2003; Walker et al., 2005). M1 is reported to be a likely site of task and effector specific representation of motor sequences in interconnection with parietal and premotor cortices (Karni et al., 1995). M1 is reported to be a likely site of task and effector specific representation of motor sequences in interconnection with parietal and premotor cortices (Penhune & Steele, 2012).

I.4.3. Motor sequence learning and the finger tapping paradigm

In the field of experimental psychology and human kinesiology the term “sequence learning” or “motor sequence learning” is applied in a number of paradigms.

<table>
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<tr>
<th>Knowledge of the sequence</th>
<th>Finger tapping</th>
<th>SRT</th>
<th>aSRT</th>
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<tbody>
<tr>
<td>explicit</td>
<td>implicit</td>
<td>implicit (may become explicit during practice)</td>
<td>implicit</td>
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<tr>
<th>Motor task</th>
<th>Finger tapping</th>
<th>SRT</th>
<th>aSRT</th>
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<tr>
<td>learning a finger sequence of varying lengths, usually as a continuous motor task</td>
<td>choosing and pushing the appropriate button from a given set (keyboard, response box, computer screen) corresponding to the presented sensory stimulus one at a time</td>
<td>choosing and pushing the appropriate button from a given set (keyboard, response box, computer screen) corresponding to the presented sensory stimulus one at a time</td>
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<tr>
<th>Variables</th>
<th>Finger tapping</th>
<th>SRT</th>
<th>aSRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>speed, accuracy, timing</td>
<td>RT, accuracy compared to random stimulus</td>
<td>RT, accuracy compared in low and high probability triplets/sequences of stimuli</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Tasks used to study sequence learning using finger movements
Regarding finger movements, FT, SRT and aSRT tasks are the most frequently used paradigms (Doyon et al., 2002; Karni et al., 1998; Song et al., 2007). While these tasks have common components, e.g., all use the flexion of hand fingers, there are several differences between them (Table 1).

FT is a fine motor task that has been used as a tool to address plasticity in the motor system (Doyon et al., 2002; Karni et al., 1995). In this task, the motor sequence is introduced to the performer. The goal is to perform a predetermined sequence with the fingers of the hand as accurately and as fast as possible. That is, a motor strategy is chosen to perform in the most effective way, and a sequence is built from muscle contractions that are not independent from each other. It is a continuous task, with ongoing planning and motor action. During learning, the spatial and temporal consistency of the sequence is formed.

SRT and aSRT tasks (Howard & Howard, 2001) are more implicit in nature, which means that the performer is unaware of the sequence presented during the task. Here, the main task is a reaction time task, selecting/coupling a usually visual or auditory (or other sensory) stimulus to a motor response. Response is given by choosing the appropriate finger to bend (e.g., press a key) to a given stimulus. Motor response is discrete; motor sequence is not formed from the elements. Knowledge of the learned sequence may become /or manipulated to become explicit during the course of learning an SRT (Robertson, 2007). Underlying neural mechanisms (Destrebecqz et al., 2005; Witt, Laird, & Meyerand, 2008), including involvement of sleep dependent mechanisms (Németh et al., 2010) may differ in the above tasks.
I.4.4. Measuring performance in the finger tapping paradigm

I.4.4.1. Development of the data glove

<table>
<thead>
<tr>
<th></th>
<th>Keyboard</th>
<th>Video</th>
<th>Data glove</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification of a tap</td>
<td>Digital</td>
<td>Visual judgement</td>
<td>Digital</td>
</tr>
<tr>
<td>Identification of a sequence</td>
<td>Digital</td>
<td>Visual judgement</td>
<td>Digital</td>
</tr>
<tr>
<td>Task duration</td>
<td>Digital</td>
<td>Analog</td>
<td>Digital</td>
</tr>
<tr>
<td>No visual motor control</td>
<td>Yes/No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Apparatus</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Free movement</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Movement</td>
<td>finger flexion</td>
<td>finger opposition</td>
<td>finger opposition</td>
</tr>
</tbody>
</table>

Table 2. Comparison of data acquisition methods in the FT paradigm

Several variations of the finger tapping task are known (Table 2.). In one type of the task, participants press buttons on a computer keyboard or a response box connected to a PC (Walker et al., 2002; Walker, Brakefield, Seidman, et al., 2003). Here, data acquisition and measurement of variables such as accuracy and speed are based on key presses. As a consequence of the fix positioning of the keys, there is little space for interindividual variability in motor execution that promotes controllability. However, the fix positioning of keys put different constraints on the performers of different anatomical characteristics due to development or disorder. Working in the extrapersonal space may cause difficulty for populations such as children or those with visuospatial deficit when the task is performed with no visual feedback (eyes-closed). Since we
intended to work with populations in a large age span and having visuomotor deficits, we had to
develop another method to measure motor performance in an FT task.

Another form of measurement in FT is the finger opposition task. Here, performers touch the
thumb with the other finger in a given order as accurately and fast as possible (Karni et al.,
1995; Karni et al., 1998). In this version of the FT task, no external cues and devices (such as
keyboard) are used. Participants use their hand free during execution. This task is usually
performed with closed eyes; the visual control of the movement is eliminated. Since this type of
task does not put external constraints on the learner, it seemed to be ideal to use with children
and persons with motor difficulties as well. Traditionally, data acquisition is performed by video
recording and the analysis of sequence is made by visual judgement of the experimenter.

In order to make the measurement method more objective and more automated in the finger
opposition task I have planned a new acquisition method that was called the „data glove”. It
combines the advantages of a data acquisition pad and free movement. It consists of metal
electrodes put on the distal phalanx of the fingers, the thumb and fingers II-V. have opposite
charge. When the index (1), middle (2), ring (3) or little (4) fingers are touched to the thumb,
the time and order of the taps can be identified (Fig.4.).

Figure 4. The data glove
I.4.4.2. Task considerations

Wide age span and participants with special needs made it necessary to reconsider the previously used sequence type. The number of elements and transition types in the motor sequence determine the complexity of the FT task. Previous studies usually used five-element-sequences or longer with transitions (switch between key presses) with varying difficulties (Adi-Japha, Badir, Dorfberger, & Karni, 2014; Dorfberger et al., 2009; Karni et al., 1995; Karni et al., 1998; Kuriyama et al., 2004). Children of younger age and participants with WS tend to have altered working memory characteristics compared to TD adults. Persons with WS tend to have a shorter digit span both in the verbal and visual-spatial domains (Pléh, Lukács, & Racsmány, 2003; Vicari, Bellucci, & Carlesimo, 2006). For this reason, the length of the sequence applied in the present study was shortened to four elements compared to the five-element-sequences used in previous studies.

Another characteristic of the task is that it is performed by eyes-closed in the learning phase. In intellectual disability, visual feedback may have a differential effect on performance compared to TD and the removal of visual input may enhance performance in, e.g., aiming tasks (Digby Elliott & Bunn, 2004). In WS, visuospatial difficulties have been shown in a number of tasks. We have considered that WS individuals have atypical processing in the visual domain while there has been no such report regarding other domains (Bellugi, Lichtenberger, Jones, Lai, & St George, 2000; Reiss et al., 2004). Therefore, keeping visual feedback unavailable may lead to similar feedback and learning strategies through TD and WS groups in the present study.

I.4.4.3. Variables to measure motor performance

Performance in FT tasks is characterized by speed and accuracy. In the present work, we used sequential but not temporal information for motor learning. Speed and accuracy measures are dependent on each other characterized by speed-accuracy trade-off (Fitts, 1954). Therefore, apart from measuring speed and accuracy separately we had to consider how these measures change together during learning, taking both measures into account.
In previous studies (Karni et al., 1998; Walker et al., 2005), the basis of the performance analysis was the sequence to be learned. Speed was measured as the number of sequences carried out in a given time (e.g., number of sequences/30s). Accuracy/error was characterized by either (1) the number of erroneous sequences/all sequence or (2) the number of correct sequences in a given time. A major problem with the above method is that there was no exact characterization of what is considered to be a sequence/erroneous sequence and how these are identified. In the case of the TD adult population it may not have been an important issue since accuracy of the learners was high and errors were low. Therefore, a small number of erroneous sequences, that may have had different length within and between participants, did not influence results in a great extent. Previous studies probably used this supposition when measuring performance (Walker et al., 2003).

During the preparation of the present study, motor performance showed great variability both in speed and accuracy in the 5-30-year-old TD population and in WS individuals. Our experience was that there was a great difference in sequence length when making errors. Sequences could be 1 to more than 10 elements (finger taps) long. It raised the need for measuring performance based on finger taps rather than on sequences in order to make performance evaluation more precise and comparable among our participants.

**Accuracy** was defined as the ratio of the number of finger taps in correct sequences and all finger taps (%). Each finger corresponded to a number as follows: index finger – 1, middle finger – 2, ring finger – 3, little finger – 4. A sequence was identified from the first element of the sequence to the next first element. For example, when a sequence of „1324” was the task, sequences were identified and separated as follows: 1324-1324-13224-13-1324-1324.

**Speed** was defined as the number of finger taps in a second (taps/s).

**Performance rate** was calculated as multiplication of accuracy and speed (taps/s) as a combined measure of speed and accuracy.

**Maximum motor speed** was defined as number of finger taps in a second (taps/s).
**Corrected tap interval.** Initial speed in this task also relies on the age of the performer (Dorfberger et al., 2009), most probably due to the myelination level of the corticospinal (CS) tract (Bartzokis et al., 2010). Apart from the age effect, motor speed in FT task may be altered in WS due to atypical myelination of the CS tract. Since the removal of such an effect was desirable, I introduced a measure that was not previously used in the field in order to get a closer measure of cortical/brain related changes during development and learning. The effect of age and myelination level of the CS tract was minimized by taking into account both sequential FT speed and maximum motor speed, the latter being related to conduction velocity of the CS tract. That is, speed was corrected by maximum motor speed in the following way: first, we calculated the FT tap interval as 1/speed (s), then subtracted the tap interval gained as 1/maximum motor speed (s) from it.

To further eliminate the speed/accuracy trade-off, we used a combined measure of corrected tap interval and accuracy. It was the **corrected performance rate (PR)** calculated as the sum of Z-scores of the corrected tap interval and accuracy measures based on TD age group data. Thus, we gained a PR measure that is both corrected for speed-accuracy trade-off and myelination effect of corticospinal tract providing a closer measure of motor cortex related changes during motor learning.

**I.5. Williams syndrome**

**I.5.1. Overview of Williams syndrome**

Williams syndrome (WS) is a rare developmental disorder due to a microdeletion on one copy of chromosome 7 in the q11.23 region. The deletion is continuous in 99% of WS individuals and involves approximately 25 genes including the gene for coding elastin. Its prevalence is estimated between 1 in 7500-20,000 births (Stromme, Bjornstad, & Ramstad, 2002). The main physical symptoms of WS include growth retardation, distinct facial appearance, cardiovascular, endocrine and gastrointestinal abnormalities. These symptoms are at least in part related to the altered coding of the connective tissue protein, elastin. Altered mineral metabolism and
transient hypercalcemia was found in childhood (Morris, 1993; Morris, Lenhoff, & Wang, 2006). Gene candidates involved in neuron development such as “frizzled 9” (FZD9) (Chailangkarn et al., 2016) and genes involved in migration and white matter formation such as LIMK1 and CYLN2 are involved in WS (Marenco et al., 2007).

I.5.2. Neurological and neuroanatomical findings in WS

The neurological status of individuals with WS is not static along the lifespan. Muscular hypotonia, failure to thrive is present after birth. Cerebellar and extrapyramidal soft signs are characteristic with extrapyramidal signs such as muscle rigidity and tremor increasing with age especially after 14 years of age in males (Chapman, du Plessis, & Pober, 1996; Gagliardi, Martelli, Burt, & Borgatti, 2007). Pyramidal sign of hyperreflexia may be present (Pober, 2010; Pober & Morris, 2007). Premature ageing has been suggested due to neurological and sleep EEG findings in WS (Bódizs, Gombos, Gerván, et al., 2014; Gagliardi et al., 2007). An atypical sleep pattern has been recently reported (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2013; Bódizs, Gombos, & Kovács, 2012; Gombos, Bódizs, & Kovács, 2011; Mason, Arens, Sharman, Pack, & Kaplan, 2009; Mason et al., 2011).

WS is characterized by an altered cerebral shape (Schmitt, Eliez, Bellugi, & Reiss, 2001), a decreased brain and cerebral volume but a relative preservation of cerebellar volume. Decreases in white matter and relative preservation of cerebral cortical grey matter with a greater frontal to parietal ratio in cortical thickness was found compared to TD (Reiss et al., 2000). The latter is due to reduction in occipital and parietal grey matter volumes (Osorio et al., 2014; Reiss et al., 2004; Reiss et al., 2000). Subcortical grey matter in the hippocampus and basal ganglia is decreased. Gyrification and sulcal depth is also altered – i.e., increased in a number of cerebral cortical areas but preserved in part in motor regions (Gaser et al., 2006; Kippenhan et al., 2005; Thompson et al., 2005). Superior parietal lobe gray matter volume is decreased that may underlie visuospatial and visuomotor problems (Eckert et al., 2005). An association between functional abilities and grey matter structures in cerebrum and cerebellum has been found including visual spatial and visuomotor domains (Menghini et al., 2011). Foti et al. (2013)
suggested that structural deficits in bidirectional interconnections of the basal ganglia and the cerebellum with cortical structures may cause inability to reach the automatization phase in a visuospatial motor task in WS.

Regarding connectivity between different brain regions, the thickness and shape of the corpus callosum is different in WS when measured by structural MRI. Decreased and altered curvature, reduced thickness of the corpus callosum, but increased relative thickness compared to length was found (Sampaio et al., 2013). Furthermore, resting state connectivity measured by fMRI shows decreased levels of within-network connectivity in the somatomotor network compared to TD (Vega, Hohman, Pryweller, Dykens, & Thornton-Wells, 2015).

On the cellular level, neurons had longer dendrites with more dendrite spines and synapses in cortical layers V/VI. It was accompanied by altered calcium transport and network connectivity in a human induced pluripotent cell model (Chailangkarn et al., 2016). Nevertheless, these abnormalities may not be evenly represented throughout the cerebral cortex. Neuron density in layers II/III and V/VI of the cerebral cortex has been found similar in WS and TD regarding the primary motor cortex and has an increased density in the somatosensory cortex (Lew, Brown, Bellugi, & Semendeferi, 2016).

I.5.3. Cognitive characteristics in WS

WS is usually associated with mild to moderate intellectual disability. Full scale IQ is between 40 and 90 (Bellugi et al., 2000; Howlin, Davies, & Udwin, 1998). The cognitive profile is typically described by certain strengths and weaknesses. Strengths include relatively good abilities in the verbal domain, recognition of faces, and auditory processing (Bellugi et al., 2000). Friendliness and sociability are characteristic features (Karmiloff-Smith, Klima, Bellugi, Grant, & Baron-Cohen, 1995). While these socio-cognitive abilities are relatively intact, some underlying processing may be atypical (D'Souza et al., 2015). On the other hand, inattention (Costanzo et al., 2013; Menghini, Addona, Costanzo, & Vicari, 2010), hyperactivity and anxiety are present. Furthermore, individuals have difficulties in reading and writing and have deficits
in visuospatial abilities (Foti et al., 2013; Jarrold, Baddeley, & Hewes, 1998). During spatial judgements the performance of WS individuals lagged behind age-matched TD individuals both in egocentric and allocentric conditions (Bernardino, 2013). On the other hand, spatial coding uses more egocentric than allocentric information during navigation but it may improve with age. Building spatial relations during pathfinding remains difficult even after extensive practice (Broadbent et al., 2014; Broadbent, Farran, & Tolmie, 2014, 2015). Spatial working memory performance lagged behind TD during spatial sequence learning but it may benefit from observational learning strategies in WS (Foti et al., 2013). Spatial deficits extend to binocular depth perception and control of movement (Hudson & Farran, 2014).

Planning and implicit learning is affected in WS (Don, Schellenberg, Reber, DiGirolamo, & Wang, 2003; Menghini et al., 2010; Vicari, 2001; Vicari, Bellucci, & Carlesimo, 2001). Procedural memory is affected in a number of tasks (Bellugi et al., 2000). On the visual level, both baseline and learning capacity were decreased during long term learning of a contour integration task involving low level processing in V1 (Gerván, Gombos, & Kovács, 2012). Learning playing a string instrument was also affected (Lense & Dykens, 2013). The lifelong presence of fine motor problems may also suggest the involvement of procedural memory.

1.5.4. Sleep in WS

Sleep problems are common in WS. While individuals with WS may spend a sufficient amount of time in bed during the night, they report sleepiness during the day. Prevalence reaches 40% in sleep latency, and 97% regarding sleep maintenance in school-aged children (Goldman, Malow, Newman, Roof, & Dykens, 2009). Although sleep problems may improve with age (Annaz et al., 2011), an atypical sleep pattern has been reported including WS in various age groups (Annaz et al., 2011; Ashworth et al., 2013; Gombos et al., 2011; T. B. Mason et al., 2011).

When sleep was investigated by questionnaires, actigraphy or PSG recordings, delayed sleep onset (Annaz et al., 2011; Ashworth et al., 2013), frequent awakenings (Annaz et al., 2011;
Ashworth et al., 2013), reduced sleep efficiency and increased wake after sleep onset were found (Gombos et al., 2011; Mason et al., 2011). Macrostructural alterations included reduced sleep cyclicity, reduced REM sleep (Gombos et al., 2011), altered frontal delta wave and region independent decreased alpha activity. Sigma wave activity was decreased in the low (<13 Hz) and increased in high (>13 Hz) frequencies (Bódizs, Gombos, Gerván, et al., 2014; Bódizs et al., 2012; Bódizs, Gombos, Szöcs, et al., 2014; Mason et al., 2009; Mason et al., 2011). It was proposed that the dysregulation of the sleep-wake cycle is related to increased cortisol and decreased melatonin levels at bedtime (Sniecinska-Cooper et al., 2015). The above sleep related issues are suggested to have a role in attentional (Ashworth, Hill, Karmiloff-Smith, & Dimitriou, 2015) and behavioral problems during daytime (Santoro, Giucheti, Rossi, Campos, & Pinato, 2016). As a result, learning abilities (Annaz et al., 2011; Santoro et al., 2016) may be decreased due to disturbance in sleep dependent memory consolidation (see Thesis IV. page 52).

I.5.5. Motor development and motor behavior in WS

Motor symptoms are present from early on. Developmental milestones in early childhood such as rolling, crawling, sitting, standing and walking are shown to be achieved later than in typical development (Carrasco, Castillo, Aravena, Rothhammer, & Aboitiz, 2005; Gagliardi et al., 2007; Tsai, Wu, Liou, & Shu, 2008). Decreased muscle tone seems to be present from early age, which may be associated with late motor development and difficulties in trunk control necessary to upper extremity function. Muscle tone may change during development and tends to increase into adulthood resulting in muscle rigidity, especially in males (Gagliardi et al., 2007). Muscle hypotonia may further lead to secondary musculoskeletal deformities such as scoliosis and joint contractures later in life. Altered mineral metabolism also affects bone metabolism causing decreased bone mineral status (Stagi et al., 2016). Radioulnar synostosis may be present at birth (Pober, 2010; Pober & Morris, 2007). Fine and gross motor dysfunction, clumsiness, deficits in motor coordination have been common findings (Gagliardi et al., 2007; Pagon, Bennett, LaVeck, Stewart, & Johnson, 1987; Trauner, Bellugi, & Chase, 1989). While motor deficits
have been known for decades, research on motor function emerged only in the last decade. Studies on motor function in WS focused on two main topics: the control of visually guided movement and the control of posture and gait.

In a series of experiments, Hocking et al. investigated gait characteristics of individuals with WS. They found hypokinetic gait with reduced speed and stride length. As speed increased, stepping frequency increased disproportionately (Hocking, Rinehart, McGinley, & Bradshaw, 2009). Such gait pattern may suggest basal ganglia-parkinsonian deficits in the internal regulation of stride length (Hocking, McGinley, Moss, Bradshaw, & Rinehart, 2010). When stride length had to be adapted (lengthened) to either internally or to external visual cues, participants with WS showed reduced speed and increased intra-individual variability compared to controls with DS and typical development (Hocking et al., 2010). During obstacle crossing, individuals with WS also showed late adjustments in foot positioning to spatiotemporal gait constraints (Hocking et al., 2009). Difficulties with walking in various/different terrain have also been reported. When descending stairs with variable height, people with WS present with dysmetria (Cowie, Braddick, & Atkinson, 2012).

Motor performance has also been examined regarding arm and hand movements. During visually guided reaching, rapid arm movements were slowed and accompanied with more online correction than those in other developmental problems and in typically developing people. The removal of visual feedback had the same impact on performance in visually guided reaching in WS as in other neurodevelopmental delays (Elliott, Welsh, Lyons, Hansen, & Wu, 2006). The performance of people with WS has been slowed, and time on target increased as task difficulty increased in a reciprocal aiming task. Testing visuomotor integration resulted in a performance level of a 5-year-old TD child (Heiz & Barisnikov, 2016). Gait and coordination abnormalities persist among older subjects, indicating that these are not simply maturational problems (Chapman et al., 1996). These coordination deficits have been attributed either to cerebellar dysfunction (Hocking, Rinehart, McGinley, Moss, & Bradshaw, 2011), or to the dysfunction of
the parietal lobe in the visual guidance of movement (Cowie et al., 2012; Elliott et al., 2006; Hocking et al., 2011).

Handedness develops late in WS, around the age of 5 to 8 years. Mixed handedness (Bellugi et al., 2000) or less right hand and right foot preference was found compared to TD (Carlier et al., 2011; Gerard-Desplanches et al., 2006). The fact that inconsistent laterality and brisk deep tendon reflexes do not change by age (Gagliardi et al., 2007) may suggest a deficit in cortical motor control. On the other hand, reduced curvature and thickness of the corpus callosum (Schmitt, Eliez, Warsofsky, Bellugi, & Reiss, 2001; Tomaiuolo et al., 2002) may also play a role in less differentiated handedness. Altered myelination of the corticospinal tract (Marenco et al., 2007) may also influence speed of voluntary movements resulting in decreased speed in WS. The above characteristics on motor development and motor control in WS suggests that fine motor performance and learning would be affected in WS (see Thesis III. page 52).
II. Theses

Thesis I. Age and gender related characteristics of fine motor development as measured by the finger tapping task

First I mapped the developmental trajectories of fine motor performance in typical development. I hypothesized that the accuracy and speed of finger movements improve with age from childhood to adulthood both in simple repetitive and sequential tasks, however, gender differences in development may also be present, and may be dissociated in simple repetitive and sequential tasks (Study I. page 55, Study III. page 79 and Study V. page 104.).

The two tasks were a repetitive index finger tapping task and a sequential finger tapping task. Performance was measured by a self-designed data gloves providing advanced and reliable tools for assessments in developmental and clinical populations. The data gloves are novel in the field of fine motor movement assessments in the finger tapping task, and contribute an important technical development to the field (see I.5.4.1.).

Since CS tract development influences motor speed (see I.2.1.), and I attempted to examine motor skill development related to brain development, i.e., motor cortex development, I introduced a new measure of motor performance. I corrected the speed in sequential motor performance by the speed in the repetitive task that is related to CS tract maturation (see I.5.4.2.). This provided a better measure of motor performance based on cortical development.

Developmental trajectories of repetitive and sequential finger movements were characterized first in a large sample of TD children, adolescents and adults (n=80) between 6-30 years of age (Study I.). I found that fine motor performance is improving with age until adulthood both in the index finger tapping task (Study I.Fig.3.A. page 60; Study I. addendum page 64), and in the sequential finger tapping task (Study I.Fig.2.B. page 59). When motor performance was corrected for index finger tapping speed, initial performance still increased until adulthood
suggesting the involvement of brain structures such as motor cortices in development (Study I. Fig. 3.B. page 60, Study I. addendum page 64).

While it did not reach statistical significance, the developmental trajectory showed an unexpected peak at early puberty with respect to baseline performance in different age groups (Study I. Fig. 2.B. page 59). Therefore, the investigation of the combined effect of age and gender seemed to be an important next step. I expected a marked female advantage in both sequential and repetitive tasks. 118 males and females between the ages of 10 to 20 participated in the study (Study III. and Study V.). Index finger tapping with both hands and sequential finger tapping with the non-dominant left hand was measured. I found that fine motor performance in females is ahead of males at the age of 10 years and performance reaches a plateau at the age of 14 years both in sequential and repetitive tasks (Study V. Figure 2. page 64, Figure 4 page 64 and Study III. Fig 2.B. page 83). However, males continued baseline improvement even after 16 years of age in the simple repetitive FT task (Study V. Figure 2. page 64). These results are in accordance with previous studies demonstrating a male advantage in simple repetitive movement tasks from adolescence on.

**Thesis II. The development of fine motor learning**

With respect to the developmental aspects of motor plasticity, I hypothesized a continuing learning capacity until adulthood. My research question targeted the developmental trajectories of learning from childhood to adulthood, between 6 to 30 years of age (Study I. and Study II.). I found that improvement gains were marked in the fast phase of learning, then the speed of learning slowed down in all age groups during the course of a five-day learning period in the finger tapping task. Performance gains were greater in childhood and early adolescence (Study I. Fig. 2.B. page 59 and Study I. Fig. 3.B. page 60, Study I. addendum page 65). Baseline performance and the amount of learning exhibited a strong negative correlation. Learners with low initial performance presented the greatest improvement (Fig. 5.A. page 74).
Thesis III. Fine motor skills in Williams syndrome

I hypothesized that motor performance in finger tapping in Williams syndrome is below the TD level both in repetitive and sequential tasks. The hypothesis is motivated by the fact that there are fine motor difficulties and also sleep problems in Williams syndrome. I expected impaired learning capacity both in terms of speed and accuracy that, in turn, may be associated by the disordered sleep characteristics in WS. I studied baseline performance and learning capacity during a five-day practice in a sequential task in WS (n=11) and compared their results to TD baseline and learning characteristics (Study II.). I found that both baseline performance and learning capacity lagged behind TD, but WS participants showed a great individual variability in both measures (Study II., Fig.2. page 71). I also found that impaired performance in terms of speed was not due to speed decrements associated with altered CS tract myelination. WS participants reached a speed maximum in the sequential task, in other words, speed and accuracy dissociated during learning, with speed not improving, and accuracy improving during the five days learning period (Study II., Fig.3. page 72).

Thesis IV. Sleep dependent learning in Williams syndrome

I hypothesized that altered sleep characteristics lead to impaired learning capacity in WS (Study IV.). This study tested if the formerly reported specific alterations of broadband sigma (8-16 Hz) activity in WS (see I.5.4. page 44) are associated with deficits in offline fine motor learning. Speed and accuracy were studied separately, since in Study III. there was lower baseline and impaired learning in WS regarding especially in speed during a five day learning session. Baseline and online/offline performance changes were correlated with sigma activity measures in NREM. It was found that WS individuals with the smallest decrease in z-normalized low sigma power present the highest offline gains in motor accuracy. Moreover, accelerated sigma peak frequency correlated negatively with offline motor accuracy gains. I also found a positive correlation between the z-normalized low sigma power and online gains in
motor speed (Study IV, Fig. 4., page 92). These results support previous studies showing an
association between NREM sigma frequency activity and motor learning and provide evidence
that the alteration of neural activity in this frequency band may lead to impaired learning in the
motor domain. Furthermore, among individuals with a neurodevelopmental disorder,
characteristics of sigma band activity closer to that of TD resulted in superior learning, with
retained/higher slow sigma activity being associated with higher offline improvements.
III.  Studies


IV. Berencsi, A., Gombos, F., László, S., Bódizs, R. & Kovács, I. Sigma frequency dependent motor learning in Williams syndrome. *Accepted for publication in Scientific Reports*.

Study I.

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.

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 intra-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 MRI [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 function 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.

**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 (8x; where \( \lambda \) 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°, 5°, 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

| Table 1. Age groups of participants in the CI and FT tasks. |
|-------------------|-----------------|-----------------|-----------------|
|                  | Age group      | CI task         | FT task         | R/L handed     |
|                  | Age (mo)       | Age (mo)        | Age (mo)        |                |
|                  | M               | F               | M               | F               |                |
| 7 years          | 89.4            | 5               | 84.9            | 6               | 4              | 9/1            |
| 9 years          | 103.6           | 4               | 100.8           | 4               | 5              | 7/2            |
| 11 years         | 132.5           | 5               | 132.6           | 5               | 5              | 9/1            |
| 13 years         | 153.6           | 6               | 150.5           | 5               | 5              | 9/1            |
| 15 years         | 176.1           | 5               | 173.2           | 4               | 5              | 7/2            |
| 21 years         | 249.6           | 5               | 246.5           | 5               | 5              | 9/1            |

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set to 1280×1024. Images subtended 19.97° 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/m².

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 1-2-2-1 (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 were very relevant to carry out in FT in order to see whether prolonged or multisection learning involves use-dependent changes in connectivity within the neuronal populations in the primary motor cortex, in which case, lateralized motor representation results that are 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 – 1-3-2-4 – 1-3-2-4 – 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 combination of performance ratio (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 x 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 x age x 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(4,210)=156.43, p<0.01). These data confirm that contour integration has a slow developmental course as it has been indicated earlier [38]. 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(20,210)=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.
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) = 24.05, p < 0.01). These results are in accordance with previous findings, where a developmental 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 [39,38,40,53,34], 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 [53]. 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 [42,46–50] 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 (7y: 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
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 ($F_{1,27} = 14.74$, $p<0.01$) and learning condition ($F_{2,106} = 30.45$, $p<0.05$) with significant age×learning condition interaction ($F_{2,106} = 6.13$, $p<0.05$). We found significant differences between CI and FT performance at age 7 (CI z-score = $-1.264$, FT z-score = $-5.2053$, $t = -5.190$, 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 ($t = -2.413$, 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
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 seems to exist, 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(138,115),(661,587) 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 predominately 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 neuronal 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 GABAeric mechanisms in postmortem tissue have shown that the relevant changes start to occur between the ages of 10 and 13 years of age [68]. Although there are no postmortem studies on GABAergic mechanisms in the motor cortex, it has been shown that both N-methyl-
Dysparapal 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 maturation 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.

References

Addendum to Study I.

For the examination of Thesis I., additional statistical analysis on the data of Study I. was performed.

Performance rate (Study I. Figure 2.B.)

Two-way mixed model ANOVA (age × day) performed on performance rate data showed significant main effect of age ($F_{5, 52} = 10.76, p < .01$) with significant main effect of day ($F_{4, 208} = 248.05, p < .01$) and day × age interaction ($F_{4, 20} = 1.81, p < .05$). Significant simple main effect of age was present at all practice days ($p < .01$). Furthermore, main effect of day was significant at all age groups ($p < .01$).

On the first practice day, 7-year-old group had the lowest baseline performance compared to other age groups ($p < .05$). There was no significant difference between 9, 11 and 13 years old children ($p > .05$). 15 and 21 year-old groups showed superior performance compared to other groups ($p < .05$).

Correlation of index finger tapping speed with age (Study I. Figure 3.A.)

Index finger tapping speed significantly correlated with the age of the performer ($R^2 = 0.6251, p < .05$) between 7 and 21 years of age.

Corrected intertap interval (Study I. Figure 3.B.)

Two-way mixed model ANOVA (age × day) indicated significant main effect of age ($F_{5, 52} = 10.76, p < .01$) with significant main effect of day ($F_{4, 208} = 27.97, p < .01$) with a marginally significant main effect of age ($p=0.069$) and no significant day × age interaction ($p > .05$).
On the first day, 7-year-old participants showed lower performance than 13, 15 and 21-year olds (p < .05) but not differed significantly from 9 and 11-year-olds (p > .05). 21-year-old participants had superior performance compared to other age groups (p < .05).

Rate of learning (Study I. Figure 4.)

Two-way mixed model ANOVA (age × learning etap) performed on the rate of learning (using corrected intertap interval data as a ratio to day 5 performance of 20-year-old group) showed significant main effect of age (F\textsubscript{5, 52} = 10.971, p < .01) with significant main effect of etap (F\textsubscript{3, 156} = 35.852, p < .01) and age × learning etap interaction (F\textsubscript{15, 156} = 8.585, p < .05). 7-year-old participants showed significantly greater improvement than other age groups (p < .05) and the improvement was the highest in the first learning etap (from Day 1 to Day 2) (p < .05). Rate of improvement decreased by increasing age and the number of etaps (p < .05).
Study II.

Special Issue

Capacity to improve fine motor skills in Williams syndrome

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Abstract

Background Individuals with Williams syndrome (WS) are known to have difficulties in carrying out fine motor movements; however, a detailed behavioural profile of WS in this domain is still missing. It is also unknown how great the capacity to improve these skills with focused and extensive practice is.

Method We studied initial performance and learning capacity in a sequential finger tapping (FT) task in WS and in typical development. Improvement in the FT task has been shown to be sleep dependent. WS subjects participating in the current study have also participated in earlier polysomnography studies, although not directly related to learning.

Results WS participants presented with great individual variability. In addition to generally poor initial performance, learning capacity was also greatly limited in WS. We found indications that reduced sleep efficiency might contribute to this limitation.

Conclusions Estimating motor learning capacity and the depth of sleep disorder in a larger sample of WS individuals might reveal important relationships between sleep and learning, and contribute to efficient intervention methods improving skill acquisition in WS.

Keywords fine motor, finger tapping, motor learning, sleep efficiency, Williams syndrome

Introduction

Williams syndrome (WS) is a rare neurodevelopmental disorder because of a microdeletion on chromosome 7 in the q11.23 region involving approximately 25 genes. WS is usually associated with mild to moderate intellectual disability. Individuals may show relatively good abilities in the verbal domain and in the recognition of faces. On the other hand, deficits in visuospatial abilities are also present (Jarrold et al. 1998; Belfugi et al. 2000; Foti et al. 2011). The main physical symptoms include growth retardation, distinct facial appearance, cardiovascular, endocrine and gastrointestinal abnormalities. WS can be associated with skeletal problems such as hyperextensible joints, joint contractures, and scoliosis or radioulnar synostosis (Morris et al. 2006; Pober & Morris 2007; Pober 2010). Neurological signs such as hyperreflexia and increasing cerebellar and extrapyramidal soft signs by age may be present (Gagliardi et al. 2007; Pober & Morris 2007).

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An atypical sleep pattern has been reported in WS, including sleep macrostructural and microstructural alterations. Sleep fragmentation, frequent awakenings, decreased sleep efficiency, total sleep time and rapid eye movement (REM) sleep, increased slow wave sleep (SWS) and sleep latency are characterising the sleep in WS (Arens et al. 1998; Goldman et al. 2009; Annaz et al. 2011; Gombos et al. 2011; Mason et al. 2011; Bodizs et al. 2012; Ashworth et al. 2013). An increased number of leg movements during sleep (Arens et al. 1998; Gombos et al. 2011), and fragmented and disorganised sleep cycles were also reported (Gombos et al. 2011). Moreover, microstructural differences were found in the non-REM (NREM) sleep EEG of WS patients, increased frontal delta activity and region-independently decreased alpha and sigma activity, as well as accelerated sigma peak frequencies were shown (Gombos et al. 2011; Bodizs et al. 2012; Bodizs et al. 2014b). Accelerated age-dependent declines in sleep efficiency, steeper age-related rises in wakefulness, and wake after sleep onset and REM sleep time refer to premature ageing in WS (Bodizs et al. 2014a). The sleep regulating melatonin and cortisol metabolism is possibly disturbed in WS: a reduced decrease in cortisol and a smaller increase in melatonin levels at bedtime, and an increased cortisol level before bedtime were found as compared to controls (Sniecinska-Cooper et al. 2015). From our perspective, which is the perspective of looking at motor learning capacity, it is very relevant that numerous studies found sleep obligatory/beneficial for off-line improvement of explicitly learned motor sequences (Fischer et al. 2002; Walker et al. 2003).

Motor symptoms are present from early on in WS. Developmental milestones in early childhood are shown to be achieved later than in typical development (TD) (Kataria et al. 1984; Carrasco et al. 2005; Gagliardi et al. 2007; Tsai et al. 2008). Decreased muscle tone seems to be present from an early age. Motor dysfunction, clumsiness and deficits in motor coordination have been common findings (Trauner et al. 1989; Elliott et al. 2006; Gagliardi et al. 2007). Regarding gross motor function, altered gait and difficulties in the adaptation of walking and stair descent have been found (Hocking et al. 2009; Hocking et al. 2010; Cowie et al. 2012). Performance in visually demanding motor tasks has been reportedly low (Hocking et al. 2011b; Foti et al. 2013).

During reaching, rapid arm movements were accompanied with more online corrections (Elliott et al. 2006). In WS, handedness may develop later, and mixed handedness and less right hand and right foot preference can be found compared to TD (Carlier et al. 2006; Gerard-Desplanches et al. 2006; Carlier et al. 2011). In the above studies, movement speed has been found to slow during various types of movements in WS (Elliott et al. 2006; Hocking et al. 2009; Hocking et al. 2010; Hocking et al. 2011b).

Based on the above behavioural findings, dysfunction in numerous motor related brain areas has been suggested in WS. Coordination deficits have been attributed either to cerebellar dysfunction or to the dysfunction of the parietal lobe in visual guidance of movements (Elliott et al. 2006; Hocking et al. 2008; Hocking et al. 2011b; Cowie et al. 2012). Gait pattern revealed basal-ganglia-disorder-like pattern (Hocking et al. 2011a). Neuroanatomical findings in cerebellum and basal ganglia, and occipito-parietal cortex in WS (Reiss et al. 2006) may underlie these hypotheses. Furthermore, inconsistent laterality and brisk deep tendon reflex (Gagliardi et al. 2007) may suggest deficit of cortical motor control in WS. On the other hand, altered myelination of the corticospinal tract (Marenco et al. 2007) may also influence speed of voluntary movements in individuals with WS. The persistence of fine and gross motor deficits into adulthood raises the question whether motor learning abilities are affected in WS. In the course of learning, movement economy of both speed and accuracy of movement improves over time. Improvement follows a logarithmic curve with fast initial improvement followed by slow changes in performance. The fast stage and the slow stages of learning of a serial motor task have been associated with distinct changes in activation patterns in numerous cortical and subcortical areas (Karni et al. 1995; Floyer-Lea & Matthews 2005; Lehericy et al. 2005; Dayan & Cohen 2011). Interaction between functional circuits such as cortico-striato-thalamo-cortical loop and cortico-cerebello-thalamo-cortical loop (Doyen et al. 2003) or frontoparietal-associative striatum-cerebellar circuit and M1 sensorimotor striatum-cerebellar circuit (Hikosaka et al. 2002) has been hypothesised during the course of motor learning. Performance gains occur not only during practice but also off-line between acquisition sessions.
Finger tapping (FT) is a fine motor task that has been used as a tool to address plasticity in the motor system. In the FT task, participants have to touch their thumb with one of their other fingers in a given order (Kami et al. 1998; Gervan et al. 2011). Performance in the task is characterised by speed and accuracy. As these two measurements are dependent on each other, characterised by the speed-accuracy trade-off (Fitts 1954), both measurements should be taken into account in case of performance analysis. Initial speed in this task is also affected by the age of the performer (Dorberger et al. 2009; Gervan et al. 2011), most probably because of the myelination level of the corticospinal (CS) tract (Bartoszkis et al. 2010). Apart from the age effect, motor speed in the FT task may be different in WS because of atypical myelination of the CS tract. CS tract myelination level and conduction velocity are related to maximum motor speed measured by repetitive index FT because it is responsible for controlling independent finger movement during voluntary movements (Bartoszkis et al. 2010). Therefore, the effect of age and myelination level of the CS tract can be minimised by taking into account both serial FT speed and maximum motor speed on conduction velocity of the CS tract (Gervan et al. 2011).

Up-to-date, studies that examine motor learning characteristics in WS are sparse. Regarding procedural learning, Gervan et al. (2012) examined long term learning in a visual contour integration task. They found reduced baseline and reduced learning performance in WS compared to age-matched typically developing controls. Moreover, participants with WS showed great variability both in baseline and learning performance with a likely dissociation between factors determining initial performance and learning capacity. The present study aimed to investigate whether the above behavioural pattern can be found in the motor domain. We asked whether individuals with WS differ in speed and accuracy from their age group, and whether they are able to improve their performance during learning in a serial FT task. Apart from performance in the serial FT task we also measured maximum motor speed by a non-serial index FT task. This was done in order to study the possible effects of CS tract myelination and conduction velocity on the speed of serial task performance. Our hypothesis was that motor performance will be less accurate and slower in the serial FT task, and maximum motor speed will also be slower in WS than in their corresponding typically developing age group. Because improvement in the FT task relies on sleep and sleep-dependent learning was previously found impaired, we also hypothesised that in WS, learning performance will lag behind that of the TD age-matched group.

Methods
Participants
Williams syndrome participants
Eleven participants (four males and seven females, age range: 11 to 26 years, eight right-handed, one left-handed, two mixed-handed) took part in the study. WS diagnosis was confirmed by fluorescent in situ hybridisation (FISH) tests showing deletion on chromosome band 7q11.23. Participants had no known skeletal deformities. Participants who had explicit tremor during the execution of the task or could not perform three consecutive trials error-free were excluded from the study. All WS participants in the present study also participated in polysomnography studies carried out previously (Gombos et al. 2011; Bodizs et al. 2012; Bodizs et al. 2014a).

Typical development participants
Eighty typically developing participants were recruited from elementary schools, high schools and colleges. Participants had no known musculoskeletal or neurological problems. Professional musicians were excluded from the study. During the course of the experiment participants were asked to report the length of their night sleep every day. Those with less than 6 h of sleep per night were also excluded from the study. Participants were naive to the task at the outset of the experiment and were not paid for their participation.

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.
Task and design

Participants were seated, forearm and hand lying on a table supine. They performed an FT task: touching the thumb with the other fingers in a given order as fast and as correctly as possible. Non-serial and serial FT tasks were performed. The non-serial FT task was performed to measure maximum motor speed. Participants were asked to touch the thumb with the index finger with both dominant and non-dominant hands as fast as possible. Blocks of 64 index finger taps were repeated three times with at least 2 min rest between them.

In the serial FT task, the practice sequence was a four element sequence of 1–3–2–4 (1 = index, 2 = middle, 3 = ring, 4 = little fingers). While previous studies used a five element sequence, we applied a four element sequence because of working memory deficits in WS shown in the present population (Peh et al. 2003). Participants were instructed not to correct errors, and to 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 was started when participants were able to produce three correct sequences successively with their eyes closed. Ten blocks of 16 sequences were performed with the non-dominant hand each day. Rest periods were self-paced between practice blocks. The acquisition lasted five consecutive days. On the fifth day, transfer of the practice sequence to the dominant hand (T1), and transfer to a new sequence consisting of identical component movements of 4–2–3–1 in both hands were also tested (T2 and T3). The three transfer tests were randomly ordered (Fig. 1).

Data acquisition was performed by a ‘data glove’ consisting of metal rings paced on the distal phalanges of the fingers. Each metal ring electrode corresponded to a given finger (1 = index, 2 = middle, 3 = ring, 4 = little fingers) detecting the order and time of a given finger touching the thumb that was also applied with a metal ring electrode. All electrodes were connected to a laptop computer through a USB-Serial converter. On the computer, JAVA based data-acquisition software collected the data, and initiated and terminated data acquisition blocks during practice. The beginnings and endings of practice blocks were marked with a ‘beep’ sound generated by the software. The ‘data glove’ enabled participants to both use their hands freely and close their eyes during the task; thus, no external visual cues were required during performance.

Dependent variables

The beginning of a new sequence was identified each time the first element of the expected sequence (e.g. index FT in the 1324 task) occurred in a block. Each sequence was terminated by the next identified first element. If each tap in a sequence was exactly in the appropriate order, the sequence was considered correct, otherwise as wrong. Task variables were calculated on the basis of finger taps rather than on the basis of sequences as seen in previous studies (Karni et al. 1998; Walker et al. 2003).

Maximum motor speed (taps/second) was defined as the average number of finger taps within one second in the non-serial FT task (tapping thumb with index finger).

Speed (taps/second) was defined as the average number of finger taps within one second in the serial FT task.

Corrected tap interval (seconds) was defined as 1/Speed – 1/Maximum motor speed. Thus, serial FT speed was corrected by the non-serial maximum FT speed to eliminate the influence of CS tract myelination level.

Accuracy (%) was defined as the number of finger taps in correct sequences divided by all finger taps (finger taps in correct sequences plus finger taps in wrong sequences).

Performance rate (PR) was calculated as the Z-score of accuracy minus the Z-score of corrected tap interval. Z-score was calculated based on the corresponding TD age group data both in WS and TD participants. Thus, we gained a measure that is both corrected for the speed-accuracy trade-off and the myelination level of the CS tract.

Learning performance was defined as the improvement in performance between Day 1 and Day 5 and calculated as (PR of Day 5) – (PR of Day 1).

Corrected learning performance was defined as the learning Z-score corrected with the regression coefficient of the correlation between baseline (Day 1) performance and learning performance of the TD group. Thus, we eliminated the potential baseline effects on learning performance.
Statistical analysis
A mixed model of analysis of variance (ANOVA), with independent variables of age groups, was performed on each dependent variable with repeated measures on Day 1, Day 5 and the three transfer tests (day/transfer). ANOVA was performed in WS and TD to compare means in accuracy, speed and corrected tap interval measures. Multiple comparisons with LSD were performed when necessary. Age groups for WS and TD participants are shown in Tables 1 and 2.

Correlation between maximum motor speed and speed in serial task was calculated. Correlation between baseline performance and learning performance was also calculated regarding PR. SPSS (version 16.0) was used to analyse the data. A P-value of 0.05 was taken as significance level for all statistical tests.

Results
Accuracy
In the WS group, ANOVA (day/transfer x age) performed on accuracy data showed no significant main effect of age ($F=7.501$, df = 2, $P=0.012$). There was a significant main effect of day/transfer ($F=8.459$, df = 4, $P<0.001$, $\eta^2_p=0.544$). Significant improvement was found between Day 1 and Day 5 ($P<0.001$), with day 5 performance level increasing above all transfer tests (T1, T2 and T3) ($P<0.05$). There was no other significant difference between the measures (Fig. 4.).

In the TD group, ANOVA (day/transfer x age) showed a significant main effect of age ($F=7.501$, df = 2, $P<0.001$, $\eta^2_p=0.422$) and a significant main effect of day/transfer ($F=49.666$, df = 4, $P<0.001$, $\eta^2_p=0.735$). Accuracy increased by age ($P<0.05$).

### Table 1 Demographic data of participants with WS

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Mean age (years)</th>
<th>SD age (years)</th>
<th>Male (n)</th>
<th>Female (n)</th>
<th>Right-handed (n)</th>
<th>Left-handed (n)</th>
<th>Mixed-handed (n)</th>
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<td>1</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>17–18</td>
<td>17.3</td>
<td>0.57</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Adult</td>
<td>24.25</td>
<td>1.26</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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### Table 2 Demographic data of TD participants

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Mean age (years)</th>
<th>SD age (years)</th>
<th>Male (n)</th>
<th>Female (n)</th>
<th>Right-handed (n)</th>
<th>Left-handed (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>7.1</td>
<td>0.5</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>8.3</td>
<td>0.4</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>11</td>
<td>11.1</td>
<td>0.7</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>12.4</td>
<td>0.6</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>14.3</td>
<td>0.5</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>17</td>
<td>17.7</td>
<td>0.8</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
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<td>0.7</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>30</td>
<td>32.3</td>
<td>5.9</td>
<td>5</td>
<td>5</td>
<td>9</td>
<td>1</td>
</tr>
</tbody>
</table>

Accuracy was significantly higher on Day 5 than on Day 1. Day 5 performance level increased above all transfer tests ($P < 0.001$) (Fig. 4.).

**Speed**

In the WS group, ANOVA (day/transfer $\times$ age) showed no significant main effect of age ($F = 0.373$, $df = 2$, $P = 0.700$) for speed. There was a significant main effect of day/transfer ($F = 4.609$, $df = 4$, $P = 0.005$, $\eta^2_p = .366$). Significant improvement was found between Day 1 and Day 5 ($P = 0.008$), with Day 5 performance level increasing above all transfer tests (T1, T2 and T3) ($P < 0.05$) (Fig. 2.).

In the TD group, ANOVA (day/transfer $\times$ age) showed significant main effect of age ($F = 9.387$, $df = 7$, $P < 0.001$, $\eta^2_p = .477$) and significant main effect of day/transfer ($F = 152.872$, $df = 4$, $P < 0.001$, $\eta^2_p = .899$). In general, speed increased with age ($P < 0.05$). Speed was significantly higher on Day 5 than on Day 1 and Day 5 performance level increased beyond all transfer tests ($P < 0.001$).

**Maximum motor speed**

In WS, maximum motor speed showed a great variability, and some of the participants remained in the lower band of TD range or even below it (Fig. 3. A.). The correlation between speed in the serial task (practice sequence Day 1) and maximum motor speed is measured by index FT did not reach significance $r = 0.465$, $P = 0.149$ (Fig. 3. B.).

In the TD group, maximum motor speed followed a developmental curve increasing up to about 20 years of age.

**Corrected tap interval**

In the WS group, ANOVA (day/transfer $\times$ age) showed no significant main effect of age ($F = 0.255$, $df = 2$, $P = 0.781$) for corrected tap interval. There was a significant main effect of day/transfer ($F = 3.186$, $df = 4$, $P < 0.05$, $\eta^2_p = .285$). LSD test indicated significant improvement between Day 1 and Day 5.
(P < 0.05), with Day 5 performance increasing above all transfer test (P < 0.05) (Fig. 4).

In the TD group, ANOVA (day/transfer × age) showed significant main effect of age (F = 7.975, df = 7, P < 0.001, η² = 0.437) and significant main effect of day/transfer (F = 121.661, df = 4, P < 0.001, η² = 0.628). Corrected tap interval decreased by age (P < 0.05). Corrected tap interval was significantly lower on Day 5 than on Day 1. Day 5 performance exceeded performance in all transfer tests (P < 0.001).

Performance rate

Learning showed significant negative correlation with baseline performance both in WS (r = −0.929, P < 0.001) and in TD participants (r = −0.876, P < 0.001). The lower the baseline, the greater is the improvement by the fifth day (Fig. 5A). In order to eliminate differences in baseline on learning performance, learning data of each individual was corrected by the regression coefficient of TD group (−0.79066). Baseline Z-scores with corrected learning Z-scores are shown in Fig. 5B. After correction, TD individuals grouped together around zero, while WS individuals still showed great variability. In WS, both baseline performance and learning capacity was reduced compared to TD individuals.

WS participants also took part in a previous sleep study (Bodizs et al. 2014b). In that study, we investigated sleep efficiency (calculated as the percent of sleep time without wake time after sleep onset divided by the time in bed) in WS and in age and sex matched TD individuals. Based on these earlier data, we indicated sleep efficiency of WS individuals compared to TD, and in Fig. 5B, we presented sleep efficiency of the WS individuals expressed in standard deviations from the mean of the TD group. WS individuals showed reduced baseline and learning capacity that has been accompanied with decreased sleep efficiency as compared to TD.

Discussion

The present study investigated the fine motor performance and learning capacity in WS using a FT paradigm. During a prolonged 5-day learning session, WS participants increased their performance significantly from Day 1 to Day 5 (Fig. 2) as a group. Transfer tests administered to measure specificity of motor learning related to motor cortices showed a similar pattern in WS and in TD participants, with lower absolute values in WS (Fig. 4). Task specific learning in both groups was indicated by significant improvement from Day 1 to Day 5, with Day 5 performance being higher than that of the transfer tests in both speed and accuracy measures. This is in accordance with previous findings in TD (Karni et al. 1998; Fischer et al. 2002; Walker et al. 2003). Task specific representation in explicit serial tasks is primarily thought to be related to motor cortices (e.g. M1, supplementary motor area, presupplementary motor area, premotor cortex) and basal ganglia networks, accompanied by specific changes in the activation pattern in these areas (Karni et al. 1998; Lehericy et al. 2005; Walker et al. 2005; Debas et al. 2010; Debas et al. 2014). M1 is reported to be a likely
site of task and effector specific representation of motor sequences in interconnection with parietal and premotor cortices (Kami et al. 1995; Müllbacher et al. 2002; Nitsche et al. 2003; Penhune & Steele 2012).

In spite of the fact that learning took place in WS at a group level, characteristics of baseline and learning performance were different from that of TD participants. Results showed that initial performance lagged behind TD age-group level both with respect to speed and accuracy (Fig. 2), and none of the WS participants provided better performance than the TD baseline (Fig. 5A). This is in accordance with previous findings with respect to the speed of various types of movements in WS (Elliott et al. 2006; Hocking et al. 2009; Hocking et al. 2010; Hocking et al. 2011b). Regarding decreased motor speed in WS, muscle fatigue is a possible factor to be discussed. The present task was designed to avoid muscle fatigue by carefully positioning the forearm and hand, and asking for a light touch between the two fingers sufficient for a tap. Furthermore, practice was distributed into ten blocks, and rest periods between practice blocks were self-paced by participants. Although fatigue cannot be ruled out completely, none of the participants reported muscle fatigue during the course of the experiment; therefore it is probably not a major limiting factor of motor speed in WS. In order to eliminate differences in CS tract conduction speed on serial motor performance because of age, experience and WS, we corrected speed by maximum motor speed; however, speed still remained below the TD level (Fig. 4). Maximum motor speed was variable among WS participants, some of them were in the TD range while others were below –2SD. Decreased maximum motor speed in WS may be related to altered myelination and conduction speed of the CS tract. While influence of

![Graph](image-url)

**Figure 4** Day 1, Day 5 and transfer performance in WS and in TD. Accuracy and corrected tap interval. Error bars indicate standard error.
an altered CS tract function might have been present, there was no correlation between maximum motor speed and serial performance. Serial speed reached its plateau at about 1.3 taps/s in WS even when maximum motor speed was in the TD range (Fig. 3A). We can conclude that the limitation of maximum motor speed in WS does not provide a full explanation of decreased speed in the serial task. In TD, both serial and index FT increase with age until adulthood (Gervan et al. 2011); however, in WS performing a serial rather than a simple repetitive task puts a constraint on the speed of the performance.

With respect to learning capacity, PR that is a combined measure of speed and accuracy Z-scores showed a decreased baseline coupled with similar or increased learning performance compared to the TD age group. The relatively increased learning probably compensated for the decreased baseline performance. This was supported by the strong negative correlation between baseline and learning performance (Fig. 5A). After eliminating the effect of baseline on learning performance, most of WS individuals showed decreased learning performance relative to TD individuals (Fig. 5B). The study on visual procedural learning in WS (Gervan et al. 2012) showed that baseline determined learning performance in a similar manner. Individual variability in performance was greater in WS than in TD in both learning paradigm regarding both baseline and learning performance.

Regarding speed, not only baseline but improvement was also limited in WS. In TD, speed improvement in a serial FT task has been related to activation in ipsilateral spinocerebellum and contralateral M1 related to movement time and bilateral activation in the putamen, motor cortices and the cerebellum related to time spent between finger movements showing distinct and interacting neural networks (Orban et al. 2011). Task specific speed improvement in FT was also accompanied by shifts in activation from the associative to the sensory-motor putamen during prolonged learning (Laher et al. 2009). Decreased serial FT speed and learning ability on the affected side, and normal movement speed with learning problems on the unaffected side, were found in basal ganglia dysfunction (Parkinson's disease) (Oseso et al. 2009). Decreased maximum and self-paced FT speed is accompanied by parallel striatal volume reductions in Huntington's disease (Paus et al. 2008). In WS, BG structures showed both structural (Reiss et al. 2004; Chiang et al. 2007) and functional (Mobbs et al. 2007) changes studied by MRI. Increasing mild extrapyramidal signs may appear and increase in WS with age (Gagliardi et al. 2007). Decreased speed and
a decreased amount of learning in terms of speed in WS may suggest basal ganglia dysfunction/basal ganglia-cortical circuit dysfunction during motor behaviour.

Regarding accuracy, it reached TD initial performance level by the 4th day on a group level. Improvement in the FT task shows sleep dependency regarding both speed and accuracy (Walker et al. 2002; Walker et al. 2003; Kuriyama et al. 2004). Specific sleep parameters, such as sleep-spindles and spontaneous delta and fast-sigma oscillations in the supplementary motor area contralateral to the trained hand, especially during slow-wave sleep, have been shown to correlate with post-sleep improvement (Barakat et al. 2011; Barakat et al. 2013; Tamaki et al. 2013). Sleep problems are common in WS. Recently, atypical sleep pattern has been reported in WS participants of the present study, and altered frontal delta wave and region independent decreased alpha and sigma wave activity were revealed (Gombos et al. 2011; Bodizs et al. 2012; Bodizs et al. 2014a,b).

Therefore, it is reasonable to suggest that altered neural activity during sleep in WS reported in the above studies may be related to the reduced motor sequence learning capacity in WS.

A possible limitation of the present study is the relatively low number of participants. This is explained partly by methodological reasons, because only those WS individuals could take part in the study who were able to perform three consecutive errorless FT sequences. Furthermore, the present study did not allow for cross syndrome comparisons. Fine motor problems are known in other neurodevelopmental disorders such as Down syndrome (Latash 2007; Vimercnta et al. 2015) and autism spectrum disorder (Green et al. 2009; Duffield et al. 2013; Mephillips et al. 2014) involving altered movement speed and accuracy. Future studies shall clarify whether the present pattern of fine motor characteristics is specific to WS.

Conclusions

Fine motor performance and learning were decreased in WS as compared to TD age-matched groups both in terms of speed and accuracy. Both initial performance and learning showed great individual variability with close to negative correlation between initial performance and improvement. After correcting learning performance for baseline, learning levels still lagged behind that of the TD subjects. Speed of performance was limited when a serial FT task was performed compared to a repetitive FT task. Impaired learning capacity may relate to impaired sleep function. Further investigations of the relationship between sleep characteristics and sleep-related motor learning parameters may help to reveal the contribution of sleep disorders to motor learning problems in WS.

Conflicts of interest

All authors declare that they have no conflicts of interest, including financial, personal or other relationships that could be perceived to influence this paper.

Acknowledgements

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References


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Motor learning in Williams syndrome


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Posterior–Anterior Brain Maturation Reflected in Perceptual, Motor and Cognitive Performance

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Based on several postmortem morphometric and in vivo imaging studies it has been postulated that brain maturation roughly follows a caudal to rostral direction. In this study, we linked this maturation pattern to psychological function employing a series of well-established behavioral tasks. We addressed three distinct functions and brain regions with a perceptual (contour integration, CI), motor (finger tapping, FT), and executive control (Navon global–local) task. Our purpose was to investigate basic visual integration functions relying on primary visual cortex (V1) in CI; motor coordination function related to primary motor cortex (M1) in FT, and the executive control component, switching, related to the dorsolateral prefrontal region of the brain in the Navon task. 122 volunteer subjects were recruited to participate in this study between the ages of 10 and 20 (females n = 63, males n = 59). Employing conventional statistical methods, we found that 10 and 12 year olds are performing significantly weaker than 20 year olds in all three tasks. In the CI and Navon global–local tasks, even 14 years old perform poorer than adults. We have also investigated the developmental trajectories by fitting sigmoid curves on our data streams. The analysis of the developmental trajectories of the three tasks showed a posterior to anterior pattern in the emergence of the developmental functions with the earliest development in the visual CI task (V1), followed by motor development in the FT task (M1), and cognitive development as measured in the Navon global–local task (DLPC) being the slowest. Gender difference was also present in FT task showing an earlier maturation for girls in the motor domain.

Keywords: contour integration, finger tapping, Navon global–local task, V1, M1, DLPC, brain maturation, gender differences

INTRODUCTION

Early postmortem (e.g., Huttenlocher, 1990; Huttenlocher and Dabholkar, 1997) and positron emission tomography (Chugani et al., 1987; Chugani, 1994) studies on cortical gray matter development have already suggested that maturation does not proceed in a homogenous temporal and topographic sequence, but shows a characteristic posterior to anterior direction. Structural MRI studies strengthened the earlier findings and demonstrated that the caudal to rostral direction
is discernible on a large scale (Reiss et al., 1996; Sowell et al., 1997). However, more recent imaging studies revealed that the timing of the regional maturation is far more complex than a canonical back-to-front progression; the temporal sequence of maturation is more connected to the function served by the specific area rather than its location (e.g., Sowell et al., 2003, 2004, 2007; Gogtay et al., 2004). These studies have shown concordant results on the earliest development of cortical brain regions' underlying basic sensory (i.e., primary visual area in occipital lobe, primary sensory areas of parietal cortex, primary areas for olfaction and taste in the frontal operculum, etc.) and motor functions (precentral gyrus of the frontal lobe). Furthermore, findings also demonstrated that areas connected to complex pattern processing (inferior, posterior temporal areas) or spatial orientation and attention (inferior parietal regions) mature next, and finally, regions involved in complex executive functions and multimodal integration (orbitofrontal and superior temporal areas) develop well into adolescence.

Similar to gray matter maturation, white matter (WM) also shows a massive change during childhood and adolescence (e.g., Courchesne et al., 2000; Matsuzawa et al., 2001; Sowell et al., 2003). Several cross-sectional structural MRI studies (e.g., Girard et al., 1991; Paus et al., 2001) and a longitudinal study (Thompson et al., 2000) reported that the age-related pattern of myelination also proceeds along a caudal-rostral arc; however, others failed to find these systematic regional differences in WM developmental changes (e.g., Giedd et al., 1999; Courchesne et al., 2000). Diffusion tensor imaging studies showed that the somatosensory pathway matures early in infancy (Ji et al., 2008), while frontotemporal tracts showed extended maturational trajectories persisting over adolescence (e.g., Lebel et al., 2008; Asato et al., 2010). These results agree with the earlier mentioned anatomical MRI studies on cortical gray matter maturation.

Gender differences in brain maturation are present already in fetal life. Sex steroids and other hormones significantly affect neural development (see e.g., Giedd et al., 1997). Adolescence, with a massive change in hormone levels, results in further sexual dimorphisms in brain development (see e.g., Lenroot and Giedd, 2010). The elevations in luteinizing hormone and inhibin B levels are clear endocrinological markers of the onset of puberty in both genders (Lahlou and Roger, 2004). Increased production of sex steroids in both males and females also accompanies these changes. The onset of hormonal puberty occurs later in boys. Puberty onset determined by inhibin B levels is between the age of 11 and 12 years in boys (Crockton et al., 2003), and between 10.1 and 10.4 years in girls (Addo et al., 2014). These results are in good agreement with imaging studies that have shown differences in the temporal pattern of brain maturation between the genders. An approximately 1–2 years shift between girls and boys has been reported in terms of peaks in gray matter: 8.5 years in females, and 10.5 years in males (Lenroot et al., 2007). Also indicating an earlier maturation for girls, more prominent cortical surface area expansion was found in males compared to females between 8 and 14 years of age (Koolschijn and Cronen, 2013). There are gender differences in WM development in terms of timing and volumetric changes as well. During childhood and adolescence females have an overall earlier maturation of WM tracts than males (Asato et al., 2010), while boys show a far more prominent WM volumetric increase than girls (De Bellis et al., 2001; Lenroot et al., 2007). Current MRI studies seem to validate the view that WM volume increase during the teenage years is associated with testosterone levels and androgen receptor genes in adolescent boys (Perrin et al., 2008; Paus et al., 2010), and luteinizing hormone levels in both genders (Peper et al., 2008).

Our purpose was to investigate whether the posterior-anterior wave of cortical structural changes, possibly determined by pubertal hormones, can be matched to a similar wave of improvement in behavioral function. The issue of matching whole-brain cortical structure to function is a complex one, especially in the developmental domain. However, an approximation with probes at strategic points both in terms of structure and function, and in terms of developmental time might be a good start. To this end, we use a well-established behavioral task that is believed to be localized differently along the sagittal axis of the brain. We use these tasks to probe how anatomical maturity might be linked to developmental trajectories of different functions (see Figure 1).

**Behavioral Tasks as Probes of Posterior–Anterior Brain Maturation**

**Contour Integration Task**

Stimuli consist of a collinear chain of Gabor patches embedded in the background of randomly positioned and oriented noise elements (see e.g., Figure 1A). This paradigm has been developed to test the long-range intrinsic cortical connections in the primary visual cortex (Field et al., 1993; Kovács and Julesz, 1995). This paradigm has been extensively studied in the last several decades in the field of visual integration, and it has a well-established account on the underlying neural mechanisms. Neurophysiological studies described a correlation between the responses of neurons in V1 and the perceptual saliency of contours (Li et al., 2009), supporting the idea that V1 has a cardinal role in contour integration. Optical imaging of contextual interactions in monkeys (Kinoshita et al., 2009), human neurophysiological (Giersch et al., 2000), and fMRI (Almazan et al., 2002; Kourtzi et al., 2002) studies also indicate the relevance of low-level visual areas in detecting and integrating the contour elements embedded in noise.

**Finger Tapping Task**

Finger tapping is a motor coordination paradigm. It has many variations in terms of the complexity of the tapping task and a 'pacing' stimulus. Here we used a self-paced version where participants have to touch the thumb with the other fingers in a given four-element sequence (see Figure 1B). Motor function of distal arm and hand movements is controlled by four distinct regions in the frontal lobes: the primary motor cortex (M1), supplementary motor area, the lateral premotor cortex and the cingulate motor area (Todorov, 2000; Lemon, 2008). Direct input to the spinal cord from these areas is shown to be necessary for manual dexterity in primates (Dum and Strick, 2004, 2005). The
MATERIALS AND METHODS

Subjects
One hundred and twenty-two volunteer subjects participated in this study (female n = 63, male = 59). Subjects were voluntarily recruited via the Internet by publicizing and advertising our research. All participants were healthy, right-handed individuals with normal or corrected to normal vision. Participants had no history of psychiatric or neurological illnesses, including ADHD, and were free of any medication. Adult participants or the legal guardians of subjects under the age of 18 were provided with written information, and were asked for consent before participating in the study. Subjects participated in two experimental sessions at the Developmental Neuroscience Laboratory of the Institute of Psychology at PPCU, and were paid for their attendance.

The sample included subjects between the ages of 10 and 20, in 5 age groups. Five subjects were excluded based on their inadequate performance on at least one of the subtests. Additional subjects were recruited subsequently. Table 1 shows the demographics of the sample.

The study was approved by the Ethical Committee of the Institute of Psychology at PPCU.

Procedure

Contour Integration Task
Stimuli were composed of a collinear chain of Gabor elements forming a horizontally placed egg shape on a background of randomly positioned and oriented Gabor patches (see Figure 1A). The relative noise density (D) was varied throughout six difficulty levels. D is defined as the ratio of average noise spacing over contour spacing (see Kovacs and Julesz, 1993). In our study, D ranged between 1.1 and 0.6, and was varied with a step size of 0.1. Blocks of images were presented in an increasing order of difficulty, starting with the easiest (D = 1.1) level, and followed by more difficult levels (up to D = 0.6), in a two-alternative forced-choice procedure. The CI task was presented using a HP ProBook 450 G3 laptop computer with a 15.6 inch monitor, and was programmed in Delphi language. Stimulus duration was 2000 ms, with a fixation cross between stimuli (0.5 s, or until the subject responded). The task was to indicate which side of the screen the narrower part of the egg was pointing to by pressing one of two assigned buttons on the keyboard. Subjects were tested binocularly and were seated at about 0.4 m away from the monitor in a normally lit testing room.

The size of the stimulus field was 19.93 × 26.57 degrees of visual angle.

Finger Tapping Task
Participants were asked to touch the thumb with the other fingers of the non-dominant hand (see Figure 1B) in a predetermined order, and as fast and as correctly as possible. 160 repetitions of a four-element-sequence (index-ring-middle-little finger) were distributed into 10 practice blocks with rests between them (the length of the rest was controlled by the subjects). Data acquisition was performed by a custom made data glove. It consisted of metal rings placed on each fingertip that were connected to a PC with a Java-based data acquisition software that detected exact timing and order of finger taps.

Taking the speed/accuracy trade-off into account, motor performance was monitored both in terms of speed and error rate. Performance rate was calculated by multiplying the time between finger taps (speed) with the ratio of the number of finger taps in incorrect sequences compared to all sequences (error rate). In order to eliminate the effect of different corticospinal tract myelination levels (due to e.g., age) on speed, participants had to carry out an additional task where they were asked to touch the thumb with the index finger of the non-dominant hand as fast as they could (maximum finger tapping speed). The above calculated performance rate in the sequential FT task was corrected with the maximum motor speed by subtracting the time between finger taps in the maximum motor speed task from the time between taps in the sequential task, then it was multiplied by the error rate of the sequential task.

Navon Global–Local Task
The Navon global–local task consisted of hierarchical stimuli of geometric shapes, often called Navon figures (Navon, 1977, see Figure 1C), presented on a computer screen. In a Navon figure, the lines of a larger, "global" shape are composed of much smaller, "local" figures, 10th the size of the large ones. In this version of the task, geometric shapes (circle, triangle, x, and square) were used instead of letters to rule out the effect of reading experience in younger subjects. The Navon global–local task was presented using a HP ProBook 450 G3 laptop computer with a 15.6 inch monitor, and was programmed with the OpenSesame 3.0 software (Mathôt et al., 2012). Participants were instructed to identify the shape, either at the global or the local level, depending on the color of the background, which was blue or yellow, respectively. Subjects were asked to provide button-press responses on the computer keyboard. Stimuli were organized into three blocks. The first and second blocks involved 24 randomized non-shifting trials (only blue/global or only yellow/local) and the third consisted of 48 quasi-random shifting trials, where 25 of the trials required a switch from local to global features or vice versa. The order of non-shifting trials was alternated among subjects, half of the subjects started with the global set of the task followed by the local set and vice versa. Each block was preceded with instructions and a practice block with 6 stimuli for the non-shifting, and 12 stimuli for the shifting condition. Stimuli appeared for 600 ms, followed by a visual cue for the location of the corresponding keys, and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic data of the participants.</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean age</td>
</tr>
<tr>
<td>10 years</td>
<td>21.57</td>
</tr>
<tr>
<td>12 years</td>
<td>22.53</td>
</tr>
<tr>
<td>14 years</td>
<td>18.52</td>
</tr>
<tr>
<td>16 years</td>
<td>16.59</td>
</tr>
<tr>
<td>18 years</td>
<td>15.57</td>
</tr>
<tr>
<td>20 years</td>
<td>20.61</td>
</tr>
</tbody>
</table>
the trial ended with a resting screen. Responses were allowed only after the stimulus ceased from the screen. Reaction time (RT) and precision were recorded. We expressed the 'cost' of switching by calculating the difference between the RT of the correct responses in the alternation trials (participants were required to switch rules between two consecutive stimuli) and the average RT of the correct responses in the repetition global and local trials (participants did not have to switch rules).

RESULTS

Data Analysis

For descriptive statistical analysis IBM SPSS Version 21.0 (IBM Corp., Armonk, NY, USA) was used. Performance less than 60% correct on one of the conditions or outliers with greater values than 2 SDs at age and gender group-level per condition were excluded from the analysis, which amounted less than 10% of the sample. Table 2 presents the descriptive statistics of the data.

Multivariate ANOVA was used to analyze the relationship between each behavioral task, gender, and age.

Higher levels of contour integration (CI) performance were associated with development [$F(5,99) = 14.210$, $p < 0.001$, $\eta^2_p = 0.418$], and gender [$F(1,99) = 5.296$, $p = 0.023$, $\eta^2_p = 0.051$], females demonstrating better performance. Gender × development interaction was not present [$F(99,546) = 0.809$, $p = 0.546$, $\eta^2_p = 0.039$]. Simple contrasts test revealed $t_1(35) = 6.273, 3.35, p < 0.001, r^2 = 0.79$, $t_2(3) = 1.844, p < 0.001, r^2 = 0.623$, and 14 [$t(26) = -2.469, p = 0.016, r^2 = 0.381$] years old adolescents showing a significantly poorer performance than the 20 years old group (adults).

Higher levels of finger tapping (FT) performance were associated with age [$F(5,102) = 10.326, p < 0.001$, $\eta^2_p = 0.336$], but there was no main effect of gender [$F(1,102) = 1.723$, $p = 0.192$, $\eta^2_p = 0.017$], or gender × age interaction [$F(5,102) = 1.777, p = 0.124$, $\eta^2_p = 0.080$]. Simple contrasts test indicated significant differences between 10 [$t(35) = 5.875$, $p < 0.001, r^2 = 0.765$] and 12 [$t(37) = -3.77, p < 0.001, r^2 = 0.373$] years olds versus adults.

Higher performance on the Navon global-local task was associated with age [$F(5,102) = 7.794, p < 0.001$, $\eta^2_p = 0.276$], but there was no main gender effect [$F(1,102) = 1.159, p = 0.284$, $\eta^2_p = 0.011$] or gender × age interaction [$F(5,102) = 0.233$, $p = 0.947$, $\eta^2_p = 0.011$] evident. Simple contrasts test revealed, that 10 [$t(38) = 5.22, p < 0.001, r^2 = 0.646$] and 12 [$t(77) = 2.078$, $p = 0.04, r^2 = 0.319$] years olds performed significantly worse, than adults (20 years).

Sigmoid Curve Fitting

As a fitting method we used the Curve Fitting Toolbox of MatLab (2014b). The three data streams were transformed so that their zero value has a meaning of the entire function missing thus enabling us omitting one parameter (see Figure 2). We fitted data using the Curve Fitting Toolbox of MatLab (2014b) with the equation of

\[
\text{Predicted function level} = \frac{\text{Saturation level}}{1 + e^{-\text{Halfmax rate} \cdot \text{age}}} + \text{Baseline level}
\]

Different fittings were calculated for females and males and after the fitting process we transformed the data and the fitted curves in a way that different saturation levels of males and females were filtered out their respective saturation levels transformed to 1. Thus, we eliminated gender performance differences to concentrate purely on the developmental process dynamics of the two genders.

We also constrained the saturation level parameter between 0 and 2, the age at development deceleration parameter between 0 and 25 and development speed parameter between 0.5 and 2.5, note that age was measured in months before transformation. The descriptive details of the fitted models are presented in Table 3. A potential limitation of the interpretation of our data is that the model explains less than 50% variance. For further theoretical and technical details about the curve fitting see Supplementary Material.

Comparing Developmental Trajectories

Figure 3 illustrates the developmental trajectories of the tree tasks (Figures 2A-C) for females and males, and the maximum acceleration timings of these functions. By analyzing the developmental trajectories of the three tasks, we found a posterior to anterior pattern in the emergence of the inflection points of the fitted sigmoid functions. Inflection points are at the earliest ages in the CI task (8.75 years on average), the FT task follows (9.95 years on average), and the last is the Navon global-local task (11.6 years on average).

Gender differences were also present in all tasks showing an earlier development for girls. A small gender difference occurred in the CI task (inflection at 8.6 years for girls, and 8.9 years for boys). In the FT task the difference was larger (9.4 years for girls, and 10.5 years for boys), and it was also relatively small in the Navon global-local task (11.5 years for girls, and 11.2 years for boys).

DISCUSSION

Our purpose was to investigate the similarities between behavioral development and brain maturation during childhood and adolescence. We focused on three specific functions related to distinct cortical areas. The behavioral paradigms were well-established paradigms with extensively studied neural correlates: (i) low-level visual spatial integration relying on the primary visual area was addressed by contour integration task; (ii) fine motor control function, mediated by the primary motor cortex in the precentral gyrus in the posterior frontal lobe, was investigated by a self-paced finger tapping task; and (iii) executive control, mediated by the dorsolateral prefrontal cortical area, was studied by the Navon global-local task. After obtaining data from 122 typically developing subjects, we applied fitted sigmoid curves on
### TABLE 2 | Descriptive statistics of the data.

<table>
<thead>
<tr>
<th>Age group</th>
<th>CI Mean</th>
<th>CI SD</th>
<th>CI N</th>
<th>FT Mean</th>
<th>FT SD</th>
<th>FT N</th>
<th>Navon GL Mean</th>
<th>Navon GL SD</th>
<th>Navon GL N</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years</td>
<td>Male</td>
<td>0.34</td>
<td>0.10</td>
<td>8</td>
<td>0.45</td>
<td>0.17</td>
<td>10</td>
<td>1265.14</td>
<td>790.00</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.31</td>
<td>0.11</td>
<td>9</td>
<td>0.64</td>
<td>0.20</td>
<td>10</td>
<td>1160.65</td>
<td>598.55</td>
</tr>
<tr>
<td>12 years</td>
<td>Male</td>
<td>0.32</td>
<td>0.11</td>
<td>9</td>
<td>0.73</td>
<td>0.21</td>
<td>8</td>
<td>790.68</td>
<td>547.58</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.33</td>
<td>0.14</td>
<td>10</td>
<td>0.64</td>
<td>0.11</td>
<td>11</td>
<td>839.71</td>
<td>390.00</td>
</tr>
<tr>
<td>14 years</td>
<td>Male</td>
<td>0.83</td>
<td>0.14</td>
<td>8</td>
<td>0.77</td>
<td>0.14</td>
<td>8</td>
<td>638.94</td>
<td>320.50</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.76</td>
<td>0.06</td>
<td>10</td>
<td>0.89</td>
<td>0.31</td>
<td>10</td>
<td>672.60</td>
<td>486.59</td>
</tr>
<tr>
<td>16 years</td>
<td>Male</td>
<td>0.75</td>
<td>0.00</td>
<td>5</td>
<td>0.88</td>
<td>0.25</td>
<td>9</td>
<td>655.42</td>
<td>569.56</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.73</td>
<td>0.09</td>
<td>10</td>
<td>1.06</td>
<td>0.25</td>
<td>9</td>
<td>470.92</td>
<td>224.85</td>
</tr>
<tr>
<td>18 years</td>
<td>Male</td>
<td>0.70</td>
<td>0.28</td>
<td>10</td>
<td>0.81</td>
<td>0.27</td>
<td>9</td>
<td>592.70</td>
<td>266.07</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.73</td>
<td>0.10</td>
<td>9</td>
<td>0.88</td>
<td>0.34</td>
<td>10</td>
<td>529.07</td>
<td>220.04</td>
</tr>
<tr>
<td>20 years</td>
<td>Male</td>
<td>0.74</td>
<td>0.06</td>
<td>11</td>
<td>1.03</td>
<td>0.14</td>
<td>10</td>
<td>628.35</td>
<td>467.33</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.70</td>
<td>0.06</td>
<td>10</td>
<td>0.90</td>
<td>0.22</td>
<td>10</td>
<td>448.75</td>
<td>190.81</td>
</tr>
</tbody>
</table>

In the CI task, D ranged between 1.1 and 0.6, where the easiest level was D = 1.1 followed by more difficult levels up to D = 0.6 (lower scores reflect better performance). In the FT task, correct percentage data ranged between 0.114 and 1.69 (lower value indicates poorer performance). In the Navon global-local task, the results ranged between 8.3 and 35.99 ms (lower scores indicate better performance).

### FIGURE 2 | Derived developmental trajectories for the three tasks. The curves exhibit the characteristic 'S'-shaped curve of a sigmoid. Red and blue stands for females and males, respectively. Lighter red and blue data represent female and male normalized data, and the lighter, dotted lines depict the 95% prediction bounds. (A) fitted sigmoid curves for normalized CI performance data. (B) fitted sigmoid curves for normalized FT performance. (C) fitted sigmoid curves for normalized Navon global-local task.

The normalized and corrected raw performance data of the three tasks for females and males. Sigmoid curves have a distinguished part called inflection point which signifies the point where development is the fastest and most prominent. Acknowledging the theoretical considerations and neural correlates provided by several researches for the three tasks we employed, we found a similar posterior to anterior pattern in the maturation of the task related functions. Emergence of the inflection points of the fitted sigmoid functions is earliest in the case of the CI task (female = 8.6 years; male = 8.9 years), the FT task follows...
TABLE 3 | Details of the fitted sigmoid curves for females and males in the three tasks.

<table>
<thead>
<tr>
<th></th>
<th>Inflection point</th>
<th>95% CI lower bound</th>
<th>95% CI upper bound</th>
<th>90% saturation</th>
<th>Relative saturation</th>
<th>Relative acceleration</th>
<th>Model adjusted R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI</td>
<td>Female 8.6 years</td>
<td>6.8 years</td>
<td>10.4 years</td>
<td>14.1 years</td>
<td>0.90</td>
<td>1.28</td>
<td>35.14%</td>
</tr>
<tr>
<td></td>
<td>Male 8.0 years</td>
<td>7.2 years</td>
<td>10.6 years</td>
<td>17.5 years</td>
<td>1.01</td>
<td>0.82</td>
<td>47.29%</td>
</tr>
<tr>
<td>FT</td>
<td>Female 9.4 years</td>
<td>7.0 years</td>
<td>11.7 years</td>
<td>15.9 years</td>
<td>0.90</td>
<td>1.30</td>
<td>18.69%</td>
</tr>
<tr>
<td></td>
<td>Male 10.5 years</td>
<td>9.1 years</td>
<td>11.9 years</td>
<td>18.7 years</td>
<td>1.10</td>
<td>0.78</td>
<td>39.94%</td>
</tr>
<tr>
<td>Navon GL</td>
<td>Female 11.8 years</td>
<td>10.6 years</td>
<td>12.8 years</td>
<td>15.6 years</td>
<td>0.90</td>
<td>1.35</td>
<td>43.16%</td>
</tr>
<tr>
<td></td>
<td>Male 11.7 years</td>
<td>9.8 years</td>
<td>13.6 years</td>
<td>19.6 years</td>
<td>1.01</td>
<td>0.79</td>
<td>25.06%</td>
</tr>
</tbody>
</table>

Relative saturation is the relative measure of the point fitted modal saturation. Relative acceleration is the relative measure of the theoretical mean of the two genders' acceleration parameters.

FIGURE 3 | Developmental trajectories of the three tasks for females and males. In this figure, the most relevant areas of the fitted sigmoid curves are highlighted: these are the steepest parts of the slope between the lower and upper plateau, the so-called inflection points. The vertical lines project the inflection points of the sigmoid curves to the x-axis, showing the age when the maximum acceleration occurs according to the model. The earliest inflection points occur in the CI task (girls: 8.6 years, boys: 8.0 years), followed by the FT task (girls: 9.4 years, boys: 10.5 years). The latest inflection points occur in the Navon global-local task (girls: 11.8 years, boys: 11.7 years).

(female = 9.4 years; male = 10.5 years) and the last is the Navon global-local task (female = 11.5 years; male = 11.7 years). Imaging studies also agree on the earliest maturation of the occipital pole (Sowell et al., 2003, 2004, 2007; Gogtay et al., 2004).

Developmental changes of the frontal lobe display an inhomogeneous timing; maturation shows roughly a posterior to anterior direction with an exception of the frontal pole that matures at about same time as posterior regions (Gogtay et al., 2004). Accordingly, developmental alterations start earliest in the precentral gyrus (primary motor cortex), and the prefrontal cortex matures last (Gogtay et al., 2004). The data obtained from the sigmoid models are consistent with the imaging findings revealing a posterior to anterior direction of frontal lobe maturation, sigmoid curves of FT task show earlier inflection points than curves related to Navon global-local task.

Brain maturation displays a gender specific timing and pattern during childhood and adolescence (for review see e.g., Lassen and Giccd, 2010), girls mature earlier than boys. Our results also show gender difference in the timing of the changes in behavioral functions connected to M1 area, while there is only a slight difference between males and females in the visual and executive control task. In the fine motor task (FT), female and male developmental curves reach the inflection points by the age 9.4 and 10.5 showing 1.1 years difference between gender groups. Delayed developmental growth curves for males in the FT task could be related to later volume growth peaks for frontal GM in males (Giccd et al., 1997; Giccd and Raphoport, 2010) and earlier myelination for females (Benes et al., 1994). The earlier inflection points in females compared to males may reflect an influence of sex hormones on the maturation of
these brain regions. In the Navon–global–local task, the female and male developmental curves reach the inflection points by the age of 11.5 and 11.7, respectively. The lack of significant gender difference might be explained by the explained by the massive inhomogeneity of males’ performance in this task. In CI task, female and male developmental curves reach the inflection points by the age of 8.6 and 8.9, respectively. This is consistent with the findings of a recent structural MRI study (Koolscijn and Crane, 2013) where data show only moderate occipital volume gray matter loss after age of 8, indicating that the vast majority of structural maturational changes of this lobule have proceeded by this age. The volumetric loss in gray matter is likely associated with two simultaneous maturational processes: synaptic pruning, i.e., the elimination of unused synaptic connections (see e.g., Hottenlocher and Dubois-Bellair, 1997); WM growth, i.e., myelination (see e.g., Berens et al., 1994; Courchesne et al., 2006; Gogtay et al., 2004). However, the study of Koolscijn and Crane (2013) reports temporal, parietal and frontal gray matter volume loss in early adolescent years which could be associated with more protracted brain maturation in these lobules. The occurrence of the maximum acceleration of maturation prior to puberty, and the lack of significant gender differences in the CI task might imply that the maturation of this visual function is less hormonally driven than the other two investigated functions.

We conclude that the posterior to anterior structural and functional maturational direction of the human brain could be grasped by behavioral paradigm addressing specific cortical areas. Clearly, further research with younger age groups is needed to verify our developmental trajectory predictions regarding the exact timing of the maximum accelerations of the investigated functions.

AUTHOR CONTRIBUTIONS

IK and PG contributed to the conception and design of the research, and wrote the paper. OF coordinated data acquisition and analysis. PS fostered data analysis and the interpretation of the results. All participated in the analysis of the data. All authors discussed the results and implications and commented on the manuscript at all stages. All authors approved the manuscript and this submission.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Sigma frequency dependent motor learning in Williams syndrome

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Abstract

There are two basic stages of fine motor learning: performance gain might occur during practice (online learning), and improvement might take place without any further practice (offline learning). Offline learning, also called consolidation, has a sleep-dependent stage in terms of both speed and accuracy of the learned movement. Sleep spindle or sigma band (10-15 Hz) characteristics affect motor learning in typically developing individuals. Here we ask whether the earlier found, altered sigma activity in a neurodevelopmental disorder (Williams syndrome, WS) predicts motor learning. TD and WS participants practiced in a sequential finger tapping (FT) task for two days. Although WS participants started out at a lower performance level, TD and WS participants had a comparable amount of online and offline learning in terms of the accuracy of movement. Spectral analysis of WS sleep EEG recordings revealed that motor accuracy improvement is intricately related to WS-specific NREM sleep EEG features in the 8-16 Hz range profiles: higher 11-13.5 Hz z-transformed power is associated with higher offline FT accuracy improvement; and higher oscillatory peak frequencies are associated with lower offline accuracy improvements. These findings indicate a fundamental relationship between sleep spindle (or sigma band) activity and motor learning in WS.

Introduction

Motor learning, particularly explicit learning of fine motor sequences has multiple phases. Within-session (online) gains occur during practice, both in accuracy and in speed. The online phase is followed by a consolidation phase in which motor performance improves offline, without any further practice (Fig. 1.). Offline consolidation is brain-state dependent: time spent

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awake results in retention of performance acquired during practice, while off-line gains are sleep-dependent both in speed and in accuracy in adults. Changes in delta, sigma and beta activity in NREM sleep, and in REM characteristics have been found following practice. There is a positive correlation between offline gains in the explicit sequential finger tapping (FT) task and sigma band NREM activity in the 13-15 Hz spindle range (in spindle amplitude, number and density). Post-sleep improvement in FT is correlated with spontaneous delta and fast-sigma oscillations in the supplementary motor area, contralateral to the trained hand. Taken together, recent evidence seems to confirm that sleep spindles, especially fast sleep spindles contribute to the activation of the neural network involved in offline consolidation of fine motor sequences.

Figure 1. Motor learning task. A. A four-element FT sequence, practiced with the non-dominant hand. Thumb is touched with the index, ring, middle and little fingers in this predetermined order. A “data glove” consisting of metal ring electrodes placed on each fingertip detects the order and timing of taps. B. Each practice block is composed of 16 repetitions of the four-element practice sequence, and followed by a self-paced rest period. Beginning and end of a practice block is signalled by a computer-generated “beep” sound. C. 10 practice blocks are carried out on Day 1. The mean of the first two practice blocks is considered as baseline performance. Online improvement is defined as the difference between the baseline and the mean of the last two practice blocks. Offline improvement is defined as the difference between the mean of the last two blocks on Day 1 and the mean of the first two blocks on Day 2.
In addition to post training sleep, sleep quality before learning also affects motor learning capacity in healthy individuals\(^\text{17}\). Interestingly, sleep spindle characteristics preceding learning are related to baseline performance and offline improvement in children when learning motor finger-sequences\(^\text{18}\). As a general trait, sleep dependent learning is correlated with EEG activity in the 8-16 Hz band during NREM sleep, which is genetically determined and stable within individuals, and across nights\(^\text{19,20}\).

As we have shown earlier, the majority of the above mentioned, motor learning related sleep characteristics are altered\(^\text{21}\), and the capacity to improve during long-term FT learning is significantly limited in Williams syndrome (WS)\(^\text{22}\). WS is a genetically determined neurodevelopmental disorder due to a microdeletion on chromosome 7 in the q11.23 region, and it is characterized by mild to moderate intellectual disability, hypersociability, attention deficits, and problems with visuospatial processing\(^\text{23-25}\). Delayed motor development, gross and fine motor deficits throughout the lifespan are common findings in WS\(^\text{25,26}\). With respect to sleep, an atypical sleep pattern, including prolonged sleep latency, sleep maintenance problems and fragmented sleep\(^\text{27-29}\), decreased total sleep time\(^\text{30,31}\), increased slow wave sleep (non-REM stage 3 and 4 sleep)\(^\text{28,30-32}\); decreased REM sleep percentage and reduced cyclicity in the sleep architecture\(^\text{31}\) has been found in WS. We have found WS-related alterations in the broadband sigma (8-16 Hz) NREM sleep EEG spectral profiles: decreases and increases in low (<13 Hz) and high (>13 Hz) sigma power, respectively, as well as increased oscillatory sigma peak frequencies\(^\text{21}\). This pattern has a striking stability in time, suggesting the acceleration of thalamocortical oscillatory dynamics during NREM sleep in WS\(^\text{21}\) (Fig.2.).

Figure 2. Focus of the present study: the broadband sigma range (8-16Hz) in NREM sleep. Normalized sigma power as expressed in z-scores of EEG activity in WS subjects and
group averages (WS and TD) at derivation Cz. Spectral power densities of artifact-free, Hanning-tapered 4 second EEG epochs were calculated via the Fast Fourier Transformation method and averaged for all-night NREM sleep (data from\textsuperscript{15}) /TD data shown as a reference from\textsuperscript{21}. The 8-16 Hz range was normalized in a derivation- and individual-specific manner by z-transformation \textsuperscript{19}. TD sigma activity typically has two peaks (it is also true for the individual subjects) which could be referred to as the slow and fast sleep spindle peak frequencies, correspondingly. The slow spindle peak is usually missing or greatly reduced in WS patients and generally the second (fast spindle) peak is at a higher frequency in WS than in TD subjects\textsuperscript{21}.

Based on the above findings, here we investigate the hypothesis that the reduced capacity to improve in a motor learning task is related to the altered neural activity during sleep in WS. Specifically, we test the relationship between motor learning and 8-16 Hz NREM sleep in WS. We employed a two-day practice version of the sequential FT task in WS and TD groups, and we compared their learning capacities. The same WS individuals participated in whole night ambulatory polysomnographic recordings earlier, and we analysed the relationship between polysomnographic and FT measures. Our main assumption is that the peculiar sleep characteristics of WS (namely, decreased low sigma, increased high sigma, as well as increased sigma peak frequency Fig.2.) will influence learning capacity in terms of both accuracy and speed in a sleep-dependent learning task. More specifically, we predict lower offline motor memory improvement when WS-specific alterations in the NREM sleep EEG sigma spectral profiles are pronounced.

Results

Motor learning performance

![Figure 3. A. Online and offline improvement in accuracy in the sequential FT task. B. Online and offline improvement in speed in the sequential FT task in WS and in TD subjects. Baseline performance is significantly different, while improvements are comparable in WS and TD with respect to accuracy and offline improvement in speed. Error bars show standard deviation.](image)
Accuracy
A significant main effect of group (WS < TD: \( F_{(1,30)} = 23.939; p = .00003 \)), a significant main effect for baseline/online/offline improvement (\( F_{(2,60)} = 48.614; p = 2.8098 \times 10^{-13} \)), and a significant group×baseline/online/offline interaction (\( F_{(2,60)} = 7.465; p = .001 \)) was present. Baseline was significantly lower in WS than in TD \( (p < .05) \), but no significant difference in online and offline improvement was found between WS and TD groups \( (p > .05) \). Therefore, in terms of accuracy, baseline performance was different, while online and offline improvement in the sequential FT task was comparable in WS and TD (Fig. 3.A.).

Speed
There was a significant main effect for WS and TD groups \( (F_{(1,30)} = 71.648; p = 1.9077 \times 10^{-9}) \), with a significant main effect of baseline/online/offline improvement \( (F_{(2,60)} = 113.894; p = 3.7359 \times 10^{-21}) \), and with a significant group×baseline/online/offline interaction \( (F_{(2,60)} = 18.605; p = 5.1657 \times 10^{-7}) \). Baseline was significantly lower in WS than in TD \( (p = .05) \), and there was no significant difference in online improvement \( (p > .05) \). Offline improvement showed a marginal difference between the two groups \( (p = .065) \) (Fig. 3.B.). Lower baseline performance predicted higher online (practice-dependent) gains in terms of both accuracy \( (r = -.74, p = .001) \) and speed \( (r = -.59, p = .015) \) of motor learning in TD, but not in WS participants. Similar negative correlations between offline and online improvements were detected in both groups \( (TD r = -.63, p = .01, WS r = -.67, p = .005) \) with respect to speed, and in TD with respect to accuracy \( (r = -.74, p = .001) \).

Correlations between sleep parameters and motor learning performance

**Figure 4.** A. Positive correlation between z-scores of 12.25 Hz NREM sleep EEG power, and Day 1 to Day 2 offline motor accuracy improvement in WS participants. The z-score of the 12.25 Hz power is based on the individual-specific normalization of 8-16 Hz spectra in the right frontal derivation (F4). Offline FT accuracy improvement is expressed in terms of percent change from Day 1 to Day 2. Light and dark grey indicates ±1 and ±2 SD of the corresponding variable in TD participants, respectively. SD of TD spectral data are from ref. 21. Note that higher 12.25 Hz power is associated with higher offline FT accuracy improvement. B. Negative correlation between parietal sigma peak frequency and Day 1 to Day 2 offline motor accuracy improvement in WS participants. Highest parietal sigma peak frequency is the frequency at
which the highest observable local maxima are found in the 8-16 Hz NREM sleep EEG power spectra of WS participants. Offline FT accuracy improvement is expressed in terms of percent change from Day 1 to Day 2. Light and dark grey indicates ±1 and ±2 SD of the corresponding variable in TD participants, respectively. SD of TD spectral data are from ref.\textsuperscript{21} Note that higher oscillatory frequencies are associated with lower offline accuracy improvements.

Correlations between z-scores of the NREM sleep EEG 8-16 Hz spectra and motor learning in WS subjects are reported in terms of significant Rüger’s areas: continuous zones of descriptive (p < .05) significances in the frequency (8-16 Hz with 0.25 Hz resolution) × EEG location (10-20 system) matrices for which the area as a whole can be considered as significant (see details in Methods). No significant Rüger’s areas were revealed for baseline motor accuracy and speed performances. Bins between 11 and 13.5 Hz correlated positively with offline accuracy improvement, forming a continuous Rüger’s area involving all EEG derivations. Maximal effect occurred at derivation F4 and the 12.25 Hz frequency bin: \( r = .69, p = .004 \) (see Supplement 1. and Fig. 4.A.).

Bins in a similar, but somewhat lower frequency range (however still consistent with the low sigma range: 9.75-12.25 Hz) correlated positively with online (practice-dependent) motor speed improvement. The Rüger’s area involved the majority of EEG locations (F3, F4, Fz, C3, C4, Cz, T3, T4, T5, T6, P3, P4, Pz, O1, O2, Oz), except the anterior frontal ones (Fp1, Fp2, Fpz, F7, F8). No significant Rüger’s areas were revealed for baseline motor accuracy and speed performance.

Further characteristic features of the NREM sleep EEG broadband sigma spectral profiles are the oscillatory peak frequencies. Decreased offline accuracy gains in WS participants with higher oscillatory peak frequencies are indicated by the negative correlation between the highest parietal sigma peak frequency and offline motor accuracy improvement in the FT task (\( r = -.52, p = .03 \), (Fig. 4.B.). We found no other significant correlations between sigma peak frequencies and motor learning performances in WS participants.

Discussion

The purpose of the present work was to contribute relevant evidence on the relationship between sleep and motor learning. As it has been shown in typically developing subjects, sleep spindles contribute to the activation of the neural network involved in offline consolidation of fine motor sequences\textsuperscript{4,6-12}. Here we studied a group of subjects whose spindle activity is modulated at the group level (a single and shifted peak in the sigma domain, see Fig. 2.), and the peak frequency modulation has a great individual variability (also Fig. 2.). These two factors together gave us a unique possibility to test whether spindle modulation results in altered learning performance. Our results seem to attest to that, providing unique evidence for a relevant relationship between spindles and motor learning: sigma activity closer to the TD range is associated with better offline learning in WS.

We tested whether the specific alterations of broadband sigma (8-16 Hz) activity in WS \textsuperscript{21} are associated with deficits in offline fine motor learning. We found that two of these alterations are indeed related to affected offline motor learning phase in the FT task. The previously reported decrease in low sigma range of the z-normalized spectra of WS participants is involved in the efficiency of achieving offline performance gains. WS participants, characterized by a smaller amount of decrease in z-normalized low sigma power show the highest offline gains in motor accuracy (Fig. 4.A.). The second finding is related to the accelerated sigma peak frequency in
WS, which correlates negatively with offline motor accuracy gains. In other words, WS participants, characterized by more accelerated sigma peak frequencies exhibit less effective offline consolidation (Fig. 4.B.). We also report an unpredicted finding, namely, a positive correlation between the individual values of z-normalized low sigma power and online (instead of offline) gains in motor speed.

In terms of motor learning, WS participants show significantly lower baseline performance as compared to TD participants with respect to both accuracy and speed. On the other hand, low baseline in WS is not associated with sigma band activity as found previously in typically developing children, where, e.g., more slow sleep spindles are associated with lower baseline when polysomnography is administered during a three-day-learning session18. Our results indicate that WS and TD participants are not different in terms of online improvement at the group level in speed or accuracy in the initial phase of motor learning. Similarly, intact online learning performance has been found in other studies that focused on populations with sleep alterations. When individuals with obstructive sleep apnoea were compared to healthy controls, there was no difference in improvement during first day practice in a finger sequence task33. Moreover, schizophrenia patients were not different from healthy controls in accuracy34,35, and subjects with attention-deficit hyperactivity (ADHD) disorder were not different in speed from TD controls36 in terms of within-session improvement.

Surprisingly, online improvement in speed is correlated with low sigma power in WS in our present study. Given that most of the studies in the field focus on the relationship between offline gains and changes in post-training sleep, the studies on the interrelation between sleep characteristics and baseline and/or online improvement are scarce. A recent study of King et al.37 shows that cerebral activation during initial online learning predicts sleep dependent motor performance improvements in the elderly. They hypothesize that a given level of activation in motor networks involving the putamen, cerebellum and parietal cortex is required to induce sleep related consolidation. In healthy adults38, performance changes are related to the increased activation of putamen and medial temporal lobe including the hippocampus. During the initial online phase of motor sequence learning, performance improvement as measured by consistency is correlated with the interaction between the striatal and hippocampal systems that in turn predicts offline improvement in typically developing adults. That is, brain activation associated with performance gains during online learning may trigger and, in turn, predict offline performance changes. Since the above studies did not administer polysomnographic recordings, only an indirect relationship may be hypothesized between online improvement and low sigma band activity in the present study. Since brain activation during motor learning seems to be disease specific in spite of similar behavioural characteristics39, further studies need to clarify the functional relevance of given brain areas and their polysomnography correlates in motor learning in WS.

With respect to offline improvement, a pattern of dissociation is frequently observed in age related changes or in disrupted sleep: while online performance is retained, offline improvement is compromised9,33-36,40. Unlike in these previous studies, offline learning in WS was comparable to that of the TD participants from Day 1 to Day 2 in our study (Fig.3.). Individual differences in offline accuracy gains were correlated with WS-specific NREM sleep EEG sigma activity features (low sigma power and highest peak frequency) (Fig.4.B.). These results are consistent with findings in recent study of individuals with ADHD. Participants with ADHD had lower baseline, but similar performance on Day 2 post-test compared to TD. Authors found positive correlation between offline improvement and slow sleep spindle activity (12–13.5 Hz) during the night after training in ADHD, but not in TD controls. Participants with higher relative power in the frequency band related to slow sleep spindles, the frequency band that is in turn the more altered in ADHD, had better overnight improvement41. Similarly, in patients with major depression, overnight learning was associated with slow frequency spindle activity (10.5-12.5
Hz), and this relationship was true for healthy control participants too\textsuperscript{42}. Furthermore, typically developing children with lower initial performance but more slow spindles and slower slow waves improved more in accuracy overnight\textsuperscript{18}.

In our study, we found no association between sigma band activity and offline gain in speed in WS. We analysed speed and accuracy measures separately, since our previous study showed a lower baseline and impaired learning in WS with respect to speed during a five day motor training\textsuperscript{22}. Here we analyse an initial phase of learning, and we find only a marginal difference between WS and TD groups in terms of offline improvement in speed, not reaching significance, and not correlated with sigma activity in WS. Other studies allowing for a dissociation between speed and accuracy with respect to online and offline improvement show an incoherent picture. In TD children, improvement in accuracy in a FT task was sleep-dependent, while improvement in speed was not. In conditions with disrupted sleep, e.g., when individuals with ADHD were trained on a sequential FT task, they expressed delayed gains at 24h and at 2 weeks retention in speed, but did not improve compared to baseline in accuracy\textsuperscript{36}. On the other hand, in schizophrenia patients, while sleep dependent learning was compromised both in speed and accuracy\textsuperscript{34,35}, offline performance gains were correlated only with the stage 2 NREM sleep length but not with spindle activity when measured in the 4th quarter of the night in schizophrenia patients\textsuperscript{35}.

In spite of the exciting findings, our study also has several limitations. The number of participants is relatively small since WS is a rare disorder, and the occurrence in the population available to us is very low. The difficulty of the motor task for young individuals with WS, and the presence of motor symptoms (such as tremor) in adult individuals with WS also put restriction on the number of participants. It might occur as another limitation that data submitted to correlation analysis were not obtained at the same time point. However, since the studied sleep characteristics are genetically determined and stable within individuals, and across nights, this factor may not affect the interpretation of our data. Another limitation is that are not presenting a direct comparison in terms of sleep and behavioural data in typically developing control participants. However, the aim of the present study is to reveal the relationship between a known and confirmed alteration in sigma activity in NREM sleep and motor learning capacity in WS, and the studied sleep alteration is not present in TD subjects.

Our results are consistent with studies indicating the importance of sigma band activity in NREM sleep in motor memory consolidation, where it has been shown that among individuals with a neurodevelopmental disorder, characteristics of sigma band activity closer to that of TD subjects results in superior learning, with retained/higher slow sigma activity being associated with higher offline improvements\textsuperscript{41,42}. We have also found a more general effect by demonstrating that trait-like NREM sigma activity characteristics (not associated with the motor training) may influence motor memory consolidation in addition to changes in post training sleep. Further studies are necessary to explore the more detailed relationship between sigma band activity and online learning, and the dissociation between speed and accuracy during motor learning. The WS-specific alterations of sigma band activity are of potential interest for those aiming to unravel the neural roots of the individual differences in motor learning performance in participants with WS or other neurodevelopmental disorders.

Methods

Ethics statement

The present study was approved by the Social Sciences Ethical Review Board of the Budapest University of Technology and Economics and was conducted according to the approved guidelines. Informed consent was obtained from adult participants and the parents of participating children in the study.
Participants

Motor learning: 16 individuals with WS (6 males, 10 females) participated in the study. The age-range was 11 to 27 years, mean age was 18.4 years (SD: 5.5 years). Three participants with WS were left-handed, two were mixed handed, and eleven were right handed as measured by tool use. WS diagnosis of all WS participants was confirmed by fluorescent in situ hybridization tests showing deletion on chromosome band 7q11.23. 11 participants took part also in a previous motor learning study. Furthermore, 16 typically developing individuals (6 males, 10 females), age range 11-29 years, mean age 18.4 years (SD: 5.6 years) participated in the study. All TD participants were right handed and did not report sleep disruptions. None of the participants were professional musicians or had skeletal deformities that could influence motor performance.

Polysomnography (PSG): 20 participants with WS took part in an earlier polysomnographic study. A subgroup of these WS participants (n=13) also took part in the motor learning experiment. 4 males and 9 females (age range 11-27 years, mean age: 18.6 years, SD: 5.6 years; 9 right-handed, 3 left-handed, 1 mixed-handed) with WS participated both in the ML and the PSG the studies.

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Table 1. Sleep architecture of the Williams syndrome subjects. SWS, slow wave sleep; WASO, wake time after sleep onset; NREM, non-rapid eye movement; REM, rapid eye movement. Values are group means ± SD.
Participants were allowed to go to bed at will, and were not awakened during the PSG recording, and during the night following acquisition. Prior to PSG recording, an adaptation night with the same conditions served the subjects to get used to the experimental settings. Subjects were only included in the FT experiment if a minimum of 6 hours of night sleep was reported previously, and between Day 1 and Day 2 of testing. Sleep duration was assessed by self-reports of the participants. Sleep architecture of WS participants of the present experiment is shown in Table 1.

Experimental design

Motor learning experiment (Fig. 1.)
Task and design
The motor learning task was a four elements FT task performed with the non-dominant hand. Participants touched their thumb with the index finger, followed by the ring finger, middle finger and little finger, always in this same sequence. Data acquisition started after participants performed three successful sequences consecutively. They practiced 10 blocks of 16 repetitions on the first day, and 2 blocks of 16 repetitions on the second day. One of the participants with WS practiced only five blocks on the first day. Participants were allowed to rest between practice blocks at their own pace to avoid fatigue.

Data acquisition
Data were collected using a custom-made data glove including metal rings placed on each fingertip. The data glove was connected to a laptop computer where a Java based data acquisition software stored and processed the timing and order of finger taps. Since 11 out of 16 participants took part in a previous long term motor learning study, that database was included in the present study for performing a new analysis focusing on online and offline learning in the fast phase of learning.

Dependent variables
We monitored performance in speed and accuracy during acquisition. Speed was defined as the number of finger taps in a second (taps/s). Accuracy (%) was defined as the ratio of the number of finger taps in correctly performed sequences to all sequences. Baseline was calculated as the mean performance of the first two blocks on the first practice day, and post-training performance as the mean performance of the last two blocks on the first practice day. Online (practice-dependent) improvement was calculated as a difference between the mean of the first two blocks of a daily session and the mean of the last two blocks of the same session. Offline improvement was calculated as the difference between the last two blocks of a daily session, and the first two blocks on the following day.
Baseline performance, online and offline improvement were calculated with respect to speed and accuracy.

EEG recordings and analyses
A subgroup of WS participants from our sleep EEG study were enrolled in the FT learning session protocol. We analysed sleep EEG data with high interindividual variability and proven intra-individual stability (the sleep EEG fingerprints) of this subgroup in relation with the FT measures of the current study. Sleep EEG data were derived from whole night ambulatory polysomnographic records as follows. Home sleep was recorded according to the participants' preferred sleeping habits by using a 32 channel SD-LTM Hardware together with the BRAIN QUICK System PLUS EVOLUTION software (Micromed, Italy). We recorded EEG according to the 10–20 system (Jaspers, 1958) at 21 recording sites (Fp1, Fp2, Fpz, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, O2, Oz) referred to the mathematically linked mastoids. We also recorded bipolar EOG, ECG and submental as well as tibialis EMG. Signals
were high-pass filtered at 0.15 Hz and low-pass filtered at 250 Hz by 40 dB/decade anti-aliasing hardware input filters. Data were collected with 22 bit resolution and with an analogue to digital conversion rate of 4096 Hz/channel (synchronous). The firmware applied a further 40 dB/decade anti-aliasing digital filter which low-pass filtered the data at 463.3 Hz. The digitized and filtered EEG was subsequently undersampled at 1024 Hz. We also applied a 50 Hz digital notch filter performed by the recording software. Data were exported and converted to EDF before further analyses.

We visually scored sleep recordings according to standard criteria in 20 s epochs. Next, we manually removed the 4 s epochs containing artifacts before further automatic analyses. Average power spectral densities were calculated by a Fast Fourier Transformation (FFT) algorithm applied to the 50% overlapping, Hanning-tapered, artifact-free 4 s epochs of whole night stages 2–4 NREM sleep. We used z-scores of 8–16 Hz spectra in the statistical analyses. We introduced z-transformation in order to follow previous approaches in the field, as well as to control for potentially simultaneous differences in general EEG amplitude and delta power, the latter being supported by our own results and indirectly by the reports of an increased SWS in WS.

The z-transformation is individual and derivation-specific as described below. Spectral values (µV²/0.25 Hz) between 8 and 16 Hz (33 bins of 0.25 Hz each) are averaged (m) and the standard deviation calculated (σ). Then the original frequency bins were replaced by the individual- and derivation-specific z-scores by using the z = (x-m)/σ formula, where x is the actual value of the frequency bin (in µV²/0.25 Hz) to be transformed. This normalization results in series with a mean of 0 and standard deviation of 1, varying between 8 and 16 Hz, and reflecting the individual- and derivation-specific shapes of the spectra, previously termed as spectral EEG fingerprints of sleep, characterized by strong genetic determination and proven reliability (repeatability) in both healthy and WS participants.

Spectral peaks were processed automatically as follows: the zero-crossing points of the first order derivatives of the z-scores of 8–16 Hz spectra were considered as locations of spectral peaks if the second order derivatives were negative at these frequencies (local maxima in mathematical terms). Spectral peak processing was performed on the averaged z-scores of the left and right frontal (F3 and F4), as well as on the left and right parietal (P3 and P4) derivations. Slow peaks were defined as the slowest peak in the frontal derivations, while fast peaks as the fastest ones in parietal channels.

Statistics
Finger tapping task
We performed two-way mixed ANOVA (group×baseline/online/offline) with repeated measures on baseline/online/offline regarding all dependent variables. Mauchly’s Test of Sphericity indicated that the assumption of sphericity had not been violated, therefore correction was not performed for sphericity of the repeated measures. Post hoc test were performed by using the Fisher LSD method. To investigate the relationship between baseline, online and offline improvement, we calculated correlation coefficients between these measures both in speed and accuracy. A p-value of 0.05 was set as the significance level for all statistical tests.

Correlations between spectral values and learning performance
We calculated correlations between spectral values and learning performance as follows. We correlated individual-specific slow and fast spectral peak frequencies, as well as binwise z-scores with FT measures (Pearson product-moment correlation coefficients). The binwise calculations result in an inflation of type I statistical error, thus, we applied the Descriptive Data Analysis procedure to control this effect. As a first step, continuous regions of descriptive, uncorrected (p < .05) significances derived from binwise z-power vs motor performance correlations are defined in the frequency (between 8 and 16 Hz, with 0.25 Hz resolution) × EEG location (according to the 10-20 system) matrices. These regions are termed Rüger’s areas and are further tested in order to make global confirmatory statements with controlled uncertainty.
(at least one of the null hypotheses in the Rüger’s area is wrong). In order to refuse this global null hypothesis, at least half of the significant correlations in the respective Rüger’s area have to be significant at the level of .05/2 (.025). As our hypotheses were directional (formerly reported WS-specific features of the 8-16 Hz spectra\textsuperscript{15} were hypothesized to negatively influence motor learning), we used one-tailed tests when assessing significances. In addition, we tested the Rüger’s areas for outliers: we visually screened the scatterplots of maximal correlational effects in the potential Rüger’s areas and removed the areas where extreme values caused spurious associations from further analyses.

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Author contributions

I.K. designed the study, R.B. and F.G. processed and analysed PSG data, A.B. collected and analysed FT data. A.B., R.B., I.K., F.G. wrote the article and SZ.L. prepared figures of the article with the help of A.B., R.B., F.G., I.K. All authors reviewed the final draft of the manuscript.

Authors report no conflict of interests.
References


Supplementary Figure S1. Topographic plot of correlations of offline improvement in accuracy and 12.25 Hz z-scored EEG spectrum of NREM sleep in WS. Significance reached at r=0.55. Although the topographic plot of correlations indicate a spatially unspecific correlation between offline improvement in accuracy and 12.25 Hz z-scored EEG spectrum of NREM sleep in WS two points might be raised here. The first is that the maximum of the correlations closely corresponds with the functional localizational studies measuring motor cortex activation. These regions were shown to be at the heart of the neural underpinnings of the FT improvement. Thus, although the area of correlations is much more extended, the maximum fits the theoretical region of interest. The second point is that classical EEG localization is known to result in blurred images, extending well over the neural sources. Thus, our findings might indicate a local, motor cortical effect which is spatially blurred according to the resolitional properties of the EEG. Further studies based on high density EEG or on other functional neuroimaging methods with superior localizational properties are needed in order to more precisely localize this effect.
Study V.


Abstract

Gender differences in the pubertal trajectory of fine motor development

Puberty involves marked changes in the musculoskeletal and nervous systems and shows gender-based behavioural and morphological differences. The present study aimed to investigate developmental changes in fine motor function and map sex-related differences using a finger tapping (FT) paradigm. Age-dependent improvement of finger movements in terms of speed mainly depends on the maturation of the brain, corticospinal (CS) tract, spinal cord circuits, and periphery; while improvement in accuracy is mainly attributed to brain maturation. Speed and accuracy show a trade-off during performance. 118 typically developing participants (male n=56, female n=62) were assigned to six age groups (10, 12, 14, 16, 18, 20 years), ages counterbalanced. Repetitive (index FT with dominant and non-dominant hand) and serial (four-elements-sequence with non-dominant hand) tasks were performed.

Results showed that repetitive FT speed (index FT) increased with age at both the dominant and the non-dominant hand. With the dominant hand, significant female advantage was seen at the age of 10 that diminished later, and a significant male advantage appeared at 18 years. With the non-dominant hand, there was a significant difference between male and female groups at 18 and 20 years, a tendency similar to that of the dominant hand. There was a gender specific developmental pattern regardless of hand-dominance. Females increased speed markedly until the age of 14 years then the developmental curve slowed down. Developmental curve of male participants showed gradual increase with age, with no plateau at 14 years, resulting in a male advantage at later ages. Speed in a serial task with the non-dominant hand showed a similar developmental pattern to that of the repetitive task in male and female groups, respectively.

In order to minimize the effect of CS tract myelination and conduction speed on serial performance, we corrected the serial FT speed with the index FT speed. In the corrected speed, there was a significant difference between males and females at the age of 10 years, with the female developmental curve levelling off at the age of 14 and the male curve at 16 years. Error rate in serial performance decreased with age. After taking both corrected speed and errors into account, a significant difference at 10 years remained between the sexes. Regarding laterality, the dominant hand was faster in index FT. While speed differed in absolute values in male and female groups through the age groups, the ratio between index finger tapping speed and non-dominant / dominant hand did not differ after 12 years of age between the two genders.

The possible role of gender-based differences in developmental changes of the nervous system, such as earlier maturation of white matter in females, and a male advantage in CS tract myelination/axonal diameter will be discussed.

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Overview of the presentation

Methods

Participants

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
</tr>
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<tbody>
<tr>
<td>10</td>
<td>9</td>
<td>10</td>
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<td>12</td>
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<td>18</td>
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<td>10</td>
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<tr>
<td>20</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>56</td>
<td>62</td>
</tr>
</tbody>
</table>

Participants were typically developing children and adults all right-handed.

Task and variables:

![Figure 1. Tasks and variables of the study.](image)

Data acquisition

„Data glove” consisting of metal electrodes was placed on the distal phalanx of hand fingers and a Java based data acquisition software detected time and order of finger taps.

Statistical analyses:

Two-way ANOVA (age × gender) was performed on all variables. Post hoc analysis was performed by LSD. A p-value of 0.05 was taken as significance level for all statistical tests.
Figure 2. Index finger tapping performance by age and gender.

Dominant hand: two-way ANOVA showed significant main effect of age ($F_{5, 106} = 16.127, p < .05$) with no significant main effect of gender ($p > .05$). Gender × age interaction was significant ($F_{5, 106} = 5.331, p < .05$). Non-dominant hand: two-way ANOVA showed significant main effect of age ($F_{5, 106} = 16.565, p < .05$) with no significant main effect of gender ($p > .05$). Gender × age interaction was significant ($F_{5, 106} = 3.452, p < .05$). Significant female advantage at the age of 10 years with the dominant hand, females increase speed with both hands up to the age of 14 years then performance plateaus. Males continuously increase speed between 10 and 20 years outperforming females at 18 and 20 years.

Figure 3. Laterality measured by index finger tapping

No significant main effect of age ($p > .05$) and gender ($p > .05$) or significant interaction were found. Motor dominance shown by the ratio of non-dominant and dominant index finger tapping speed remained stable through ages and between sexes at least after the age of 10 years.
SERIAL FINGER TAPPING TASK

Figure 4.

Speed
There was a significant main effect of age ($F_{5, 106} = 14.254, p < .05$) with no significant main effect of gender ($p > .05$). Speed in serial task showed female advantage at 10 years and 14 years ($p > .05$) with an earlier plateau in females at 14 years.

Corrected tap interval
To minimize the effect of CS tract myelination on serial performance, we corrected the serial FT speed with the index FT speed. Two-way ANOVA showed significant main effect of age ($F_{5, 106} = 15.049, p < .05$) with no significant main effect of gender ($p > .05$). There was a significant difference between males and females at the age of 10 and 14 years ($p > .05$), with the female developmental curve levelling off at the age of 14 and the male curve at 16 years.

Accuracy
There was significant main effect of age ($F_{5, 106} = 5.671, p < .05$) but no difference between sexes at any age group ($p > .05$). 20 and 16 years old participants outperformed 10, 12, and 14 years old children. The 18 years old group performed better than the 10 years old.

Discussion
Female show advantage at the age of 10 years and levels off performance ahead of males at 14 years both in simple repetitive and serial tasks. It parallels earlier onset and end of puberty in females. Peak volume of thalamus, striatum and cortex is ahead of males, after reaching peak striatum surface area remains unchanged in females in this age span (Giedd et al., 2006; Raznahan et al., 2010).

Male advantage from 18 years of age in simple repetitive task may reflect prolonged myelination (Bartzokis et al., 2010) in males due to raised testosterone level (Raznahan et al., 2010). Furthermore, development of basal ganglia and cerebellar structures are prolonged in males (Tiemeier et al., 2010).
IV. General discussion and further aims

Fine motor function involving independent finger movements is mediated by motor cortices at a great extent and is in coordination with the basal ganglia and the cerebellum. The aim of the present thesis was to map developmental aspects of fine motor performance and learning in typical development by using the finger tapping paradigm. A further aim was to examine motor performance and learning characteristics through the window of a neurodevelopmental disorder, Williams syndrome, that is characterized by fine motor problems and atypical sleep.

My first hypothesis was that accuracy and speed of finger movements improve with age from childhood to adulthood both in simple repetitive and sequential tasks. I also expected gender differences in development to be present and dissociated in simple and sequential tasks. Therefore, developmental trajectories of repetitive and sequential finger movements were characterized in a large sample of TD children, adolescents and adults (n=80) between 6-30 years of age. Baseline performance had a prolonged development until adulthood in both tasks. Accuracy reached adult level at around 20 years of age and speed increased until 30 years of age in the sequential finger tapping task (Study I.). This is in accordance with the cortical developmental trajectory of grey matter structures (Giedd et al., 2006) and the prolonged myelination of the CS tract that results in increasing motor speed (Bartzokis et al., 2010) both in repetitive and sequential tasks. While did not reach statistical significance, the developmental trajectory showed an unexpected peak at early puberty with respect to baseline performance in different age groups (Study I.Fig. 2.B. page 59.). This motivated our further study, the systematic investigation of gender and age effect on the baseline of fine finger task performance in puberty (Study III. and Study V.). We hypothesized female advantage in both sequential and repetitive tasks in the assessed age span (10-20 years). Our results showed that behavioral results paralleled sexually dimorphic maturational changes in the central nervous system: there was a female advantage in sequential tasks until adolescence, then performance levelled off at the age of 14 in females (Study V.). At his age, musculoskeletal maturation is complete and a majority of grey matter and white matter maturation is achieved in females (see I.2.4.). After the
age of 14 years developmental trajectories showed a differential pattern between genders. Males showed superior performance in repetitive tasks that increased beyond puberty (Study V.). Regarding laterality, the dominant hand was faster in index FT. While speed differed in absolute values in male and female groups through the age groups, the ratio between index finger tapping speed and non-dominant / dominant hand did not differ after 12 years of age between the two genders (Study V.). While no previous studies investigated developmental trajectories of simple repetitive finger tasks in females during puberty, our result on males is partially supported by that of Bartzokis et al. (2010) who found increasing index finger tapping speed in males between the ages of 18 and 38 years. This may be related to continuing myelination (Bartzokis, 2010, I.2.1. Figure 2. page 16) related to increased testosterone levels in males (Raznahan et al., 2010). This advantage seems to diminish in more complex and sequential tasks. After correction of the CS tract myelination effect on speed, we found that the motor developmental trajectory still showed earlier maturation in females than in males (Study III., Fig.2. page 83). Since the motor cortex plays a crucial role in coding and learning independent finger movements, the developmental pattern in this sequential task may correspond to earlier cortical maturation in females (see I.2.4.2).

With respect to the developmental aspects of motor plasticity, I hypothesized a continuing learning capacity until adulthood. Our results supported this hypothesis, since continuous plasticity was found until adulthood in the motor system (Study I.), suggesting that motor cortical networks coding sequential movement should be established before gains in speed can occur. When speed and accuracy was taken together and corrected by CS tract effect, the rate of learning was the highest in the early phase of learning reaching peak in childhood and early puberty and learning capacity was extended into adult age (Study I.Fig.3.B. page 60). It parallels the maturation of the motor cortex where the selective elimination of synapses occurs around the age of twelve years (Huttenlocher, 2002). Horizontal connections in this area are implicated in the selection and coordination of motor representations (Donoghue et al., 1992). Moreover, the development of GABAerg system important for cortical plasticity is not reached adult level at this age in motor cortex (Ziemann, Muellbacher, Hallett, & Cohen, 2001).
adulthood, plasticity may subserve lifelong adaptation in the motor system and based not only on horizontal connections in the grey matter but may also be associated with myelination (McKenzie et al., 2014). 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.

In a neurodevelopmental disorder, the Williams syndrome, I examined fine motor performance characteristics and studied whether altered sleep is related to motor learning impairment. I hypothesized that motor performance in finger tapping in Williams syndrome is below the TD level both in repetitive and sequential tasks. I also expected impaired learning capacity both in terms of speed and accuracy that, in turn, may be associated by the disordered sleep characteristics in WS. The hypothesis was motivated by the fact that there are fine motor difficulties and also sleep problems in Williams syndrome. I found that WS motor performance differed from TD both in baseline and in learning capacity. The baseline was below TD both in accuracy and speed and had great individual variability between participants (Study II. Fig.2. page 71 and Fig.5. page 74). First day learning showed that the improvement in online performance was comparable across TD and WS groups. On the other hand, sleep dependent offline improvement was impaired in WS (Study IV. Fig.3. page 91). During a prolonged 5-day learning session, WS participants increased their performance significantly from Day 1 to Day 5 as a group. Transfer tests administered to measure specificity of motor learning related to motor cortices showed a similar pattern in WS and in TD participants, with lower absolute values in WS (Study IV., Fig. 4. page 92). Task specific learning in both groups was indicated by significant improvement from Day 1 to Day 5, with Day 5 performance being higher than that of the transfer tests in both speed and accuracy measures (see I.3.1.). This is in accordance with previous findings in TD (Fischer et al., 2002; Karni et al., 1998; Walker et al., 2003). Furthermore, after a period of five days of learning, improvement in accuracy and speed dissociated in WS. While there was improvement in accuracy, speed reached a plateau in the
sequential task (Study II., Fig. 2. page 71). This is in accordance with previous studies reporting decreased the speed of various types of movements in WS (Elliott et al., 2006, Hocking et al., 2010, Hocking et al., 2009, Hocking et al., 2011b). On the other hand, limitation in speed was not dependent on decreased CS tract conduction velocity (Study II., Figure 3. page 72) since there was no correlation between maximum motor speed and sequential performance. Sequential speed reached its plateau at about 1.3 taps/s in WS even when maximum motor speed was in the TD range. Therefore, the limitation of maximum motor speed in WS does not provide a full explanation of decreased speed in the sequential task. In TD, both sequential and index FT increase with age until adulthood (Study I., Fig. 2 page 59 and Fig. 3. page 60), however, in WS performing a sequential rather than a simple repetitive task puts a constraint on the speed of the performance.

Since WS is associated with sleep alteration in the sigma frequency band in NREM sleep (Bódizs, Gombos, Gerván, et al., 2014; Bódizs et al., 2012), it raised a question whether the decreased amount of learning in this sleep dependent learning task is related to alteration in sigma band activity (Study IV.). It was hypothesized that sigma band alteration in WS shows association with offline learning capacity. In WS, baseline, first day online and offline learning performance were correlated with sigma band activity. Improvement in accuracy was comparable both online and offline in this first phase of learning in WS and TD groups. Offline improvement in accuracy was related to higher 11-13.5 Hz z-transformed power, while higher oscillatory peak frequency in sigma band was associated with decreased learning performance (Study IV. Fig. 4. page 92). In other words, sigma frequency band characteristics closer to TD resulted in superior learning in WS. These results support the role of sigma band activity in motor learning. As an unexpected result, online improvement in speed was correlated with low sigma power in WS. Moreover, there was no association between altered sigma band activity and the lack of offline gain in speed that in WS. Further studies are necessary to explore the more detailed relationship between sigma band activity and online learning, and the dissociation between speed and accuracy during motor learning. The WS-specific alterations of sigma band activity are of potential interest for those aiming to unravel the neural roots of the individual
differences in motor learning performance in participants with WS or other neurodevelopmental disorders. Since similar results were found in other disorders such as ADHD (see I.3.4. page 28), it would be a desirable direction to map disease-specific learning alterations in atypical development to promote adequate therapy development and support special educational needs.

Regarding typical development, further research should extend to developmental aspects and gender differences in fine motor learning with respect to the adulthood and the elderly. It shall address not only the behavioral level but also sleep/sleep disorder related learning capacity that in turn may underlie therapies in this age span. On the other end of the age spectrum, sleep-dependent fine motor skill learning (such as handwriting) in school-age children can be addressed in relation with educational aspects such as daily routine, timetables and practice distribution. Mapping age-dependent dominance of learning strategies (e.g., implicit vs. explicit) in motor skill acquisition as suggested by Janacsek et al. (2012) would give new insights when developing teaching strategies. Furthermore, imaging and neurophysiological studies combined with learning tasks should extend behavioral results both in TD and atypical development to unravel age, gender and disease specific neurological underpinnings of learning mechanism.
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