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FINE MOTOR DEVELOPMENT AND LEARNING IN TYPICAL DEVELOPMENT AND IN WILLIAMS SYNDROME

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General background

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. Fine motor function involving independent finger movements is mediated by motor cortices at a great extent and is in coordination with other cortical areas, the basal ganglia and the cerebellum (Mima et al., 1999). Changes in the nervous system and the musculoskeletal system during development result in behavioral differences through ages and gender. Age-dependent improvement of finger movements depends on the maturation of the brain, corticospinal tract (Bartzokis et al., 2010), spinal cord circuits (Lundy-Ekman, 2013), periphery (Lang et al., 1985) and the musculoskeletal system (Cech & Martin, 2012). Maturation of these structures shows not only age-dependent but also gender based differences that suggests age and gender based differences in fine motor performance. Motor learning, particularly 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 (Karni et al., 1998). Offline consolidation is brain-state dependent: time spent awake results in retention of performance acquired during practice, while off-line gains are sleep-dependent both in speed and in accuracy in adults (Walker et al., 2003). 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 (Tamaki et al., 2013).

Since a systematic investigation of age and gender based characteristics of fine motor performance is lacking in the field, the first aim of the present thesis was to map developmental aspects of fine motor performance and learning in typical development (Theses I-II.).

Williams syndrome (WS) is a rare neurodevelopmental disorder due to a microdeletion on one copy of chromosome 7 in the q11.23 region. It is characterized by mild to moderate intellectual disability, hypersociability, attention deficits, and problems with visuospatial processing (Bellugi, Lichtenberger, Jones, Lai, & St George, 2000). Motor development is delayed, gross and fine motor deficits throughout the lifespan are common findings (Carrasco, Castillo, Aravena, Rothhammer, & Aboitiz, 2005). WS is also characterized by altered sleep (Gombos, Bodizs, & Kovacs, 2011). Sigma wave activity is decreased in the low (<13 Hz) and increased in high (>13 Hz) frequencies (Bódizs, Gombos, & Kovács, 2012). While fine motor deficits are described, there has been no investigation of fine motor characteristics and learning capacity in WS. Therefore, the second aim of the thesis was to determine fine motor performance and learning characteristics in WS. It was further extended by the examination of the relationship between NREM sigma band alterations characteristics to WS and learning capacity in the motor domain measured by the finger tapping paradigm (Theses III-IV.).

The finger tapping paradigm is a fine motor task that has been used as a tool to address plasticity in the motor system (Karni et al., 1998). The goal is to perform a predetermined sequence with the fingers of the hand as accurately and as fast as possible. Two tasks were introduced to the performers: a repetitive index finger tapping task and a four elements long 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.

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 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., Study III., and Study V.).

Developmental trajectories of repetitive and sequential finger movements were characterized first in a large sample of TD children, adolescents and adults (n=58) between 6-30 years of age (Study I.). Performance increased with age and showed a prolonged developmental trend until adulthood in both sequential and repetitive tasks. 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 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. 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.). 118 right handed males and females between the ages of 10 to 20 participated in the study. We hypothesized female advantage in both sequential and repetitive tasks in the assessed age span. 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 almost complete and a majority of grey matter and white matter maturation related to puberty is achieved in females (Wierenga et al., 2014). 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) 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. and Study V.). 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.

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.). Our results supported the hypothesis, since continuous plasticity was found until adulthood in the motor system during a 5-day learning (Study I.). When speed and accuracy was taken together and corrected by CS tract effect, baseline performance and the amount of learning exhibited a strong negative correlation. Learners with low initial performance presented the greatest improvement (Study II.). 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). 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). 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).

Thesis III. Fine motor skills in Williams syndrome

I hypothesized that motor performance in finger tapping in WS 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 WS. 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 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.). 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). 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.). 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 (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.), 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 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, however, in WS performing a sequential rather than a simple repetitive task puts a constraint on the speed of the performance.

Thesis IV. Sleep dependent motor learning in Williams syndrome

I hypothesized that altered sleep characteristics lead to impaired learning capacity in WS. This study tested if the formerly reported specific alterations of broadband sigma (8-16 Hz) activity in WS are associated with deficits in offline fine motor learning (Study IV.). 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. 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.

List of publications related to the thesis

I. Gerván, P., Berencsi, A. & Kovács, I. Vision first? The development of primary visual cortical networks is more rapid than the development of primary motor networks in humans. *PloS one* 6, e25572, doi:10.1371/journal.pone.0025572 (2011).

II. Berencsi, A., Gombos, F. & Kovács, I. Capacity to improve fine motor skills in Williams syndrome. *Journal of Intellectual Disability Research* 60, 956-968, doi:10.1111/jir.12317 (2016).

III. Gerván, P., Filep, O., Soltész, P., Berencsi, A. & Kovács, I. Posterior–Anterior Brain Maturation Reflected in Perceptual, Motor and Cognitive Performance. *Frontiers in Psychology* 8:674. doi: 10.3389/fpsyg.2017.00674 (2017).

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.*

V. Berencsi, A., Gerván, P., Filep, O. & Kovács, I. Gender differences in the pubertal trajectory of fine motor development. Progress in Motor Control X. Conference: Program and Abstracts *Hungarian Sport Science Booklets*; XII. (2015).

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