Center for Lifespan Psychology

Research Project 1: Neuromodulation of Lifespan Cognition (Concluding Report)

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Conceptual Overview

The central goal of this project is to understand how maturational and senescent changes in neurotransmitter systems influence neural and behavioral development across the lifespan. To this end, the project has used an integrated array of conceptual tools and empirical paradigms, encompassing neurocomputational studies aimed at theory formation, behavioral studies informed by genetics that examine the relations between neurally relevant genotypes and cognitive phenotypes, and genomic and pharmacological imaging studies that explore age-related as well as other individual differences in brain–behavior relations.

Neurotransmitters regulate neural processing from moment to moment and contribute to age-graded changes in the dynamics of neural networks (Li, 2013). A major focus of the project is on the relationship between *dopaminergic* neuromodulation and lifespan changes in brain and behavior. Formal models and empirical evidence suggest that suboptimal dopamine modulation, as observed early and late in ontogeny, contributes to greater random processing variability in neural and cognitive information processing (Li, Lindenberger, & Sikström, 2001). This, in turn, has effects on cognition, including greater trial-to-trial performance fluctuations and process dedifferentiation. In particular, the function that relates dopamine signaling to cognitive performance is generally assumed to follow an inverted *U*-shape. This nonmonotonic relationship implies that constant amounts of genetic variation in genes relevant for neuromodulation result in increasingly large differences in performance as normal aging moves individuals' neuromodulatory efficacy away from the apex of the curve. Hence, normal aging is expected to magnify the effects of genetic variation on individual differences in behavior (Lindenberger et al., 2008). During the reporting period, the project has continued to test this proposition with behavioral and electrophysiological data across a wide range of cognition-relevant genes and cognitive functions. As is true for candidate gene studies in general, the observed genotype effects need to be replicated in independent samples to substantiate the genotype-phenotype associations that have been observed thus far.

Dopamine Genotype Effects on Performance Variability and Memory Dedifferentiation in Old Age

When assessing individuals' performance on a visual perceptual selection task, we found that the reaction times of individuals carrying a greater number of beneficial alleles of the dopamine transporter (the *DAT1* gene) and receptor genes (the dopamine *DRD2* and *DRD3* genes) fluctuated less than the reaction times of individuals carrying a lower number of beneficial alleles. This effect was only observed in older adults. Moreover, older carriers of fewer beneficial alleles also exhibited a greater tendency to forget memory items encoded 1 week ago (Papenberg, Bäckman, et al., 2013). In a related study (Papenberg et al., in press), we investigated the effect of a genotype relevant for prefrontal dopamine signaling on the dedifferentiation of memory processes as a means of addressing the dedifferentiation hypothesis of cognitive functioning in old age. The results of this study showed that the correlation between working memory and episodic memory factors was stronger among older individuals whose genotype is associated with lower levels of prefrontal dopamine (Val homozygotes of the *COMT* gene; see Figure 7). Again, these genetic effects were only observed in older adults. Taken together, these results indicate that, in line with our theoretical predictions, suboptimal dopaminergic modulation contributes toward process fluctuations, which may impair multiple facets of cognitive functioning in the course of normal aging.

Several studies revealed additional magnification effects. Older adults with the *DAT1* genotype (*DAT1* 9/9), associated with higher levels of extrasynaptic dopamine, and the genotype *DRD2* CC, which is associated with

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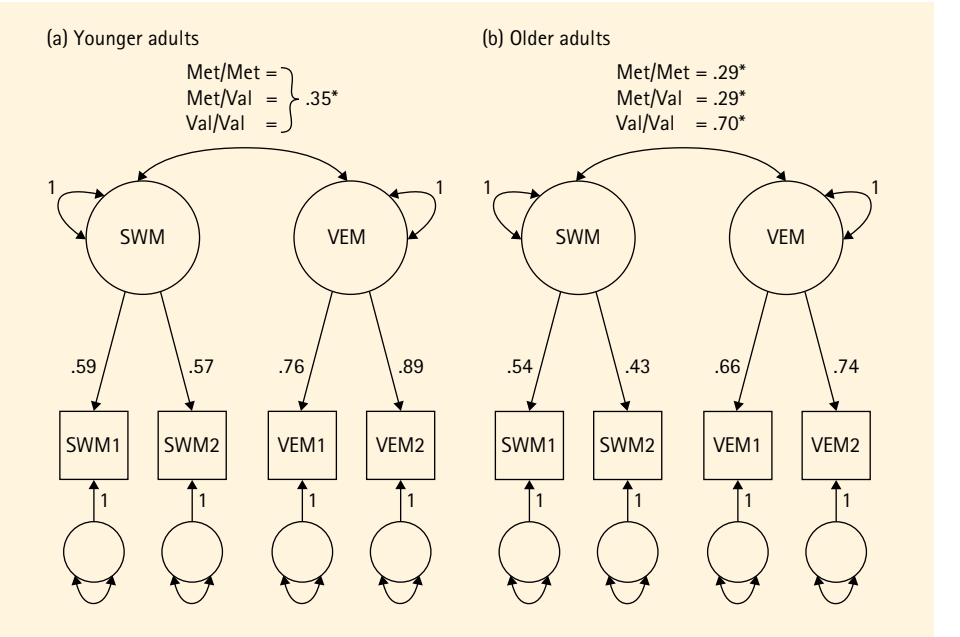

Figure 7. The correlation between spatial working memory (SWM) and verbal episodic memory (VEM) differs by age group and phenotype. The figure shows the results of a multiple-group latent structural equation model for younger (a) and older (b) adults. The two aspects of memory functions are less differentiated (i. e., more highly correlated) among older Val homozygotes of the COMT gene than in any of the three groups (adapted from Papenberg et al., in press).

higher dopamine D2 receptor density, showed better backward serial recall performance than older adults who did not carry these beneficial alleles (Li, Papenberg, et al., 2013). In a sequence learning task, older adults, in particular those with fewer of the beneficial alleles of dopamine relevant genes, had more difficulty in deriving explicit knowledge through learning than younger adults (Schuck, Doeller, et al., 2013). In both cases, the corresponding genetic effects were only observed in older adults.

Lifespan Age Differences in EEG Theta Coherence and Variability in Inhibitory Control

In a related line of inquiry, we investigated neural correlates of trial-by-trial performance fluctuations across the lifespan (Papenberg, Hämmerer, et al., 2013). Specifically, we used electroencephalography (EEG) to examine age differences in intertrial EEG coherence during a task requiring prefrontal cognitive control of inhibition from middle childhood to old age. We found that theta intertrial coherence increases from childhood to early adulthood and decreases from early adulthood to old age (see Figure 8a). Moreover, in all age groups, individuals who showed lower EEG coherence (i. e., a greater degree of temporal jitter in EEG signal across trials) also showed greater trial-by-trial reaction time fluctuations (see Figure 8b). Available evidence suggests that control signals in the medial frontal cortex (MFC) are reflected in theta band activity, suggesting that distinct brain areas work in coordinated fashion during tasks that demand executive control. Together with other findings in this field, our findings suggest that less reliable control processes in children and older adults may contribute to the greater degree of performance fluctuations in both age groups relative to adolescents and young adults.

Lifespan Development of Auditory Attention and Dopamine Genotype Effects

The efficacy of attentional regulation changes across the lifespan. Attention involves frontal-parietal networks that are innervated

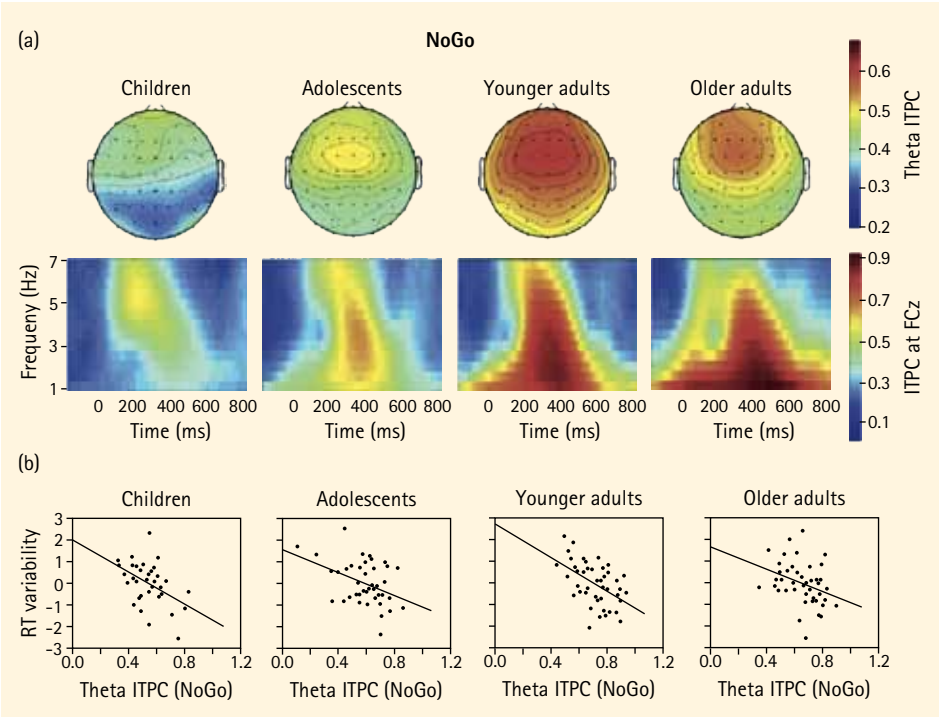

Figure 8. Intertrial phase coherence (ITPC) of the EEG during attentional processing differs by age group. (a) Topographical maps of theta intertrial phase coherence at frontal and central electrodes during the inhibition (NoGo) condition. Children, adolescents, and older adults showed a lesser degree of coherence in comparison to younger adults. (b) Scatterplots of the correlation between peak theta coherence during inhibition and trial-by-trial reaction time fluctuations during Go conditions (adapted from Papenberg, Hämmerer, et al., 2013).

by dopaminergic and cholinergic pathways. Hence, the third area of research focused on experiments that investigated age-related differences in perceptual and attentional mechanisms. In the domain of auditory attention, we used an intensity-modulated dichotic-listening paradigm to manipulate both top-down attentional control and bottom-up perceptual distinctiveness. This line of research was carried out in collaboration with Kenneth Hugdahl and René Westerhausen from the University of Bergen. Our findings indicate that the top-down control of auditory attention is not fully developed in children and severely compromised in older adults (see Figure 9; Passow et al., 2012, 2013). In line with these age-related differences in behavior, a late fronto-central negativity that peaks around 450 ms after stimulus onset (i. e., the N450 component) reliably discriminates between conditions of high versus low attention–perception conflict in younger adults, but not in older adults (Passow et al., 2014). Moreover, we found that younger adults with the genotype associated with lower dopamine receptor function (i. e., G carriers of the *PPP1R1B* gene) show less flexible attentional regulation of auditory processing as well as weaker N450 (Li, Passow, et al., 2013).

This project came to a close at the Center when Shu-Chen Li accepted an offer as full professor at the Technische Universität Dresden in August 2012 where the project is being continued and developed further.

A large sample of younger and older adults recruited by this project has formed the backbone of the Berlin Aging Study II, which is carried out at the Center (see pp. 234–238). With its emphasis on neurocomputational modeling of lifespan changes in cognition, the *Neuromodulation of Lifespan Cognition* project has contributed significantly to the scientific agenda of the Center.

Key Reference

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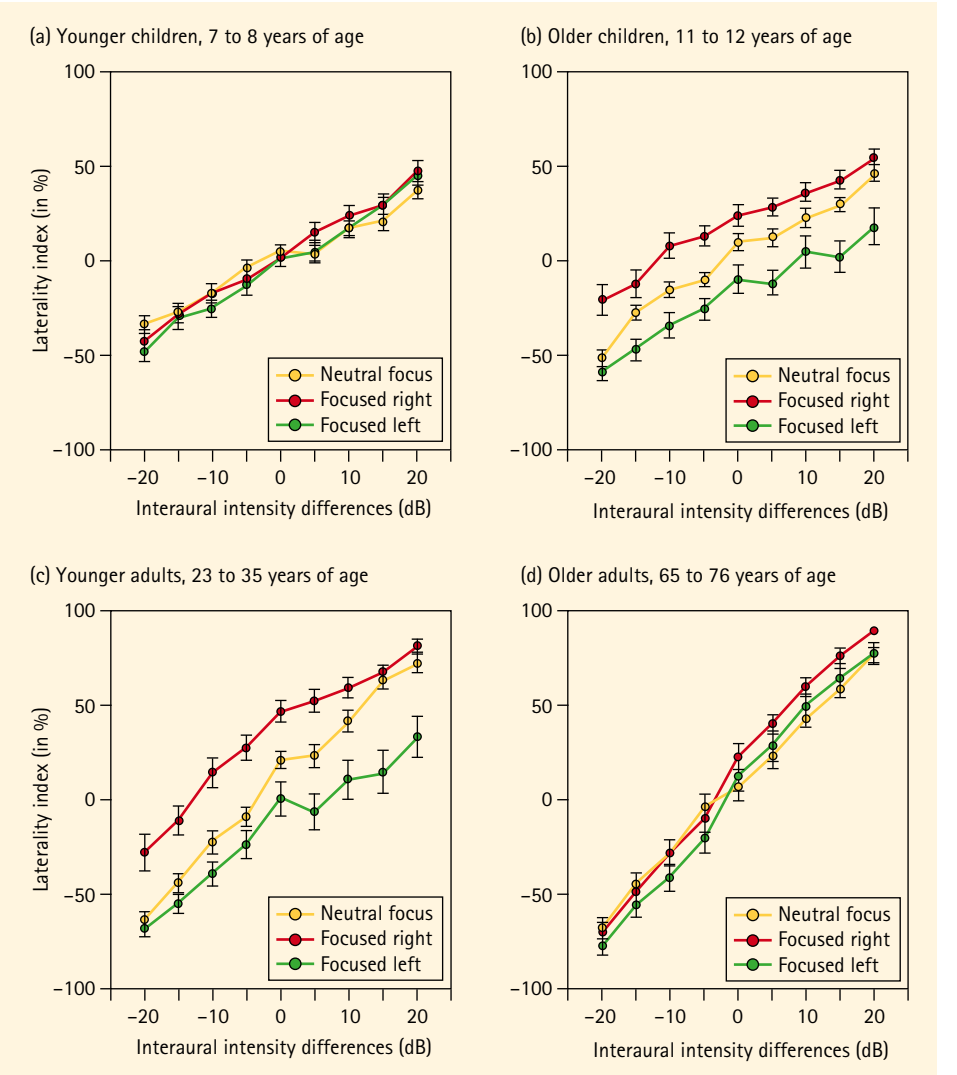

Figure 9. The attentional regulation of auditory processing differs markedly by age. Participants were presented with dichotic pairs of voiced versus unvoiced syllables (e. g., /ba/ vs. /pa/) and were asked to report the syllable heard. Perceptual saliency, shown on the x-axis, was manipulated by decreasing the intensity of either the right- or the left-ear input in 5-dB steps until a maximum difference of 20 dB between ears was reached. Negative values represent conditions in which left-ear stimuli were louder than right-ear stimuli, and positive values represent conditions in which right-ear stimuli were louder than left-ear stimuli. Attentional focus was manipulated by instructing participants to focus on the right ear, on the left ear, or on both ears (neutral focus). Reports are quantified by the laterality index, shown on the y-axis, which expresses the amount of right-ear reports in relation to left-ear reports (i. e., [(right ear – left ear) / (right ear + left ear)] x 100). The laterality index ranges from –100 % to +100 %, with positive values indicating a right-ear advantage and negative values a left-ear advantage. When the stimulus for the attended ear is louder, then attention is facilitated by saliency; when the stimulus for the attended ear is softer, then the saliency advantage of the stimuli presented to the unattended ear has to be overcome by top-down attentional control. In contrast to younger adults (c), who were capable of flexibly focusing their attention on auditory inputs from either the right or left ear, performance in older adults (d) was driven almost exclusively by perceptual saliency. Children showed rapid development of attentional control from middle to late childhood (adapted from Passow et al., 2013; see also Passow et al., 2012).