Sofja Kovalevskaja Research Group on the Plasticity of Brain and Behavior in Adulthood and Old Age (Concluding Report)

Researcher

Martin Lövdén
(for collaborators, see Box 1)

Aging-related reductions in abilities, such as working memory, reasoning, episodic memory, and spatial orientation, begin roughly around the age of 65, but different individuals perform at different levels and change at different rates. Epidemiological work suggests that individuals with a lifestyle rich in mental, physical, and social stimulation experience less cognitive decline in old age (Lövdén, Ghisletta, & Lindenberger, 2005). However, we know little about the mechanisms through which experience modulates cognitive aging. For example, we do not know whether the favorable influences of an enriched lifestyle on cognitive change come from direct effects of mental stimulation on cognitive performance or through indirect routes, such as avoidance of negative effects on cognition (e. g., depression, stress, or vascular conditions). The goal of the Sofja Kovalevskaja Research Group on the Plasticity of Brain and Behavior in Adulthood and Old Age was to fill this research lacuna (see Box 2).

The group defines plasticity as the capacity for reactive change in brain structure caused by a mismatch between functional supply and experienced environmental demands and resulting in an alteration of the possible range of functioning (Lövdén, Bäckman, Lindenberger, Schaefer, & Schmiedek, 2010). We further postulate that the possible range of functioning can be altered either by the acquisition of new knowledge or by the alteration of the efficiency of neural processing. If experiencing an extended period of supply–demand mismatch (see Figure 4) were shown to improve the efficiency of neural processes

Key References

Lövdén, M., Bäckman, L., Lindenberger, U., Schaefer, S., & **Schmiedek, F.** (2010). A theoretical framework for the study of adult cognitive plasticity. *Psychological Bulletin, 136,* 659–676. doi: 10.1037/a0020080

Lövdén, M., Ghisletta, P., & **Lindenberger, U.** (2005). Social participation attenuates decline in perceptual speed in old and very old age. *Psychology and Aging, 20,* 423–434.

Studies Conducted as a Part of the Sofja Kovalevskaja Research Group on the Plasticity of Brain and Behavior in Adulthood and Old Age

SPACE
The study investigated the practice-related changes of spatial navigation performance and underlying brain structures in younger and older adults.

Researchers: Martin Lövdén; Nils C. Bodammer, Ulman Lindenberger, Sabine Schaefer
Predoctoral Fellow: Hannes Noack
Collaborators: Lars Bäckman (Karolinska Institute, Stockholm), Emrah Düzel (University of Magdeburg), Simone Kühn (University of Ghent)

COGITO
In collaboration with the Intra-Person Dynamics project, this microlongitudinal study investigated variability and practice-related changes of intelligence and relations to underlying brain structure and function in younger and older adults (for more information on the COGITO study, see Project 2, pp. 190–194).

Researchers: Florian Schmiedek, Martin Lövdén; Markus Werkle-Bergner, Nils C. Bodammer, Ulman Lindenberger
Postdoctoral Fellow: Annette Brose
Predoctoral Fellows: Julia K. Wolff, Thomas Grandy
Collaborators: Emrah Düzel (University of Magdeburg), Simone Kühn (University of Ghent), Naftali Raz (Wayne State University)

Swedish Military School of Interpreters
Conscript interpreters in the Swedish military learn a new language from scratch to native-like proficiency within a year. Our studies of these conscripts investigated behavioral and brain changes induced by language acquisition. A new series of studies will be conducted in collaboration with Project 3 (see pp. 195–200).

Researchers: Martin Lövdén, Nils C. Bodammer
Predoctoral Fellows: Johan Mårtensson (Lund University)
Collaborators: Mikael Johansson (Lund University), Magnus Lindgren (Lund University), Lars Nyberg (Umeå University)

Box 1.

The Sofja Kovalevskaja Award

In 2006, Martin Lövdén received the Sofja Kovalevskaja Award of the Alexander von Humboldt Foundation. Financed by the Federal Ministry for Education and Research, the one-million-Euro Award enables young scientists from outside Germany to finance their own research groups at a German university or nonuniversity research institution. The funding period of the Award extended over 4 years, from 2007 to the end of 2010.

Box 2.

supporting important cognitive functions, then the hypothesis that an enriched lifestyle may positively influence adult cognitive development would be supported. Hence, cognitive interventions with training regimes that target specific brain regions and circuits hypothesized to support specific skills are a powerful tool to explore the mechanisms and amount of plasticity in adulthood.

Questions central to the Group's research agenda included: Can cognitive practice in adulthood and old age improve performance on unpracticed cognitive tasks measuring the same or different cognitive processes as the trained tasks? Which are the cognitive mechanisms and brain correlates of such performance alterations? Does experience in the form of cognitive practice alter the brain's white- and gray-matter structure in adulthood and old age? What are the biological mechanisms of such structural changes? Which environmental, cognitive, and genetic factors determine the nature and magnitude of plastic alterations of brain and behavior in adulthood and old age? We addressed these questions in three studies (see Box 1).

The SPACE Study

In the SPACE study, we investigated changes in behavior and brain induced by spatial navigation training. The main research questions were: (a) whether structural alterations in the human hippocampus occur in response to navigation practice in younger adulthood

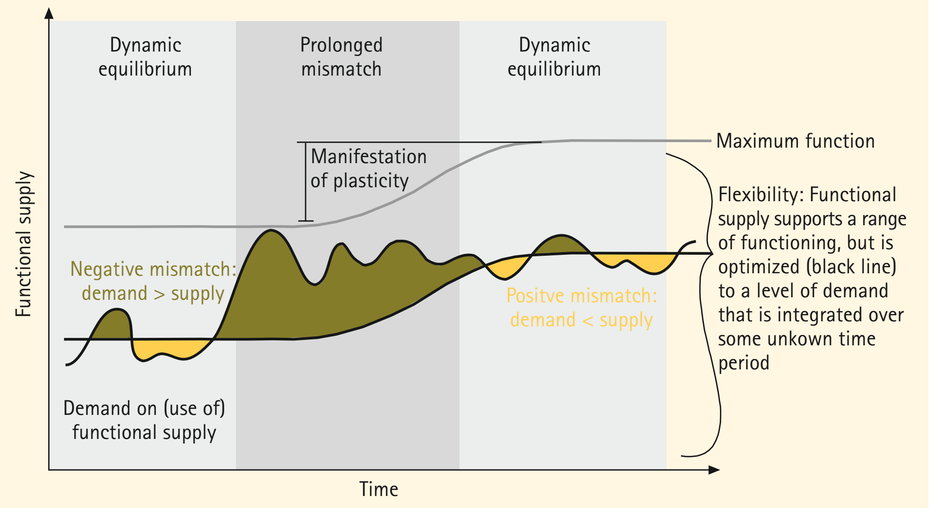

Figure 4. Schematic model of a mismatch between functional supply and experienced environmental demands caused by primary changes in demand (e.g., altered experience through cognitive training). Functional supply (i.e., the structural constraints imposed by the brain on function and performance) allows for range of performance and functioning. Flexibility denotes the capacity to optimize the brain's performance within the limits of the current state of functional supply. Due to the sluggishness of plasticity, structural supply optimizes its support for function to a level of demand (i.e., use of functional supply) that is averaged over some unknown time period, and mismatches need to be prolonged to overcome the inertia and sluggishness of plasticity, and to push the system away from its dynamic equilibrium. Deviations in demand that are within the current range of functional supply induce the mismatch that constitutes the impetus for plastic change (adapted from Lövdén, Bäckman et al., 2010).

and old age, (b) whether the magnitude of these experience-induced structural changes is reduced in old age, and (c) whether genetic influences on activity-dependent release of Brain-Derived Neurotrophic Factor (BDNF) moderate these effects. To this end, younger and older adults stratified on a common genetic polymorphism of the BDNF gene practiced spatial navigation in a virtual zoo while walking on a treadmill (see Figure 5). The practice period included 42 one-hour sessions administered every other day over a period of about 3.5 months. Control groups walked on a treadmill for a comparable amount of time. Immediately before, immediately after, and 3 months after termination of practice, cognitive performance was assessed during two sessions, and participants underwent magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), and magnetic resonance spectroscopy (MRS).

First results (Lövdén, Schaefer, Noack, Bodammer et al., in press) show that both younger and older adults performing the demanding spatial navigation task display navigation-related gains in performance and stable hippocampal volumes that were further maintained for 4 months after termination of training (see Figure 6a). In contrast, control groups displayed volume decrements consistent with longitudinal estimates of age-related decline. Hippocampal barrier density, as indicated by mean diffusivity estimated from DTI, showed a quadratic shape of increased density after training, followed by a return to baseline in the right hippocampus, but declined in the control groups and in the left hippocampus. These results thus indicate that sustained experiential demands on spatial ability protect hippocampal integrity from age-related decline. The results also provide the first longitudinal evidence indicating that spatial navigation experience modifies hippocampal volumes in humans, and confirm epidemiological results suggesting that mental experience may have direct effects on neural integrity.

Further detailed analyses of the younger adults (Lövdén, Schaefer, Noack, Kanowski et al., in press) addressed the neural mecha-

Key References

Lövdén, M., Schaefer, S., Noack, H., Bodammer, N. C., Kühn, S., Heinze, H.-J., Düzel, E., **Bäckman, L.,** & **Lindenberger, U.** (in press). Spatial navigation training protects the hippocampus against age-related changes during early and late adulthood. *Neurobiology of Aging.*

Lövdén, M., Schaefer, S., Noack, H., Kanowski, M., Kaufmann, J., Tempelmann, C., **Bodammer, N. C.,** Kühn, S., Heinze, H.-J., **Lindenberger, U.,** Düzel, E., & **Bäckman, L.** (in press). Performance-related increases in hippocampal N-acetylaspartate (NAA) induced by spatial navigation training are restricted to BDNF Val homozygotes. *Cerebral Cortex.* doi: 10.1093/cercor/bhq230

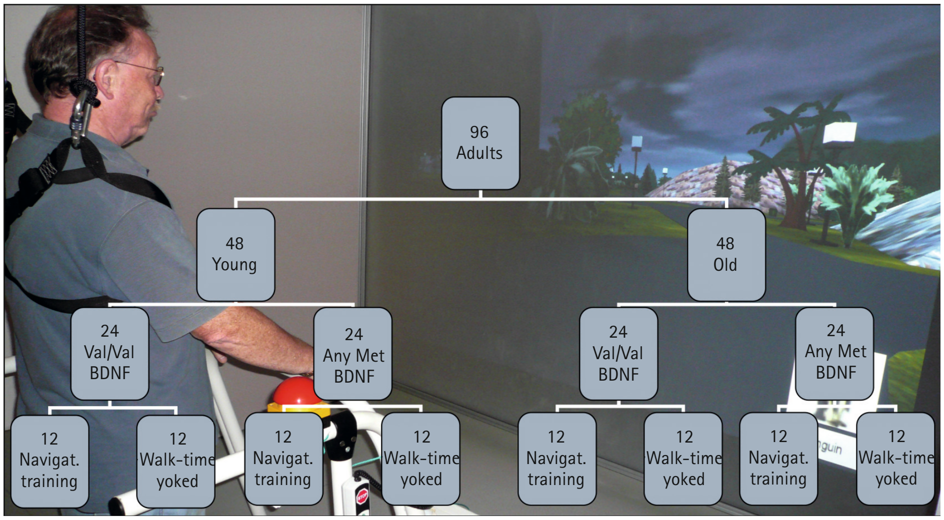

Figure 5. Design of the SPACE study. Younger and older adults stratified on a common genetic polymorphism of the BDNF gene (known to influence brain plasticity) practiced spatial navigation in a virtual zoo while walking on a treadmill. The practice period included 42 one-hour sessions administered every other day over a period of about 3.5 months. Control groups walked on a treadmill for a comparable amount of time. Immediately before, after, and 3 months after termination of practice, cognitive performance was assessed during two sessions and participants underwent MRI, DTI, and MRS. Main research questions were: (a) whether structural alterations in the human hippocampus occur in response to navigation practice, (b) whether the magnitude of these experience-induced structural changes is reduced in old age, and (c) whether genetic influences on activity-dependent release of BDNF moderate these effects.

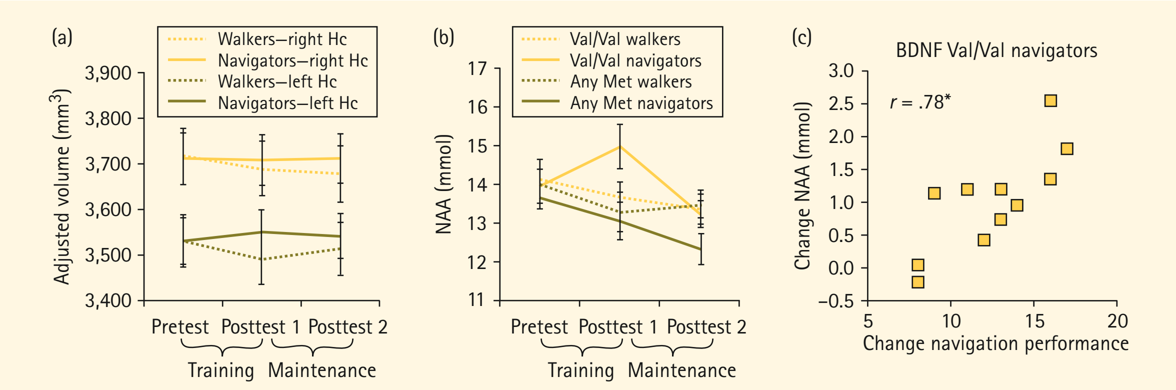

Figure 6. Spatial navigation training protects hippocampal integrity from age-related decline, confirming epidemiological results suggesting that mental experience may have direct effects on neural integrity. BDNF genotype moderates these plastic changes, which is in line with the contention that gene–context interactions shape the ontogeny of complex phenotypes and which suggests that activity-dependent release of BDNF is an important neural mechanism of plasticity. (a) Both younger and older adults performing the demanding spatial navigation task showed stable hippocampal volumes that were further maintained for 4 months after termination of training. (b) Training-induced changes in hippocampal NAA were substantial for younger BDNF Val homozygotes, but absent in carriers of the Met substitution in the BDNF gene, which is known to reduce activity-dependent secretion of BDNF. Unlike measures of brain volume, changes in NAA are sensitive to metabolic and functional aspects of neural and glia tissue and unlikely to reflect changes in microvasculature. (c) Among BDNF Val homozygotes, increases in NAA were strongly related to the degree of practice-related improvement in navigation performance. * $p < .05$ (adapted from Lövdén, Schaefer, Noack, Kanowski et al., in press).

nisms and histological nature of hippocampal gray-matter changes by examining changes in hippocampal N-acetylaspartate (NAA) as measured with MRS. Unlike measures of brain volume, changes in NAA are sensitive to metabolic and functional aspects of neural and glia tissue and unlikely to reflect changes in microvasculature. Training-induced changes in hippocampal NAA were substantial for younger BDNF Val homozygotes, but absent in carriers of the Met substitution in the BDNF gene, which is known to reduce activity-dependent secretion of BDNF (Figure 6b). Among BDNF Val homozygotes, increases in NAA were strongly related to the degree of practice-related improvement in navigation performance and normalized to pretraining levels 4 months after the last training session (Figure 6c). These findings indicate that changes in demands on spatial navigation can alter hippocampal NAA concentrations, again confirming epidemiological studies suggesting that mental experience may have direct effects on neural integrity. BDNF genotype moderates these plastic changes, which is in line with the contention that gene–context interactions shape the ontogeny of complex phenotypes and which suggests that activity-dependent release of BDNF is an important neural mechanism of plasticity.

The COGITO Study

In the COGITO study, conducted in collaboration with the Intra-Person Dynamics project, the group has examined changes in intelligence and underlying brain structure and function (for a detailed description of the COGITO study, see pp. 190–194). Here, we summarize the analyses done so far on a subgroup of participants from the main study that underwent functional and structural MRI before and after a micro-longitudinal practice phase. This phase lasted for a period of about 180 days during which younger and older adults trained for a total of 101 one-hour sessions on a set of three working memory, three episodic memory, and six perceptual speed tasks. In one study using this data set, we investigated plasticity of the white-matter tracts that connect the left and right hemisphere of the frontal lobes by using DTI and structural MRI (Lövdén, Bodammer et al., 2010). Control groups were assessed at pre- and posttest. Training affected several DTI metrics and increased the area of the anterior part of the corpus callosum. These altera-

Key References

Lövdén, M., Bodammer, N. C., Kühn, S., Kaufmann, J., Schütze, H., Tempelmann, C., Heinze, H.-J., Düzel, E., **Schmiedek, F.,** & **Lindenberger, U.** (2010). Experience-dependent plasticity of white-matter microstructure extends into old age. *Neuropsychologia, 48,* 3878–3883. doi: 10.1016/j.neuropsychologia.2010.08.026

Mårtensson, J., & **Lövdén, M.** (2011). Do intensive studies of a foreign language improve associative memory performance? *Frontiers in Psychology, 2:12.* doi: 10.3389/fpsyg.2011.00012

tions were of similar magnitude in younger and older adults. The findings indicate that experience-dependent plasticity of white-matter microstructure extends into old age and that disruptions of structural inter-hemispheric connectivity in old age, which are pronounced in aging, are modifiable by experience and amenable to treatment. Again, our results confirm epidemiological results suggesting that mental experience may have direct effects on neural integrity. Further work within the context of the COGITO study have revealed associations between individual differences in functional brain activation and decision-making processes (Kühn et al., in press) and relationships between moment-to-moment and day-to-day variability in cognitive performance and regional brain volume (Lövdén et al., in prep.).

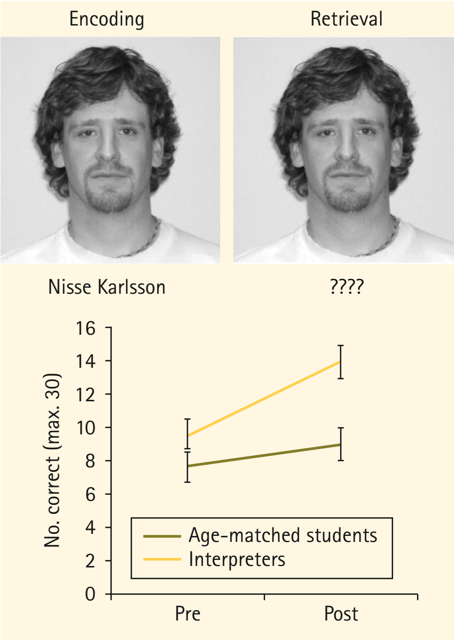

Figure 7. Conscript interpreters in the Swedish military learn a new language from scratch to close-to-native proficiency within a year. The high rate of improvement requires extremely intensive and effortful mental activities, which result in improvements in a face–name associative-memory task.

The Swedish Military School of Interpreters Study

The third line of research was conducted with conscript interpreters in the Swedish military. Here, we investigated the acquisition of a second language in adulthood and resulting functional and structural brain changes by examining conscript interpreters in the Swedish military. The conscripts learn a new language from scratch to close-to-native proficiency within a year. The high rate of improvement requires extremely intensive and effortful mental activities. During 2008, the military conscript interpreters and undergraduate students were measured on a battery of cognitive tasks in a pretest-training-posttest design (Mårtensson & Lövdén, 2011). We observed positive transfer from language training to a face–name associative-memory task, but not to measures of working memory, strategy-sensitive episodic memory, or fluid intelligence (see Figure 7). These findings provide initial evidence suggesting that associative-memory performance can be improved in early adulthood and that formal language education can have such effects. During the second half of 2009, brain structure and function before and after the conscripts' most intensive language studies have been examined with structural and functional MRI, DTI, and electroencephalography. Data are currently being analyzed (spring 2011).

Summary and Outlook

The overall goal of the Sofja Kovalevskaja Research Group on the Plasticity of Brain and Behavior in Adulthood and Old Age was to further our understanding of the mechanisms through which experience modulates cognitive aging. Using the suitable interventions, such as spatial navigation training, training of intelligence, and language acquisition, as a methodological approach, the group has fulfilled its goals by providing answers to the key questions: Experience in the form of intellectual activities has direct effects on the brain's white- and gray-matter structure in adulthood and old age. These changes can be of neuronal or glial nature and are likely to be partly mediated by activity-dependent release of neurotrophic factors, such as BDNF. Our results confirm epidemiological studies suggesting that mental experience may

have direct effects on neural integrity and support the notion that staying intellectually active into old age improves the prospect for remaining intellectually fit during the later and latest stages of the adult lifespan.
In the light of the group's productivity, Martin Lövdén and Ulman Lindenberger plan to pursue the agenda of the Sofja Kovalevskaja Research Group in a new project. This new project, tentatively labeled "Mechanisms and Sequential Progression of Plasticity," will conduct training experiments with large numbers of structural MRI scans over time within research participants to closely observe the cascade of structural brain changes that express the brain's plastic potential (Dissertation Elisabeth Wenger).