Updates in Neuroscience: How Therapy Changes The Brain

Martha S. Burns, Ph.D.

New Research Trends

- Brain Organization & Processing
- Brain Maturation
  - What sets up the brain in the early years for later academic success?
  - Neurodevelopmental factors that affect brain maturation
  - Ways to mitigate interference
  - Even the biggest skeptics are starting to “get it”
- The newest research further supports neuroscience-based interventions

Experience-Dependent Plasticity of the Cerebral Cortex (Pekna,M., Pekny, M., Nilsson,M., 2012)

- “The ability to adapt in response to the changing environment is the most fundamental property of the nervous tissue and constitutes the basis for learning.”
- Neural plasticity - neurobiological basis for ability to adapt & learn in an experience-dependent manner
  - At the structural level, neural plasticity could be defined in terms of:
    - dendritic and axonal arborization,
    - spine density,
    - synapse number and size,
    - receptor density,
    - and in some brain regions also the number of neurons.

Therapy Changes Brains

- The human brain is an experience-dependent organ
- Early-childhood experiences prepare the brain to learn
- Teachers build brains based on existing capacities – that is their main goal
- Therapists change brains through interventions designed to target and remediate underlying capacity limitations

NOW! Human Connectome Project

Author: Jenn Elam
Published: Mar 01, 2017
Study: HCP Young Adult

The Human Connectome Project (HCP) WU-Minn consortium is pleased to announce the 1200 Subjects Release of HCP image and behavioral data, its final release of new HCP Subjects. The 1200 Subjects release includes behavioral/demographic and 3T MR imaging data from 1206 healthy young adult participants collected August 1/16/2013-October 2015. Martha S. Burns, Ph.D.
Much of the change in brain structure occurs early in life.

The HCP tools and support help researchers understand how information is coded and travels in the brain.

Microscale – edges and nodes

Macroscale - connectome

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At birth, layer V neurons have more complex basal dendritic trees, which integrate synaptic inputs, than do layer IIIC neurons. Layer V neurons reach maximum complexity at 16–30 months after birth, before layer IIIC.

Synaptic spine density in the prefrontal cortex also peaks by 2–5 years and falls in adolescence.

HCP microscale measures provide open access research tools.

Example of Brain Level Microstructure Research - Max Planck Florida Institute

- http://www.youtube.com/watch?v=Raxch9I6_p8
Synaptic Architecture (Scholl, Wilson and Fitzpatrick, 2017)

- To do anything – e.g. think, touch or see
- Individual neurons need to organize inputs
- One microscale brain organizational strategy is spatial clustering of receptors on a dendritic spine

Spatial Clustering of Synaptic Inputs (Scholl, Wilson and Fitzpatrick, 2017)

Mesoscale – informs on individual nodes and circuits within the connectome and how we control them

HCP Macroscale – helps clarify multimodal cortical parcellation

Controlling Brain Networks (Bassett and Sporns, 2017) Micro-Macroscale


Macroscopic effects of network neuroplasticity from Feedforward (bottom-up) and Feedback (top down) processing with neuromodulatory control
New Research on Network Global Organization

- Shine, Breakspear, Bell et al. Nature Neuroscience | VOL 22 | FEBRUARY 2019 | 289–296 | www.nature.com/natureneuroscience

Brain Building Process

- Proliferation – neighborhood and suburb building
  - Synaptogenesis – neighborhoods connected by yards
  - Axon Development – access roads
- Pruning – clearing out the trees, unpaved roads, old empty houses, and barriers to development
  - Competitive Elimination

Brain Regions Build Based on Volume (Use)

- Essential for cognition and emotion
  - Language
  - Stress
  - Coordination of the 5 senses into a cohesive experience
- When you work these brain regions you tend to feel
  - Tired
  - Stymied
  - Frustrated
- The building starts just before birth, but is most profound before age 5

Proliferation – A. Synaptogenesis

- 1. Proliferation – neighborhood and suburb building
  - A. Synaptogenesis (neighborhoods connected by yards)

Zhang, Bao & Merzenich, Nature Neuroscience, 2001
1. The Proliferation of connections results in

- B. Axon Development
  - B. Axon development (access roads)

Proliferation - Axon development

Lebel et al., 2008

2. Pruning
  - 2. Pruning – clearing out the trees, unpaved roads, old unused houses, and other barriers to development
    - Competitive elimination
  - Zhang, Bao & Merzenich, Nature Neuroscience, 2001

3. Synaptic pruning fine-tunes circuitry
3. Pruning sculpts the brain for increased efficiency

Early in development proliferation prevails – Young children make many more new connections than adults.

Later in development pruning is more important – adults shift from a young brain that is good at learning to an older brain that is more effective and efficient but more rigid.

Dehaene-Lambertz & Spelke Neuron 2015

We get better and better at fewer and fewer things

Later Maturation: The Adolescent Brain

“A mismatch in the maturation of brain networks leaves adolescents open to risky behavior but also allows for leaps in cognition and adaptability” – Dr. Jay Giedd, University of California San Diego

Greater Networking Brings Maturity

Pruning Refines the Connectomes

Plots of grey-matter density are based on data by Gogtay et al. 2004 and illustrate the local grey-matter density in the mid-dorsolateral prefrontal cortex in red in the angular gyrus of the parietal cortex in blue, in the posterior superior temporal sulcus in purple, and in the occipital pole in green.


Summary of key aspects of brain development during adolescence.

Lateral PFC and IPS are the main regions of the cognitive control network. Although there is a consistent increase in IPS activation during cognitive control tasks into adulthood (+), the findings in the dorsal aspect of the lateral PFC are more mixed (?). The ventral aspect of the lateral PFC also shows both, increases and decreases in activation with age in tasks requiring self-control in

The MPFC, ATC and pSTS/TPJ are key regions of the mentalising network of the social brain. MPFC activation consistently decreases with age ( ) in social cognition tasks, while temporal cortex activation tends to increase with age (+).
Finally, the striatum and amygdala show peaks in activation during adolescence (*) when participants receive a reward or are presented with emotional stimuli, respectively.

Brain Maturation Mismatch

- But the prefrontal cortex, which controls impulses, does not mature until the 20s.
- This mismatch makes teens prone to risk taking but also allows them to adapt readily to their environment.

The Prefrontal Cortex

Lagging Maturation of PFC affects....

Studying individual differences in human adolescent brain development
Lucy Foulkes and Sarah-Jayne Blakemore

Nature Neuroscience | VOL 21 | MARCH 2018 | 315–323 |
www.nature.com/natureneuroscience
How to Turn Around Troubled Teens

By Scott O. Lilienfeld and Hal Arkowitz
Oct 16, 2014

Research reveals that get-tough tactics may worsen rates of juvenile delinquency

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Bottom up - the emotional and sensory brain regions lead

- It is not a half-baked adult brain, either.
- It has been forged by evolution to function differently from that of a purposeful adult

The limbic system, which drives emotions, intensifies at puberty

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Type 1 – Bottom Up Processes

Type I processes are automatic, stimulus driven, rapid, and do not require mental (EXECUTIVE) capacity.

- They are called ‘bottom-up’ as an evocative shorthand because they are elicited by sensory (external) stimuli and because human brain imaging and primate single cell recording studies link them with ‘feed-forward’ neural signaling (e.g., subcortical to cortical, or posterior to anterior cortical signaling) (Depue & Lenzenweger, 2006; E. K. Miller & Buschman, 2012).
- Bottom-up processes are not unitary (Evans & Stanovich, 2013).
SR Maturation - High Top Down Regulation

• Pre-event Goals, Values and Strategies
  – Approach –
    • Attention,
    • Working Memory and
    • Inhibition
  – Avoidance –
    • Planful risk taking and
    • Goal Management

What are some of the Major Environmental Influences on Brain Maturation?

• Poverty
• Stress
• Nutrition
• Environmental deprivation

Sensory Processing

• Generally early sensory processing builds modular maps that represent the stimuli fairly directly

Normal Development of the Brain Maps for Sound

Fig. 1 Human STG cortical selectivity to speech sounds. (A) MRI surface reconstruction of one participant’s cerebrum.

Zhang, Bao & Merzenich, Nature Neuroscience, 2001

Intermediate Tracts

N. Mesgarani et al. Science 2014;345:1006-1010

Superior longitudinal fasciculus
Body corpus callosum
Inferior fronto-occipital fas

Fig. 1a: Superior longitudinal fasciculus.
II. Recovery processes after focal brain injury

A. Recovery stages
B. Neuromodulators that drive neuroplastic change
C. The roles of intensity and frequency in brain reorganization after injury

There is also Axonal Plasticity – Remapping “Spectacular example” (Sapolsky, 2017)

- When a blind person, adept a Braille reads, there’s the same activation of the tactile cortex as anyone else
- However, there is also activation of the visual cortex
- Neurons abhor a vacuum – ergo diaschisis

“Neurons that normally send axons to the fingertip-processing part of the cortex instead have gone ‘miles’ off course, growing projections to the visual cortex” (page 144)


- Loss of function attributable to stroke results from cell death in the infarcted region
dcell dysfunction
surrounding areas


Functional spontaneous recovery involves 3 (likely) overlapping phases:

1. Reversal of diaschisis, activation of cell genesis, and repair;
2. change in the properties of existing neuronal pathways;
3. neuroanatomical plasticity leading to the formation of new neuronal connections.


The basic processes underlying phases 2 and 3 also are involved in normal learning


- In addition, the function of remote brain regions (including the contralateral areas) connected to the area of tissue damage, is compromised because of diaschisis
  - the remote depression of function in non-injured tissue (Munoz-Cespedes et al., 2005; Baillieux et al., 2010)
- which includes:
  - hypometabolism,
  - neurovascular uncoupling, and
  - aberrant neurotransmission


Areas of function attributable to stroke result from cell death in the infarcted region
cell dysfunction
surrounding areas


Loss of function attributable to stroke results from cell death in the infarcted region
cell dysfunction
surrounding areas

Neurophysiology of white matter tract recovery (Jiang, Q 2010)

- Neurorestorative treatment of stroke significantly increases both progenitor and mature oligodendrocytes in the ipsilateral hemisphere of the ischemic brain.
- Oligodendrocytes generate myelin and contribute to the integrity of white matter tracks in the brain.
- Stimulation and amplification of these cells may lead to restructuring of axons and myelin.

Maladaptive neuroplasticity

- Another principle is that not all plasticity has a positive impact on clinical status—in some cases, plasticity might have negative consequences.
  - new onset epilepsy is a common complication of cerebral trauma.

The ‘How’ of therapy: Chemical Drivers of Neuroplasticity

- The reorganization that occurs after rehabilitation is associated with upregulation chemical neuromodulators in relation to the parameters of the stimulation that occurred.

The ‘How’ of therapy: Chemical Drivers of Neuroplasticity

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But beyond early infancy, plasticity is modulated as a function of:

1. novelty
2. attention
3. judgment of error
4. punishment
5. Reward
6. et alia

See Kilgard & Merzenich, Science (1998)

- acetylcholine (focused attention/reward)
- dopamine (reward, novelty)
- norepinephrine (novelty)
- serotonin
- et alia

Different dimensions of adult cortical plasticity are enabled by the behaviorally-context-dependent release of:

In infants, exposure-based plasticity is relatively uniform.
In adults, learning-induced changes are complexly “nuanced” by differences in behavioral context that result in the differential release of 6 or 7 modulatory neurotransmitters.

In older animals and humans, the brain controls its own plasticity.

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Therapists as architects
- New knowledge builds new connections – The ‘What’ of therapy
- Practice with existing skills builds strength and speed of existing pathways – The ‘When’ and ‘How Long’ of therapy
- Augmenting neurochemistry (neuromodulators) The ‘How’ of therapy increases attention and enhances retention

Therapists as architects
- The first two years of life
- Synaptic spine density in the prefrontal cortex – the part of the brain that “does the harder thing” builds through the school-age years until adolescence

Gilmore, Knickmayer & Gao, 2018
Therapists as capacity builders

- Cognitive capacity for learning requires:
  - Fine-tuned sensory perception
  - Attention
  - Working Memory
  - Processing speed and accuracy

Therapists as Regional Planners: building dIPFC - the ability to “do the harder thing”

- Dopamine
  - Binds the value of a reward to the resulting work.
  - Immediate reinforcement drives the emotional reward center (limbic system).
  - Intermittent reinforcement drives dIPFC projections.

Working Memory Training

  - Although WM capacity has been viewed as a constant trait, recent studies suggest that it can be improved by adaptive and extended training.
  - This training is associated with changes in brain activity in frontal and parietal cortex and basal ganglia, as well as changes in dopamine receptor density.
  - Transfer of the training effects to nontrained WM tasks is consistent with the notion of training-induced plasticity in a common neural network for WM.
  - Transfer of the training effects to real life situations has mixed results.

SR - High Top Down Regulation

- Pre-event Goals, Values and Strategies
  - Approach –
    - Attention
    - Working Memory and Inhibition
  - Avoidance –
    - Planful risk taking and Goal Management

Fig. 4. Age patterns in the Stroop effect for response time (RT) in milliseconds (ms) among individuals with low, medium, and high working memory (WM) in equal blocks. The Stroop effect was calculated as the difference in RT between incongruent and neutral trials.


Figure 1. Training-related effects on brain activation and dopamine receptor density from neuroimaging studies. (a) Increases in frontal and parietal activity after training of WM (reproduced with permission from [33]). (b) Increased activity in the right hippocampus after training of WM tasks. Activity (reproduced with permission).
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Early clues to why some children may have reading woes

Other supporting research

- Auditory Processing Deficits were found in poor readers prior to school entry.
- Results support the existence of a general auditory processing impairment in developmental dyslexia that might be the cause of the phonological problems at least in a large subset of persons with dyslexia.

New Excellent Reviews on Neuromodulators


Neuromodulators and Their Role in Disease

- Different dimensions of attention and working memory are modulated by the behaviorally-context-dependent release of:
  - acetylcholine (focused attention/reward)
  - dopamine (reward, novelty)
  - norepinephrine (novelty)
  - Serotonin

Thiele and Bellgrove (2018) Neuron Volume 97, Issue 4, p769–785, 21
Acetylcholine and Functions Avery and Kirchmar 2017

Figure 8. The cholinergic system and its functions. The cholinergic system originates in the basal forebrain and sends projections to many cortical and subcortical regions. As a result, it has been implicated in a variety of functions including memory, attention, and uncertainty computations. Activity of the basal forebrain is thought to be regulated by prefrontal cortices, as well as other neuromodulatory brain regions.

DA, NA, 5HT Sapolsky on Depression

- Start at 15.5

Therapists Upregulate ACH During Direct Clinical Interaction

- Think – How TV commercials grab your attention – increased loudness, bright colors…
- Moving around the room,
- Establishing and maintaining eye contact,
- Gently touching a client’s shoulder or arm, maintains alertness
- Any, readiness or preparedness instructions “Are you ready?” “Tap when you want the next card”

ACH and DA are Oppositional

- Working memory is enhanced when small amounts of D1 agonists are applied in the vicinity of the neurons.
  - This selectively reduces activity for non-preferred memory fields.
  - This is equivalent to a noise reduction.
- WM is equally enhanced when small amounts of NA a2A agonists are applied in the vicinity of the neurons.
  - This selectively increases activity for preferred memory fields.
  - This is equivalent to signal enhancement.
- Both changes increase the SNR.

Dopaminergic System (Avery & Kirchmar, 2017)

Figure 3. Neuromodulation of WM Fields, Remote Feature Tuning, and Specificity of Dopaminergic Output Signals. Thiele and Bellgrove (2018) Neuron Volume 97, Issue 4, p.769-785, 21
How Therapists Upregulate D1 During Direct Clinical Interaction

- Timely appropriate reinforcement helps keep clients motivated and retain new information
- Therapy itself is rewarding (positive outcomes, new skills, better confidence (Dopamine)}

Noradrenalin & Functions Avery & Kirchmar, 2017

Figure 7. The noradrenergic system and its functions
How Therapists Upregulate NA During Direct Clinical Interaction

- Novel ways of presenting information,
- new materials,
- Any "wow, factor" Distinct Novelty – will get immediate retention but need to modulate
- Keep attention levels high by combining the two types of novelty that aid retention incorporating Common Novelty patient’s own past methods

Serotonin 5HT and Its Functions
Avery & Kirchmar, 2017

- Although the role of 5-HT in attention has been less intensively studied, varying levels of 5-HT do influence top-down attention and WM
- For therapists – providing a caring, safe environment for clients and patients to express their fears & needs with acceptance of their failures as part of the process likely aids with 5HT homeostasis
General Principles of Experience Dependent Neural Plasticity (Kleim & Jones 2008)

• Issues relating to the ‘what’ of therapy
  • 1. Use It or Lose It - Failure to drive specific brain functions can lead to functional degradation.
  • 2. Use It and Improve It - Training that drives a specific brain function can lead to an enhancement of that function.
  • 3. Specificity - The nature of the training experience dictates the nature of the plasticity.

General Principles of Experience Dependent Neural Plasticity (Kleim & Jones 2008)

• Issues related to ‘When’ of therapy
  • 4. Repetition Matters - Induction of plasticity requires sufficient repetition.
  • 5. Intensity Matters - Induction of plasticity requires sufficient training intensity.
  • 6. Time Matters - Different forms of plasticity occur at different times during training.

Other Factors: General Principles of Experience Dependent Neural Plasticity (Kleim & Jones 2008)

• 7. Salience Matters - The training experience must be sufficiently salient to induce plasticity.
• 8. Age Matters - Training-induced plasticity occurs more readily in younger brains.
• 9. Transference - Plasticity in response to one training experience can enhance the acquisition of similar behaviors.
• 10. Interference - Plasticity in response to one experience can interfere with the acquisition of other behaviors.

“Zone of Proximal Development”

• New concepts/skills are maximally learnable/processed because
  – they should be just difficult enough to engage the client/patient
  – yet easy enough to maintain high spirits
  – 80-20%

The ‘Why’ of Therapy

• As therapists we are scientists who always need to ask ‘why’, especially if an individual is not progressing adequately
  – If an approach is not working – why?
  – If an approach is successful with one individual but not another – why?
• It is not the problem of the client or patient – it is our problem to solve

Cognitive Training is One Component of a Broad Based Intervention Program

“Given that researchers are humans there is probably no meta-analysis without bias”

http://increasingintelligence.blogspot.com/2017/01/brain-training-controversy.html

https://www.youtube.com/watch?v=ea4SWjx1KD8&list=PLQ6fhMSBChUCw0ZBosBXTmmsCvzN8P4S&index=6&t=6s
Solutions: Neuroscience – Moving from Why to What and How

- Positive experiences after infancy have been shown to compensate to some degree for the negative behavioral consequences
  - Being exposed to an environment rich in opportunities for exploration and social play,
  - Caring and positive relationships with adults
- Computer activities designed to target the skills that are impacted can turn around some effects of poverty
  - Fast ForWord Ed-TECH exercises, because of their specific emphasis on language, attention and memory are particularly effective and offer a cost effective valuable solution