"Being ADD, when I read a book about marine life my mind allows me to travel with the fish and imagine life beneath the sea. Or I can read a book about astronomy and dance among the stars...I may not immediately comprehend that 3+4=7, but I may fully realize that n+26=51 and that the missing number is 25." - Matthew Kutz, age 13
Attention deficit disorder:

Impacts 2-5% of the population

Deficits in sustaining attention

Increased distractability

Increased impulsivity

Increased ‘temporal discounting’ of reward

Alterations in genes coding enzymes that regulate DA concentrations

Treatment with drugs that primarily target DA systems
a word about the prefrontal cortex and distraction:

rats with lesions specific to the cholinergic system show deficits in responding to simple cues

the prefrontal cortex appears to have neurons whose activity changes tonically during sessions when detection of a signal cue is complicated by the presence of distractors

the prevalence of such neurons appears to depend in part on the presence of ACh inputs to the prefrontal cortex

Gill et al., J. Neuroscience, 2000
what do we really know about DA neurons? – mostly this:

DA neurons appear to be very sensitive to differences between expected and actual reward amounts

in experiments where environmental stimuli predict subsequent rewards, DA neurons respond initially upon presentation of the reward as it was unexpected – with experience, DA neurons respond to the cue that predicts reward as its appearance is unexpected – at the same time, responses to the reward itself diminish as its presentation is predicted by the stimulus

can focused thought come to signal reward in the same way as an environmental cue or is the role of DA in attention deficit disorder related to other, presently unknown, aspects of DA function?

\[ E = MC^2 \]
‘waiting for the big one’ - DA neurons are sensitive to reward delay:

monkeys, like humans and rats, prefer immediate rewards, but will choose delayed rewards depending on the length of the delay and on the extent to which delay brings temporal discounting refers to the measured effect of reward delay on subjective reward magnitude

ADD patients tend to be ‘discounters’, preferring small immediate rewards over larger delayed rewards

DA neurons are discounters as well as the duration of their response to a reward-predicting stimulus will depend on its associated prediction of delay

cranking up DA in humans increases temporal discounting:

humans were treated with L-DOPA, a precursor to DA, to increase brain DA levels

under these conditions, they were more likely to choose smaller, immediate rewards over larger, delayed rewards (i.e., their ‘temporal discounting’ increased)

the degree of their temporal discounting correlated with changes in amygdala activity

so…boosting DA increased a symptom of ADD in normals, but alleviates that symptom in ADD patients
from sleep to attention – lecture 21 – Dec. 1, 2010

aging

101 year-old smoker, beer drinker, ..... marathon runner
healthy aging is associated with a variety of changes in brain physiology and in cognitive abilities

9.8% decrease in substantia nigra DA cell numbers per decade

2-3% decrease in brain volume per decade

cortical cell numbers unchanged with aging

spatial memory impaired in aging – data from Morris water tank tests (path length to reach escape platform) – Yang et al., JNP, 2008

auditory processing speed, memory, and ‘cognitive flexibility’ decrease with age – test yourself at: (www.positscience.com)

The ratio of AMPA-type glutamate receptors to NMDA-type increases with age – Yang et al., JNP, 2008
the ‘set-shift’ task reveals a specific extra-dimensional shift deficit in aged humans and humans with prefrontal damage.

circles = cups full of digging medium, some with reward at base   color of outer ring = digging medium (e.g., sand)
color of fill = odor (e.g., cinnamon)   star = correct choice (i.e., reward beneath digging medium)

- initial learning (odor, not medium, is relevant)
- intra-dimensional shift (i.e., odor still matters)
- extra-dimensional shift (i.e., digging medium matters)
- intra-dimensional reversal (i.e., correct odor switches)

Owen et al., Neuropsychologia, 2010
the ‘set-shift’ task reveals a specific extra-dimensional shift deficit in aged rats

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Barense et al., Learning and Memory, 2010
mediial prefrontal cortex lesions impair performance on extra-dimensional ‘set shifts’

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intra-dimensional shift (i.e., odor still matters)

extra-dimensional shift (i.e., digging medium matters)

intra-dimensional reversal (i.e., correct odor switches)

Birrell and Brown, J. Neuroscience, 2000
medial prefrontal cortex lesions impair performance on extra-dimensional ‘set shifts’, but orbitofrontal lesions impair performance on intra-dimensional reversals.

circles = cups full of digging medium, some with reward at base  color of outer ring = digging medium (e.g., sand)
color of fill = odor (e.g., cinnamon)  star = correct choice (i.e., reward beneath digging medium)

Brown and Bowman, TINS, 2002
compared to young, healthy subjects (YHE) both healthy aged subjects (OHE) and Alzheimer’s disease (AD) patients have decreased volumes of medial and dorsolateral prefrontal cortex, but not orbitofrontal cortex.

Salat et al., Arch. Neurology, 2001
I like to figure things out and solve problems.  
Temple Grandin

You have got to keep autistic children engaged with the world. You cannot let them tune out.  
Temple Grandin

I can remember the frustration of not being able to talk. I knew what I wanted to say, but I could not get the words out, so I would just scream.  
Temple Grandin

"For success in science and art a dash of autism is essential." Hans Asperger

"when taken into a room, he completely disregarded the people and instantly went for objects, preferably those that could be spun"  
Kanner

One of my sensory problems was hearing sensitivity, where certain loud noises, such as a school bell, hurt my ears. It sounded like a dentist drill going through my ears.  
Temple Grandin
autism characteristics -

i. impairments in reciprocal social interactions
ii. abnormal development and use of language
iii. repetitive and ritualized behaviors and a narrow range of interests
iv. i-iii frequently co-occur with mental retardation and/or epilepsy

autism theories -

i. impaired frontal cortex function (e.g., inability to shift attention appropriately)
ii. impaired amygdala function (e.g., poor social interaction and failure to respond to emotion-filled faces)
iii. altered structure of cortical mini-columns
iv. hyper-connectivity (intense world syndrome)
v. imbalanced local vs. global cortical processing
altered brain development appearing at around 1-2 years of age – frontal and temporal cortices and the amygdala, in particular, show rapid growth

Courchesne et al., Brain Res., 2010
the amygdala hypothesis:

Kluver-Bucy syndrome – loss of amygdala = diminished affect

amygdala activity in autistics predicts whether or not they will gaze at a face and whether or not the fusiform face area responds

amygdala lesion in monkey neonates results in subsequent development of repetitive behaviors

amygdala mediates fear conditioning in animals

Bauman et al., Behav. Neuro., 2008
frontal cortex –

prevalence of large-diameter axons is reduced in autism when actually attending to a face, autistic brains appear to respond similarly (at least as far as fMRI reflects brain activity)

but…medial regions of the prefrontal cortex exhibiting greater fMRI BOLD responses to familiar faces are not activated

other studies report decreased synchronization of frontal cortex with other regions of cortex
the search for alterations in fine structure of the cortex – mini-columns!

mini-columns were proposed by Mountcastle to compose functional units of the cortex

mini-columns grow in size in early development – in adulthood, they are twice as wide in frontal cortex as in visual cortex

frontal and temporal cortices of autism patients are associated with reduced mini-column sizes
the search for alterations in fine structure of the cortex – hyper-connectivity, hyper-plasticity, and the ‘intense world’ hypothesis

valproate, a drug used to treat epilepsy, drastically increases the incidence rate of autism when taken during a specific point in pregnancy

a rat model of autism has been created based on this phenomena – such rats have reduced social interactions, increased repetitive behaviors, are more anxious, and have long-lasting fear memories

cortical neurons in such animals are ‘hyper-connected’ and exhibit enhanced synaptic plasticity

this is proposed to lead to hyper-excitability of neurons
the search for alterations in fine structure of the cortex – local vs. global connections
evidence for connectivity changes in the resting EEG

- each dot marks the position of a recording electrode

- each line connects to recording sites where autistics show **reduced** EEG coherence relative to controls for the 8-10 Hz frequency band

- red lines correspond to relatively close electrodes (<10 cm apart) while blue and grey lines correspond to more distant connections (>10 cm apart)

- in the 8-10 Hz band, autistics show weaker coherence overall and coherence within prefrontal cortex is especially poor

-as in the figure above, this figure depicts differences in coherence between autistics and controls

-- here, however, each line connects points whose associated EEG signals show **greater** coherence in autistics in not the 8-10 Hz band, but the 3-6 Hz frequency band

-- in this 3-6 Hz band, stronger than normal EEG coherence occurs between frontal recording sites and distant electrodes

-- autistics also show high localized coherence among nearby electrodes of the temporal and parietal cortex