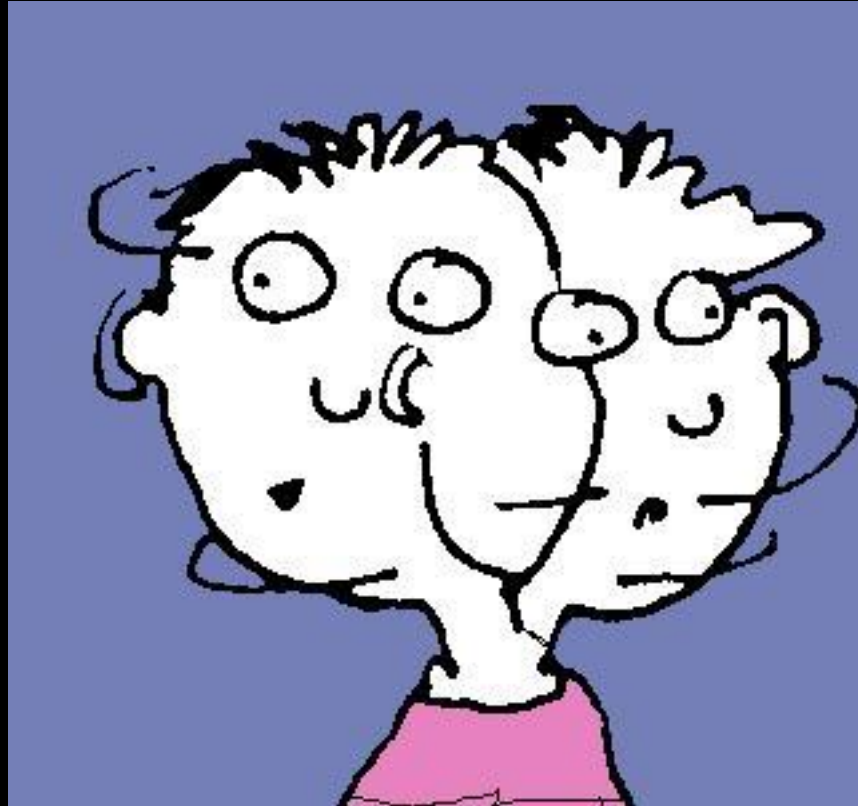


attention deficit disorder



"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

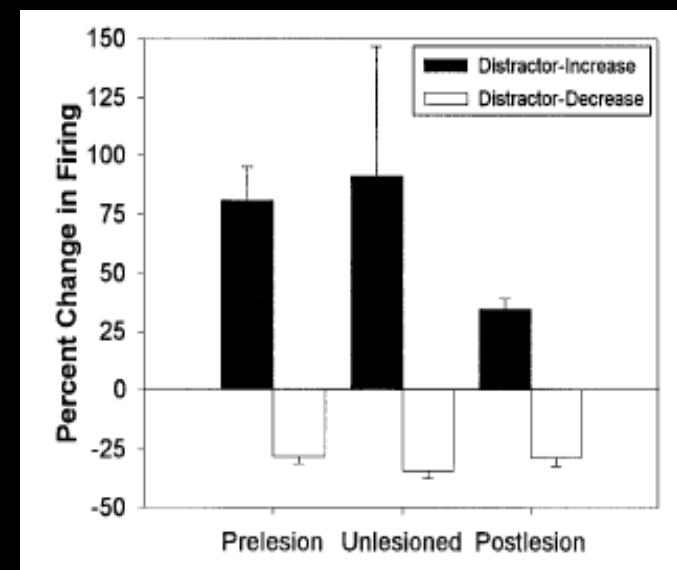
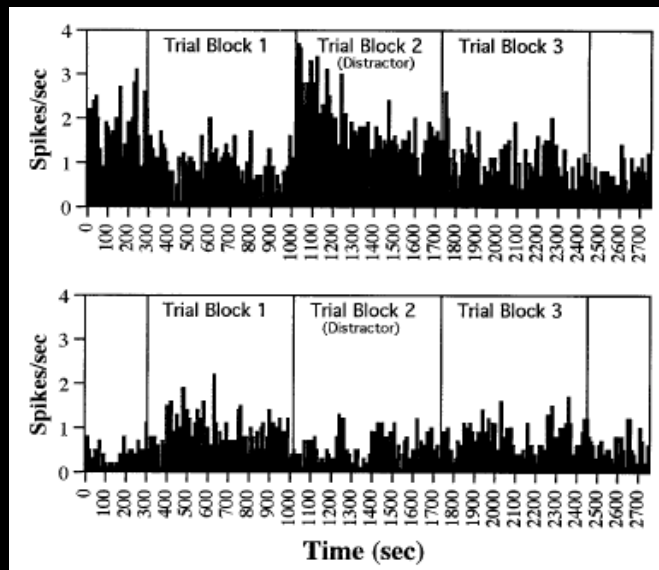
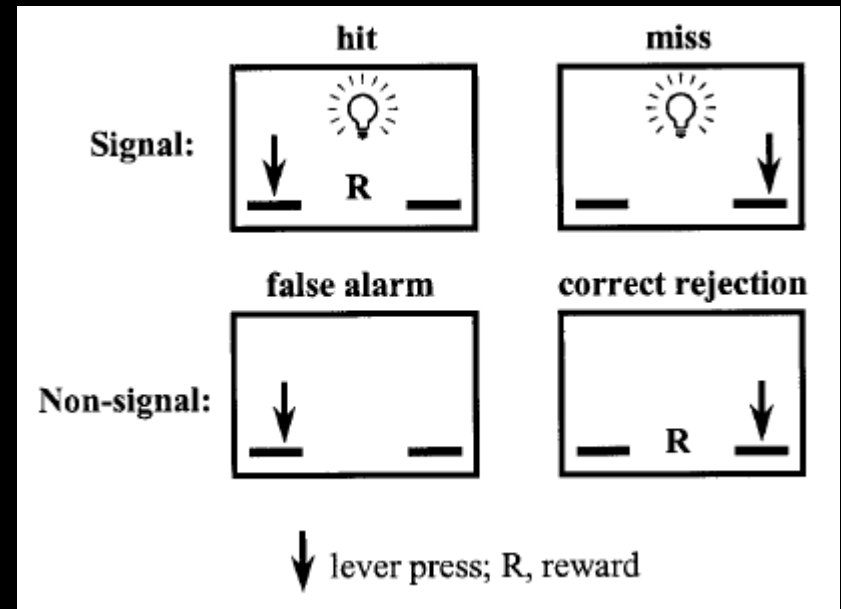
treatment with drugs that primarily target DA systems

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



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?

$E=MC^2$?





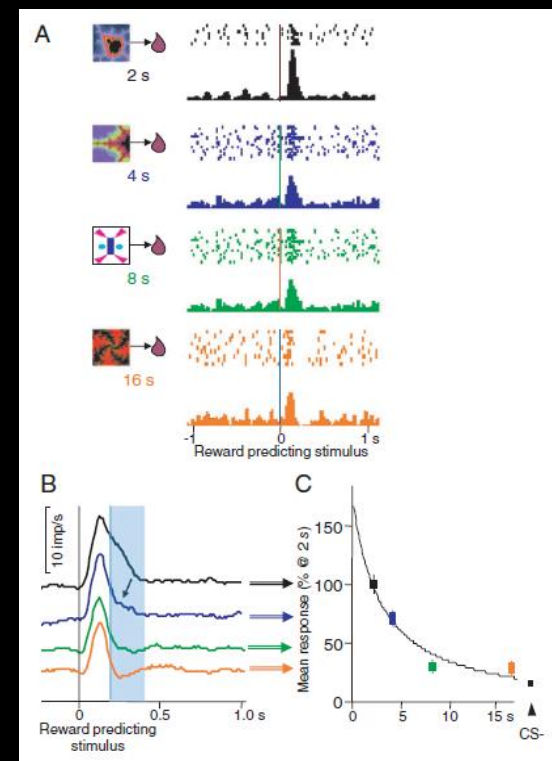
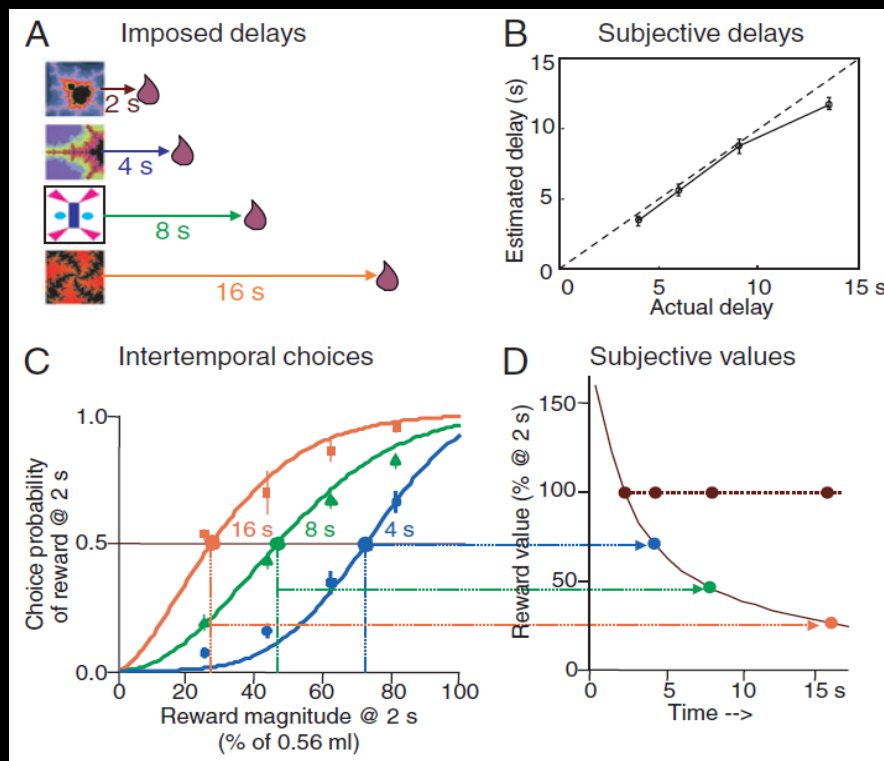
'waiting for the big one' - DA neurons are sensitive to reward delay:

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



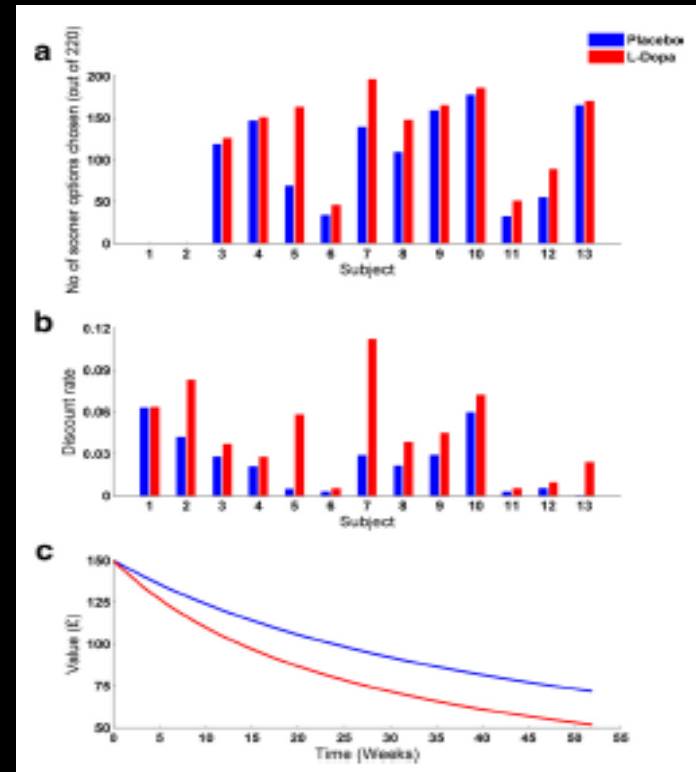
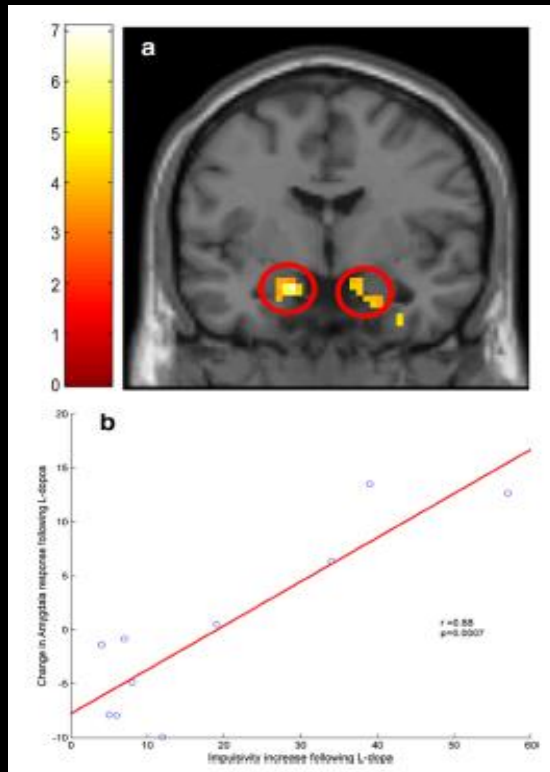
cranking up DA in humans increases temporal discounting:

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

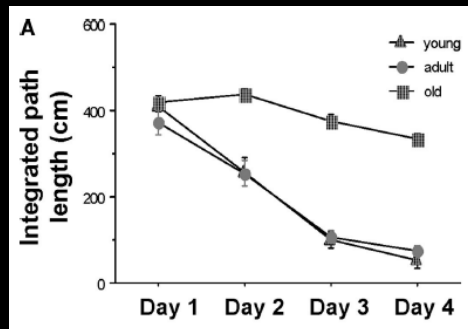
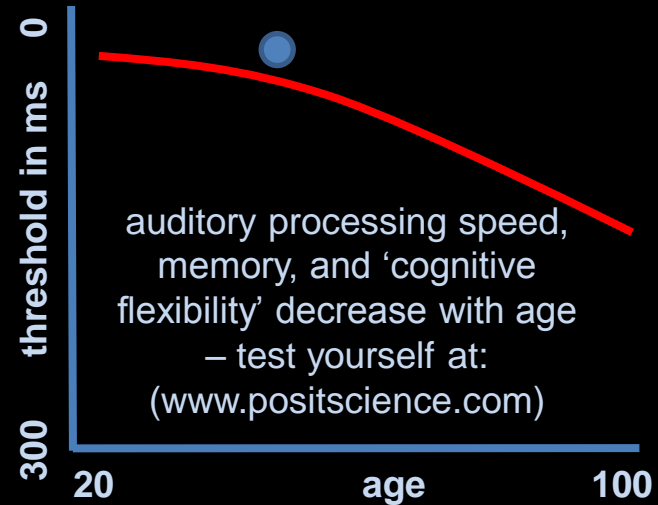
healthy aging is associated with a variety of changes in brain physiology and in cognitive abilities



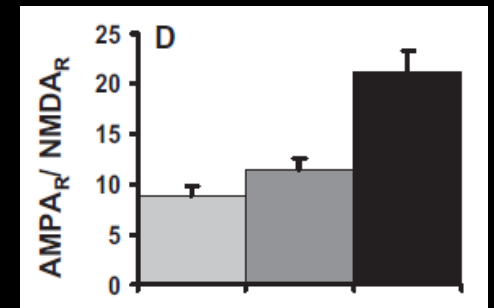
9.8% decrease in
substantia nigra DA cell
numbers per decade

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

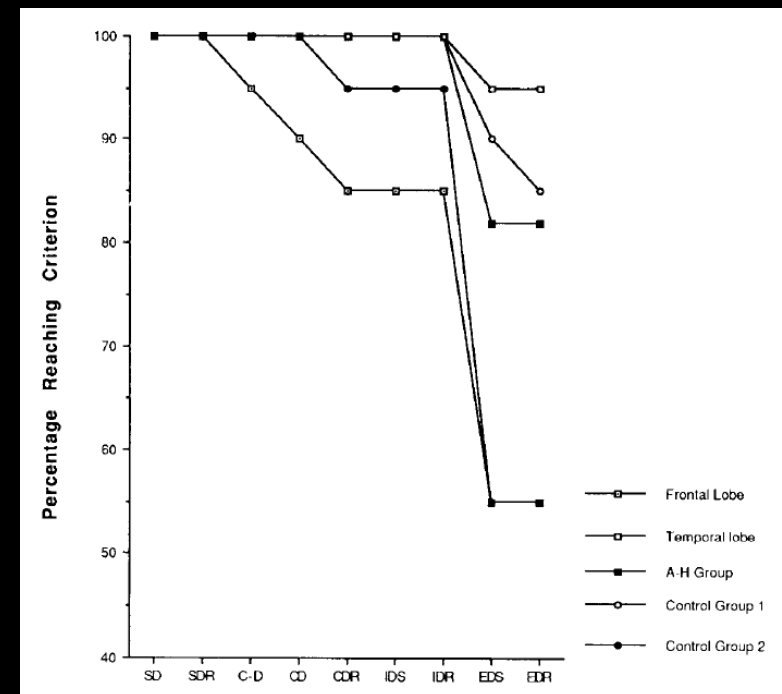
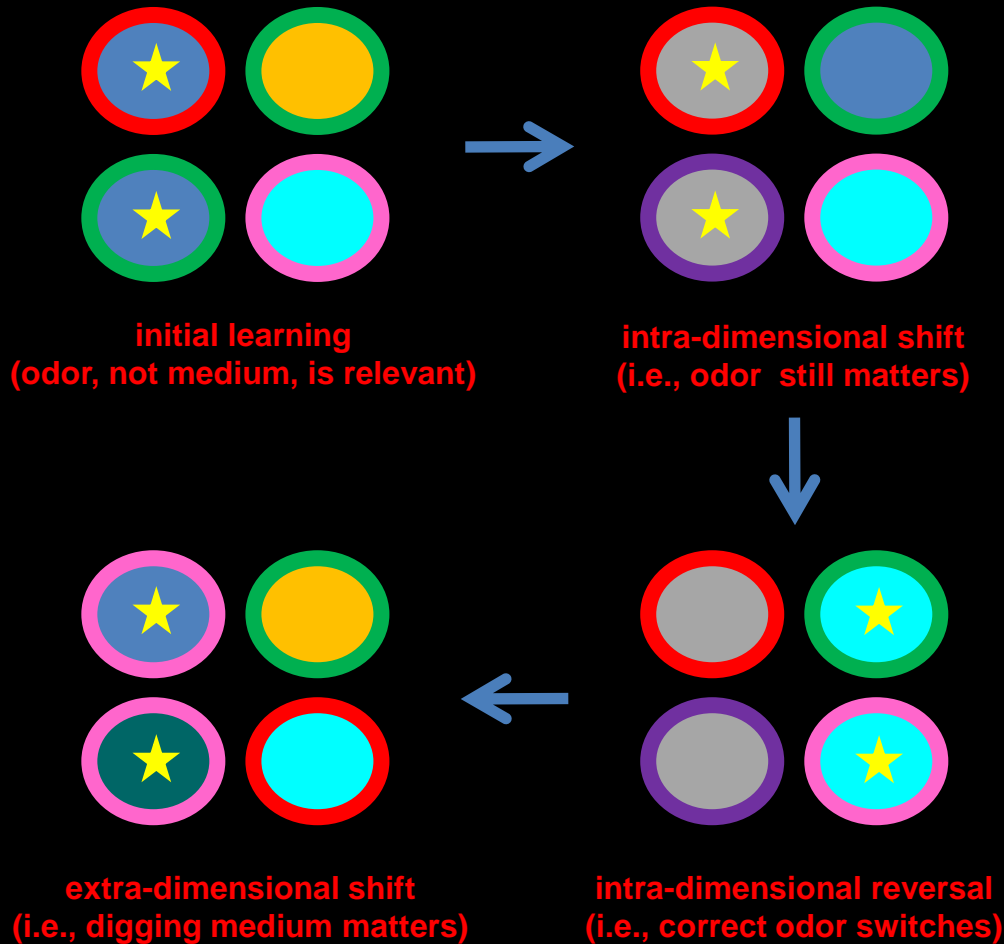


The ratio of AMPA-type
glutamate receptors to NMDA-
type increases with age
– Yang et al., JNP, 2008

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)

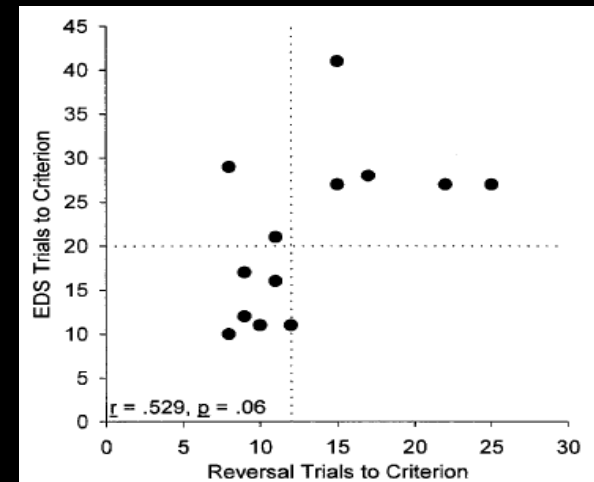
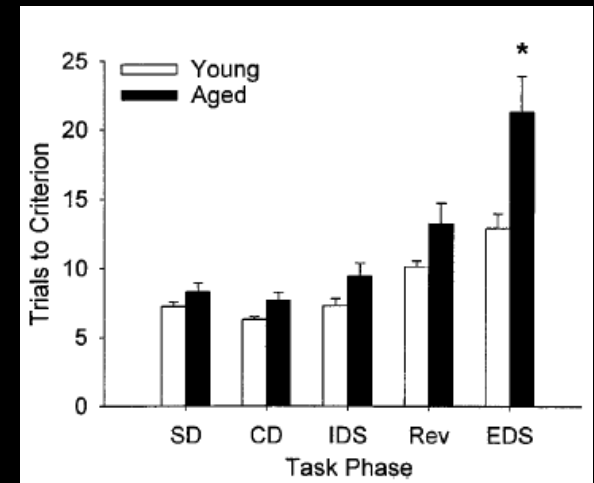
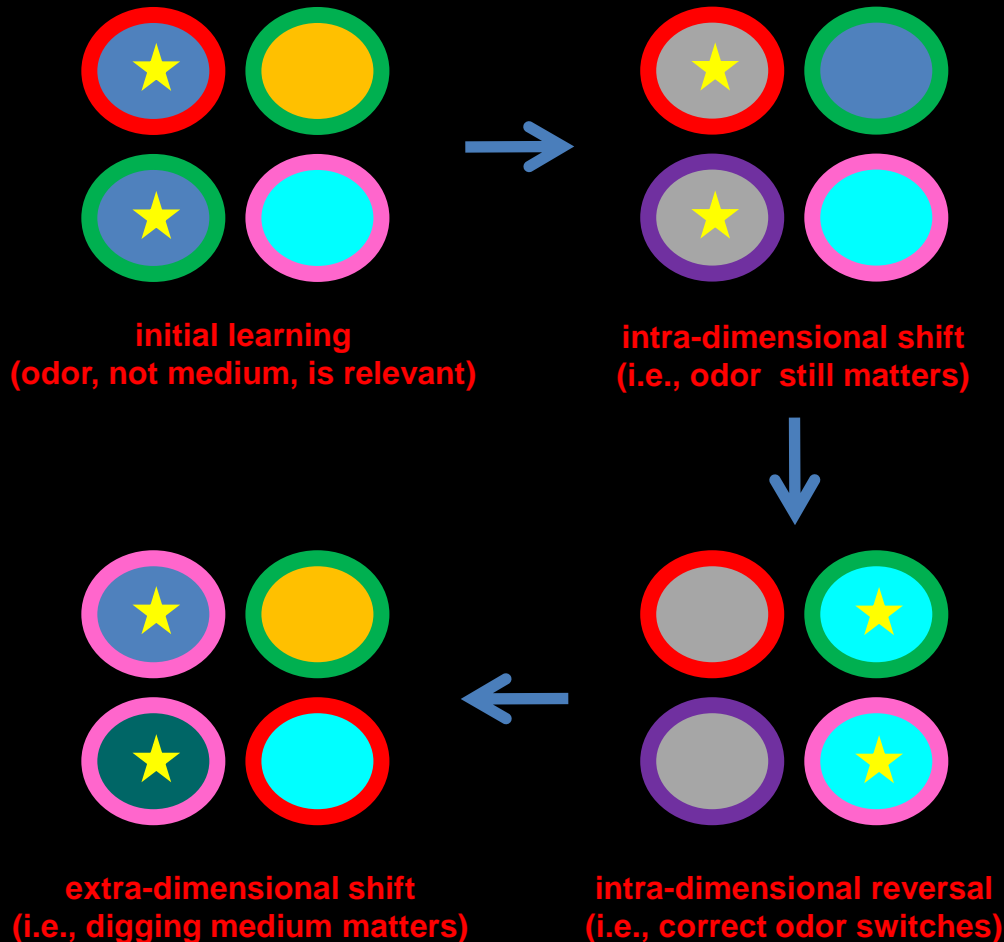


Owen et al., Neuropsychologia, 2010

the 'set-shift' task reveals a specific extra-dimensional shift deficit in aged rats

circles = cups full of digging medium, some with reward at base color of outer ring = digging medium (e.g., sand)

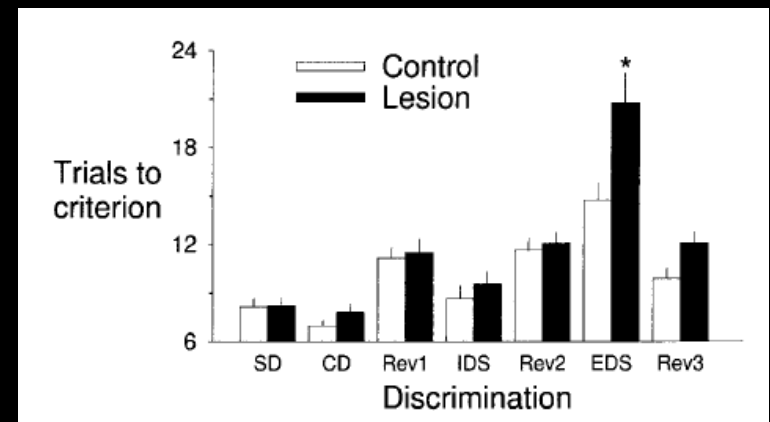
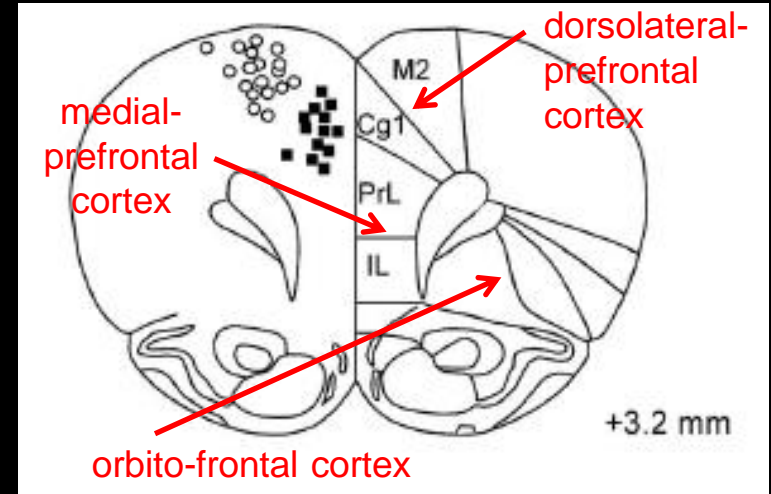
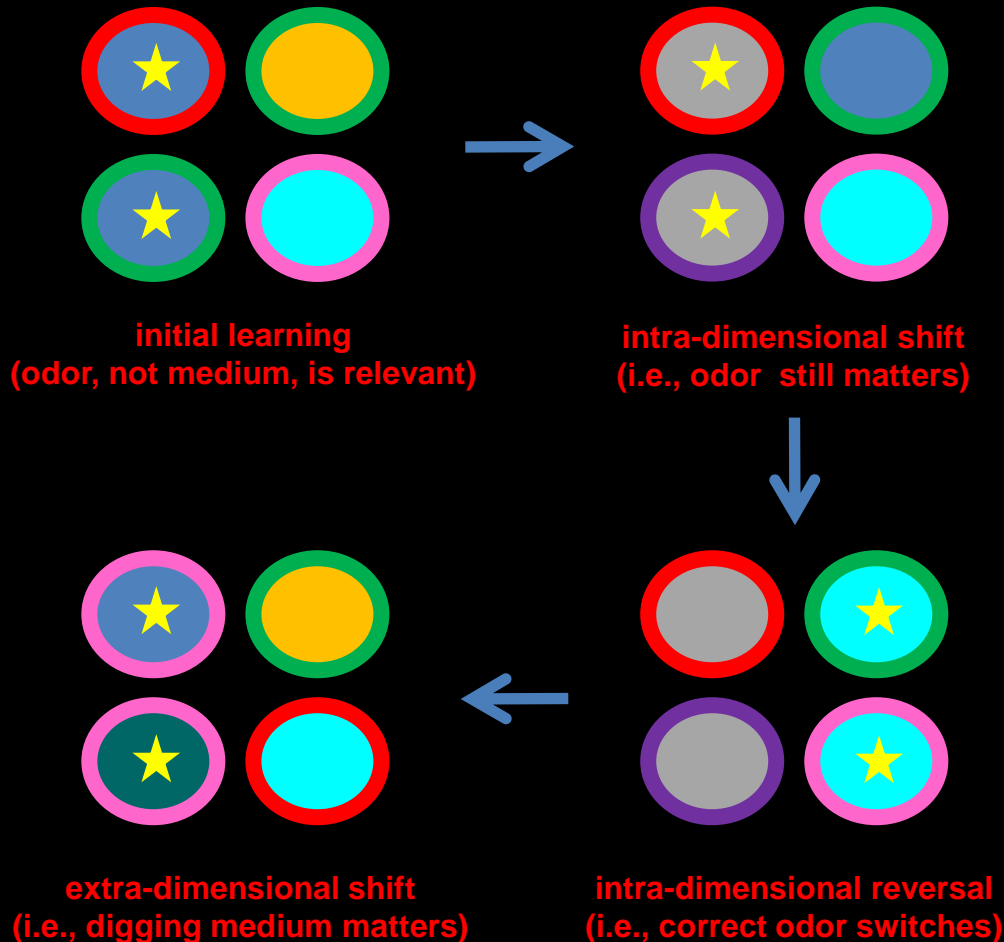
color of fill = odor (e.g., cinnamon) star = correct choice (i.e., reward beneath digging medium)



medial prefrontal cortex lesions impair performance on extra-dimensional 'set shifts'

circles = cups full of digging medium, some with reward at base color of outer ring = digging medium (e.g., sand)

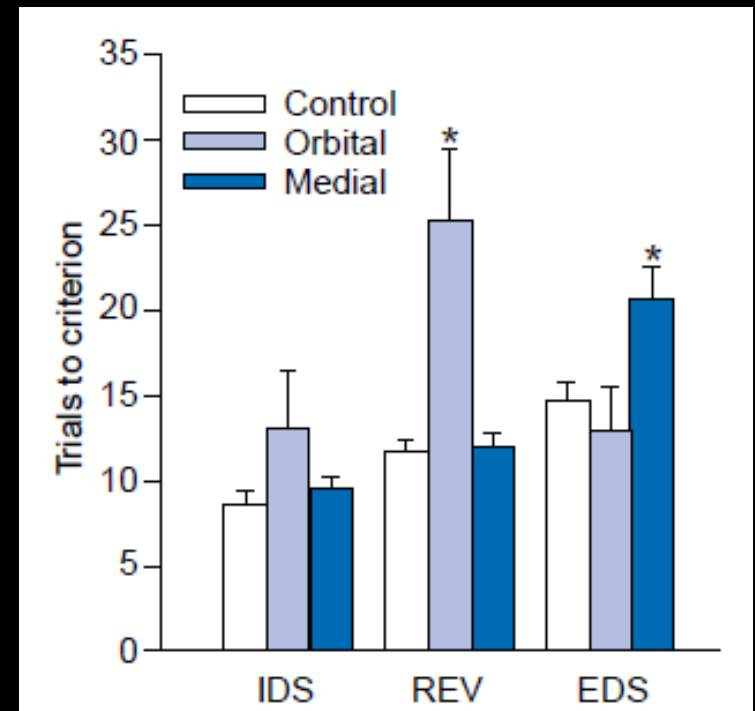
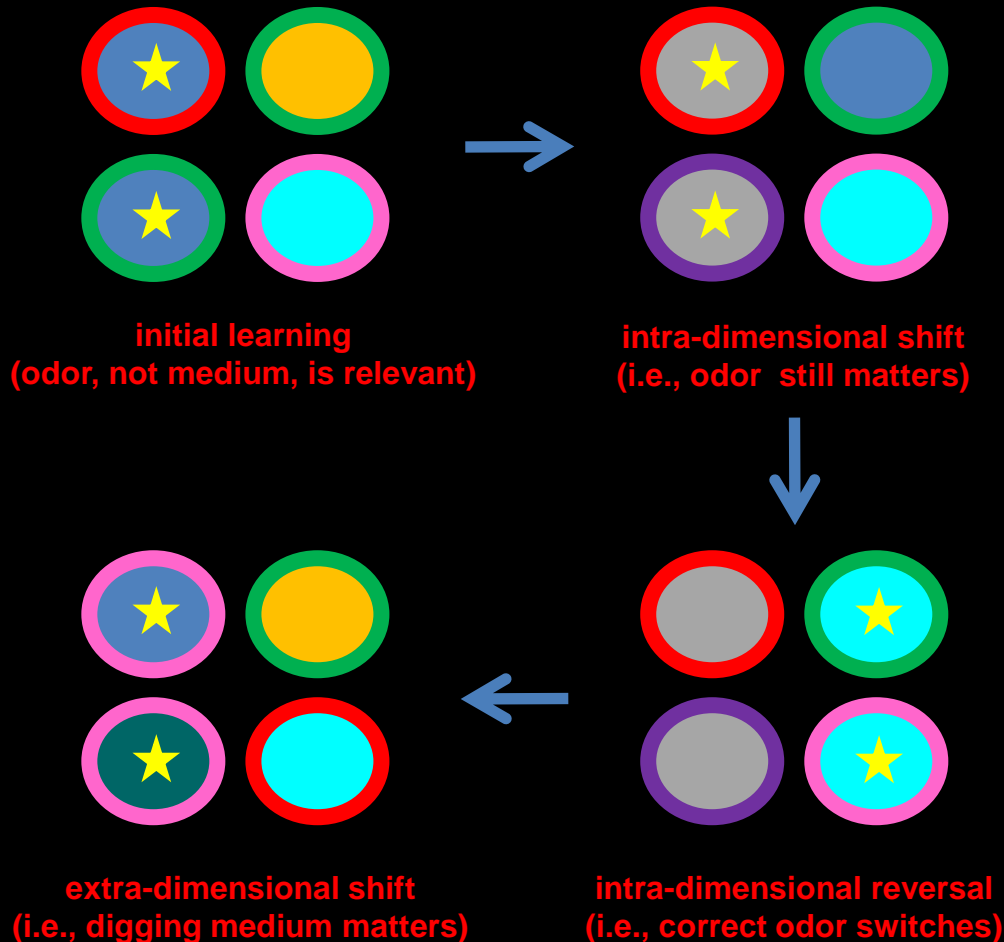
color of fill = odor (e.g., cinnamon) star = correct choice (i.e., reward beneath digging medium)



medial prefrontal cortex lesions impair performance on extra-dimensional 'set shifts', but orbitofrontal lesions impair performance on intra-dimensional reversals

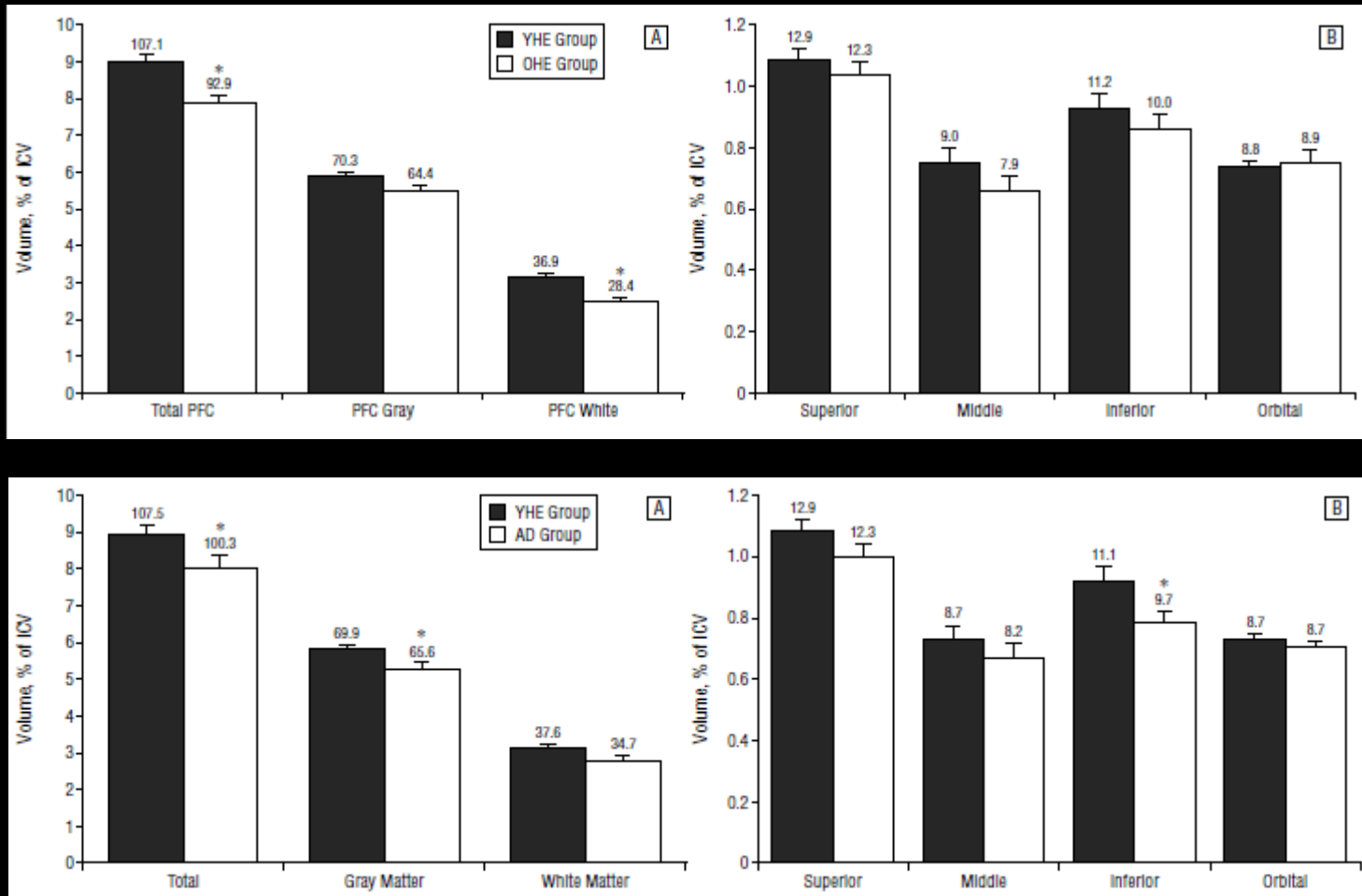
circles = cups full of digging medium, some with reward at base color of outer ring = digging medium (e.g., sand)

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



from sleep to attention – lecture 22 – Dec. 3, 2010

autism

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

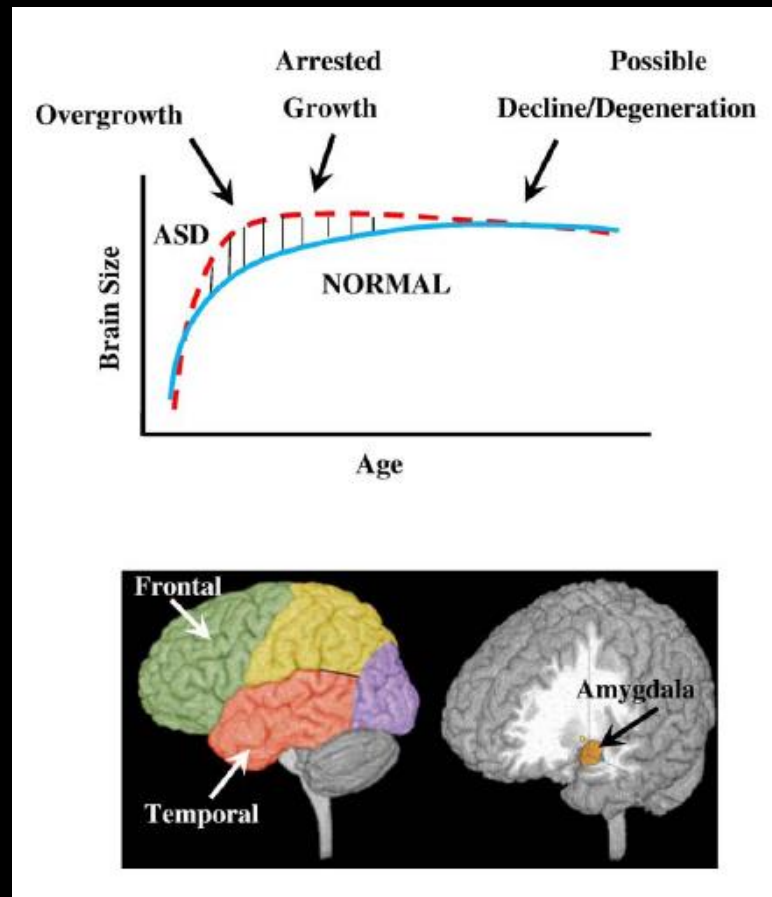
autism characteristics -

- 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

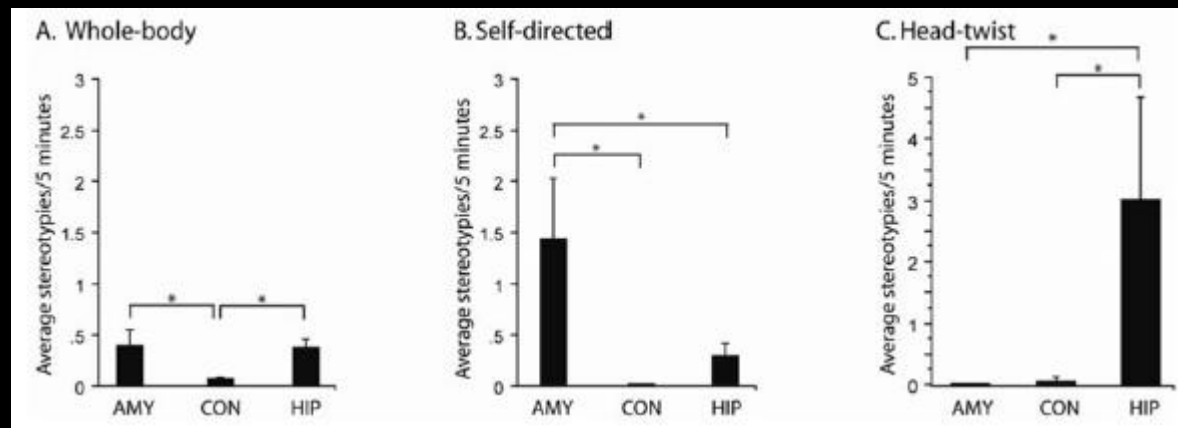
the amygdala hypothesis:

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

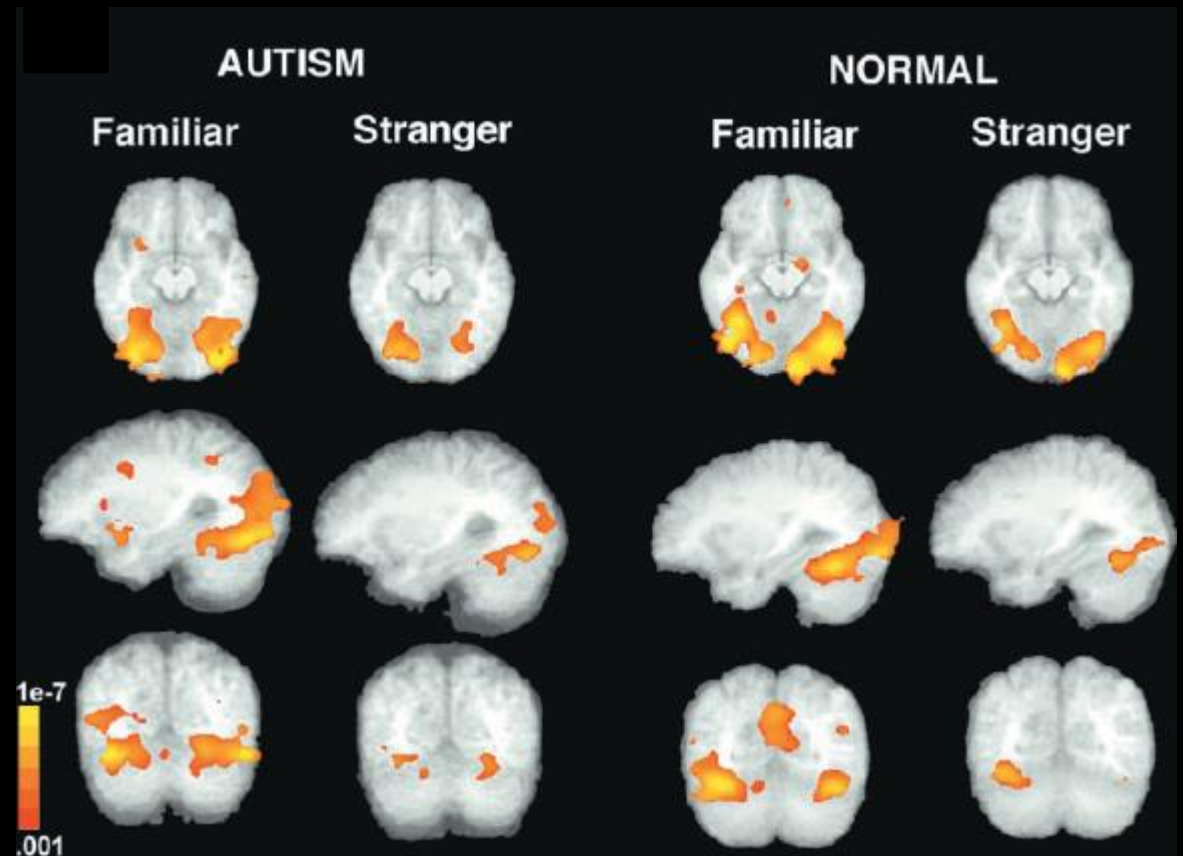
frontal cortex –

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

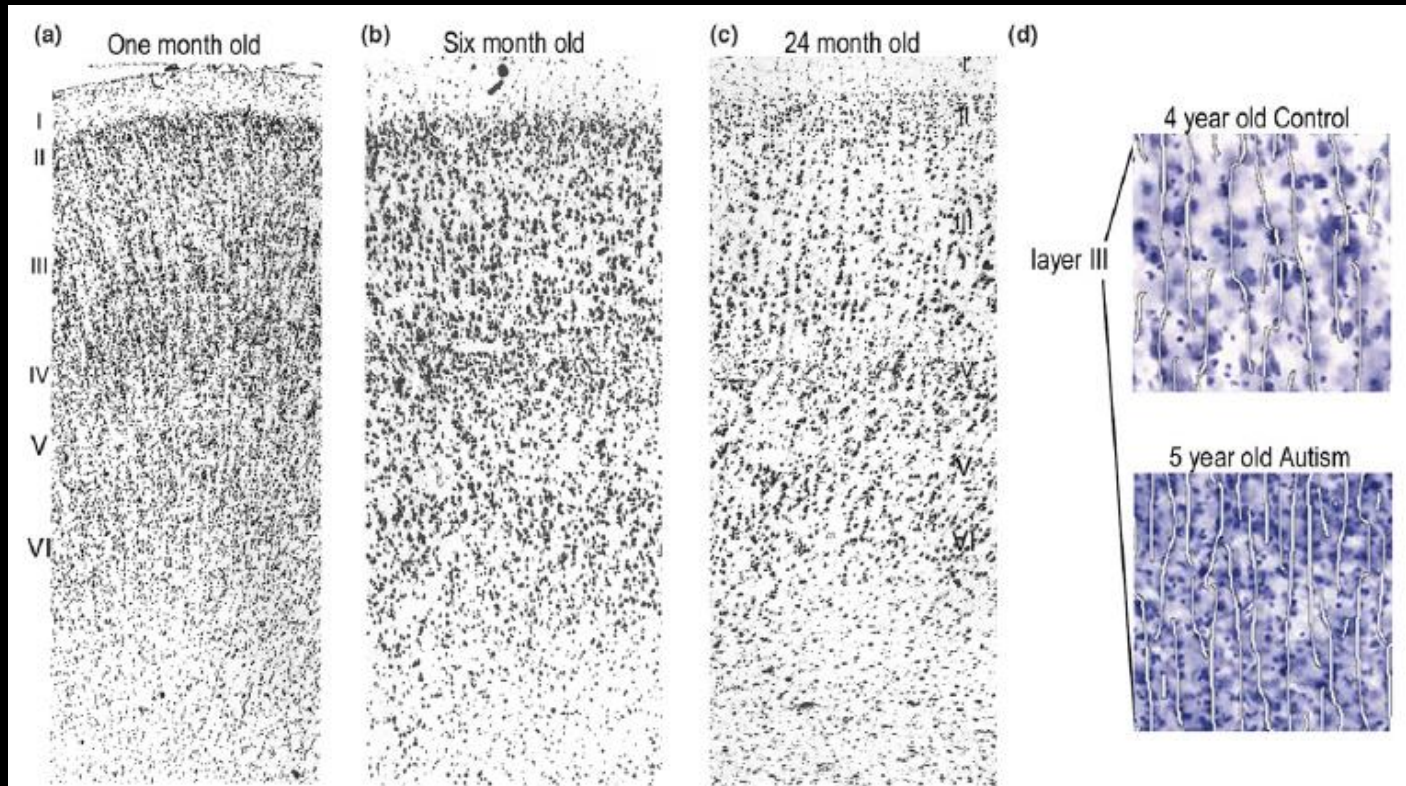


the search for alterations in fine structure of the cortex – mini-columns!

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



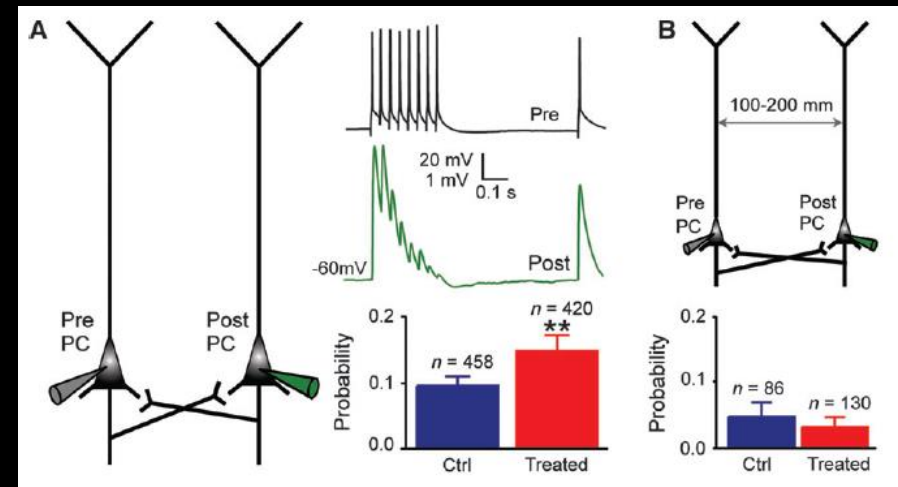
the search for alterations in fine structure of the cortex – hyper-connectivity, hyper-plasticity, and the ‘intense world’ hypothesis

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

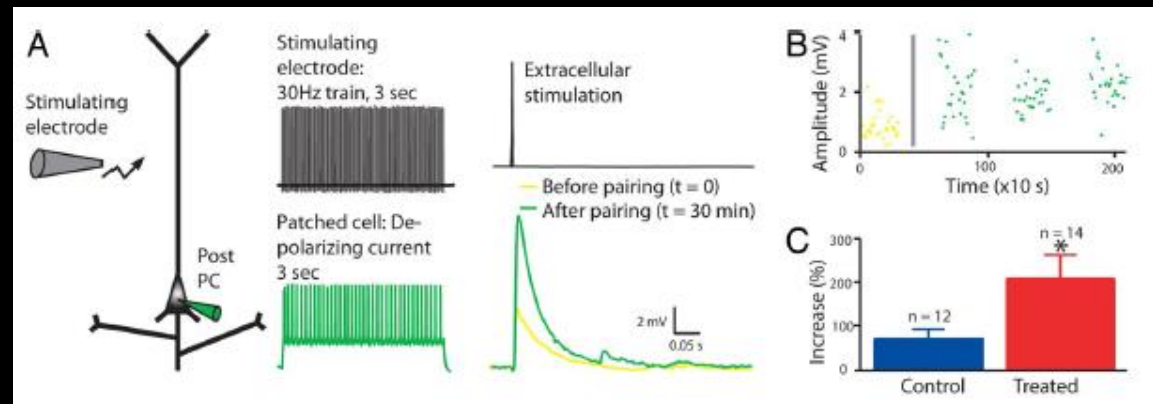
a rat model of autism has been created based on this phenomena – such rats have reduced social interactions, increased repetitive behaviors, are more anxious, and have long-lasting fear memories

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

this is proposed to lead to hyper-excitability of neurons

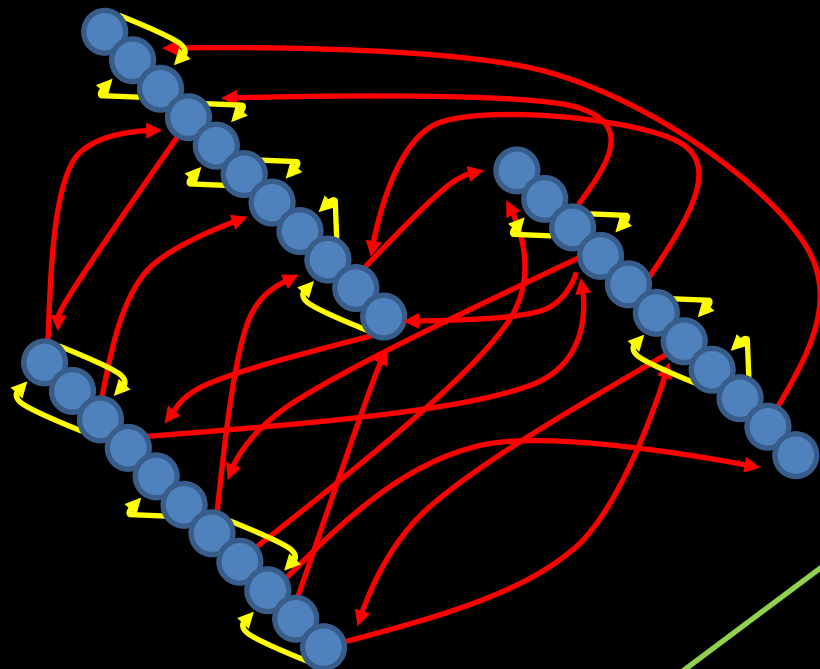


Rinaldi et al., Cerebral Cortex, 2007



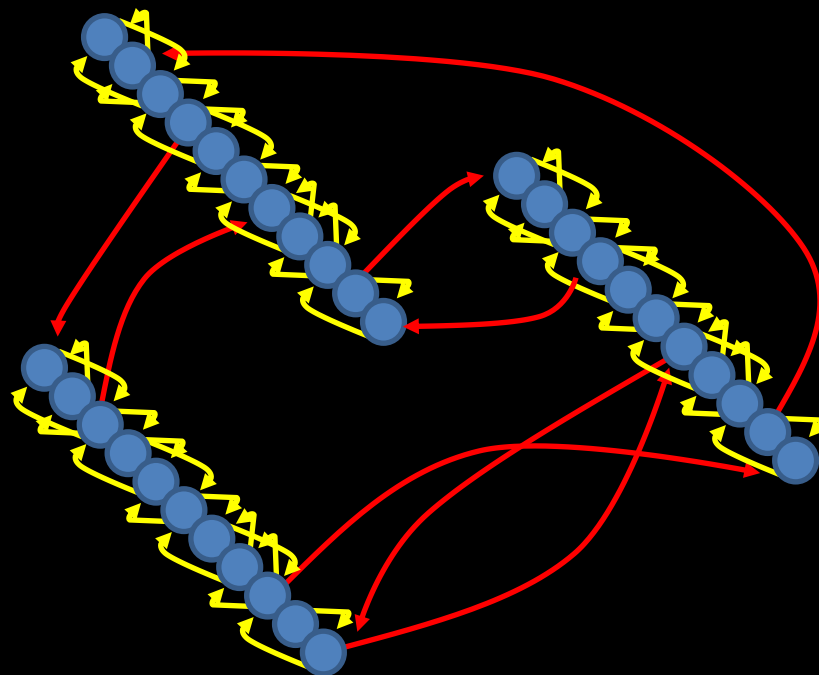
Rinaldi et al., PNAS, 2007

the search for alterations in fine structure of the cortex – local vs. global connections



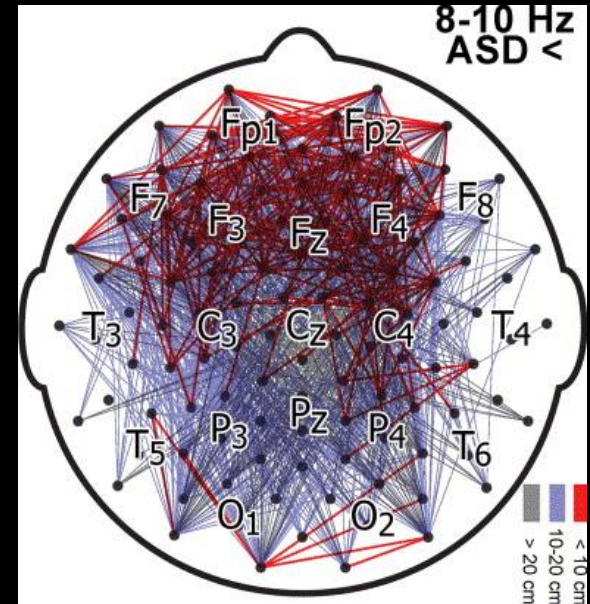
normal

autistic



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

