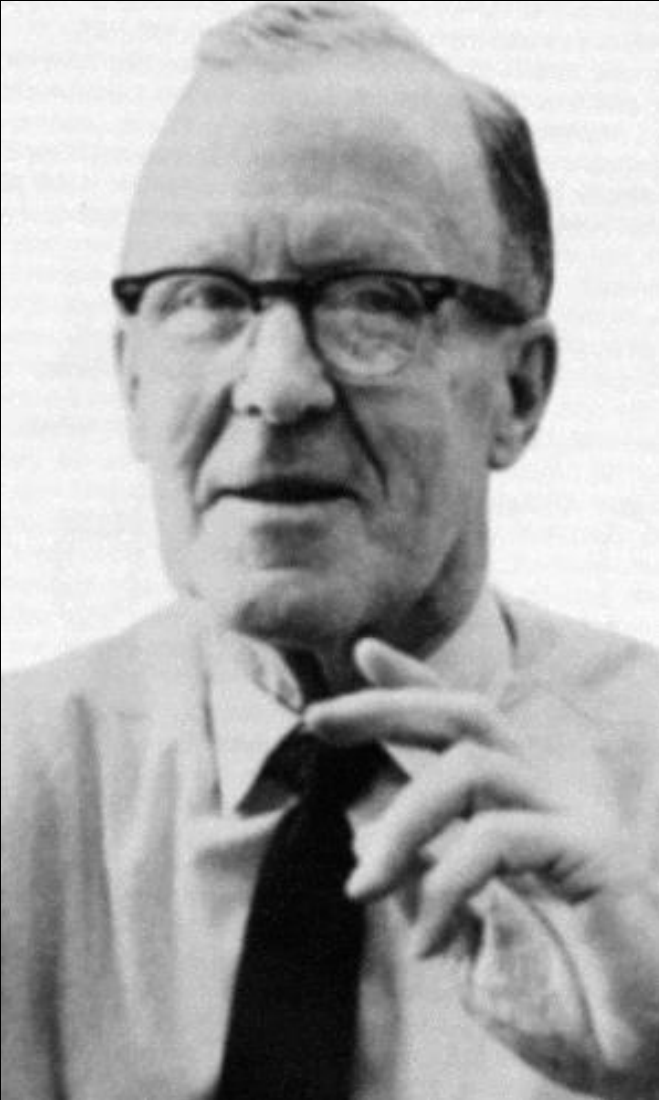


cell assemblies / attractors and schizophrenia



Nowadays the concept of *cell assembly* is used loosely to describe a group of neurons that perform a given action or represent a given percept or concept in the brain. Typically, one thinks of the group as having strong internal synaptic interactions which set them apart from other groups of neurons. Different users may use this concept with more or less permissive definitions.

-Moshe Abeles, Scholarpedia / Cell Assembly

According to the 'cell assembly' hypothesis, transient synchrony of anatomically distributed groups of neurons underlies processing of both external sensory input and internal cognitive mechanisms. A second postulated signature is that, although individual neurons may participate in many cell assemblies, not every possible combination of cells comprises a cell assembly.

-Harris et al., Nature, 2003

themes I –

Brain mechanisms for sleep and attention overlap extensively. For example, the cerebral cortex, where conscious perception is realized, undergoes radical changes in the patterning of synaptic potentials (as revealed by EEG/LFP recordings) between the lowest-attention state (stage $\frac{3}{4}$ non-REM sleep) and high attention states (waking, REM sleep).

Changes in sleep/wake state and attention are sometimes mediated by groups of neurons that are highly interconnected (brainstem reticular and thalamic reticular neurons).

The classroom can be very hot.

REM sleep appears to be associated with a maximal frequency of events associated with reorientation of attention (as in a startle response) while non-REM sleep is associated with a minimal frequency of such events. The frequency of such events in the waking state lies between the two sleep states. Oddly enough, a similar pattern is observed for brain metabolism.

Work attempting to uncover the function of sleep typically takes either a species-comparison approach, a sleep-deprivation approach, or an approach involving recording of specific neurobiological characteristics of sleep.

Theories as to the function of sleep nearly always suggest that the function pertains to the brain as opposed to the rest of the body.

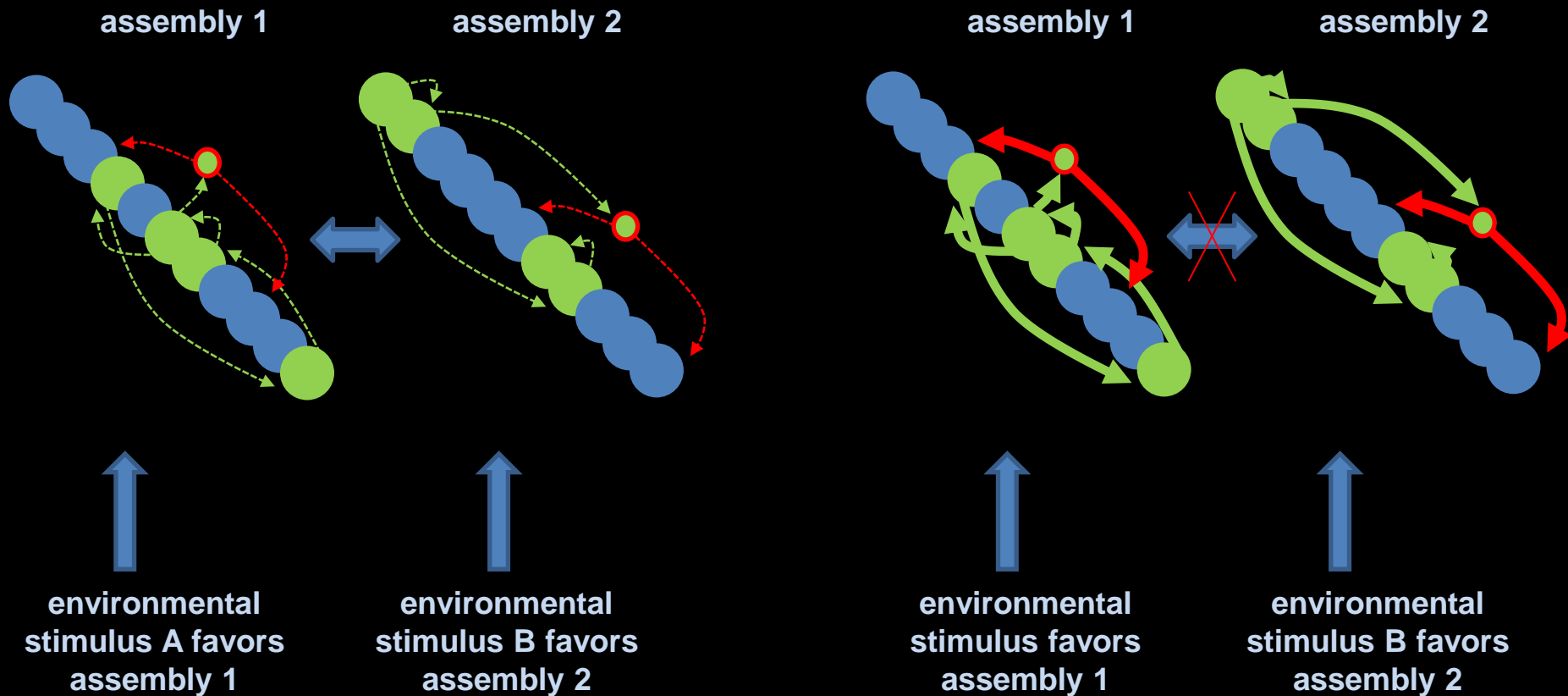
themes II –

Neurally, attention is associated with either changes in the overall patterns of firing across a group of neurons (increased action potentials in response to the attended stimulus, and fewer to the unattended stimuli) and/or changes in the temporal firing patterns of neurons (neurons responding to attended stimuli fire in tune with a gamma rhythm). Such changes may, in part, be brought about by changing the subset of synaptic inputs to which a neuron responds most strongly.

Overall, attention appears to involve changes in the neural dynamics of multiple brain regions. Does this reflect the fact that the brain is extremely complex and best studied by considering the system as a whole, or does it reflect the fact that attention is defined in so many different ways?

Normally, we think of attention as altering the responsiveness of the cerebral cortex to different types of sensory input. That is, we think of attention as a sub-cortical process that impacts what happens in the cortex or thalamus. In the case of the parietal cortex and prefrontal cortex, we seem to have two systems of the cortex itself that regulate attention. Each of these structures is nevertheless impacted by subcortical inputs (e.g., from basal forebrain or locus coeruleus) and, remarkably, appear to impact activity in the same subcortical structures. Thus, attention is a cyclical process (i.e., a chicken-and-egg type process) that is continuous where what has been attended will affect, to some extent, what is attended to subsequently.

Depending on the requirements for success in an environment (i.e., the requirements of the experimental task), attentional processes invoked by different mechanisms (e.g., one versus another neuromodulatory system) may be beneficial or may negatively impact performance.



activation of any particular assembly can be favored by 'external' as opposed to 'local' inputs

the strength of 'local' inputs may vary relative to 'external' inputs

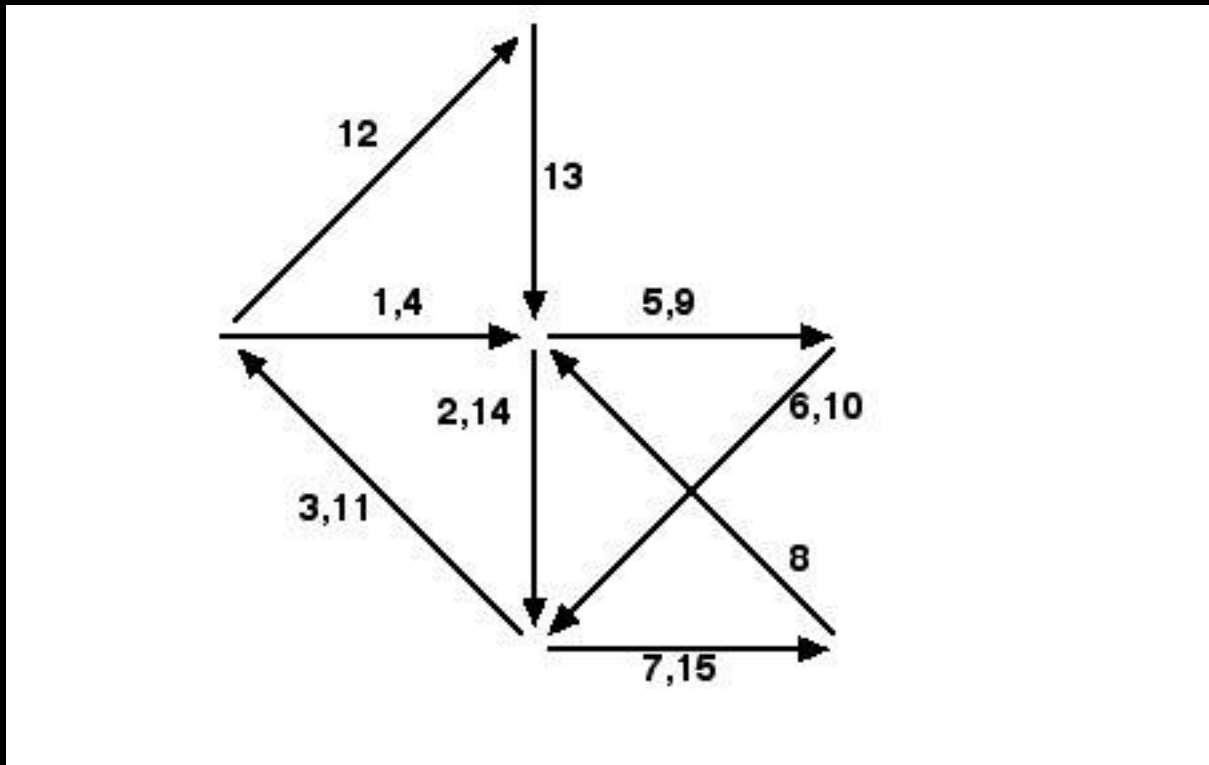
if the strength of 'local' inputs is high, then the local connections will favor continued activation of the currently active assembly

if 'local' input strength is low, cell assemblies may be more likely to be activated by 'external' sources or, in the absence of strong 'external' inputs, there may be more spontaneous movement between assemblies

the number of actual assemblies in a population of neurons is thought to be less than the total possible no. of combinations of active/inactive cells

The diagram shows a sequence of nodes arranged in a diagonal line. There are four blue nodes and three green nodes. A red arrow points from a green node to a blue node, and a green arrow points from a blue node to a green node, illustrating a transition between the two states.

interconnections may keep particular assemblies active in the absence of the 'external' stimulus responsible for activating them (as in working memory)



according to Hebb, cell assemblies may also present as sequences of patterns that repeat.

in the figure above, each nexus point corresponds to a particular pattern of activity among a population of neurons.

arrows denote movement between patterns and numbers indicate a the ordering of movement between patterns (e.g., movement from the 'west' pattern to the center initiates the sequence and repeats on step 4)

schizophrenia –

a late onset disorder (manifesting during transition to adulthood and therefore coinciding with maturation of the prefrontal cortex)

symptoms include:

- disordered thought and/or speech
- flat affect
- catatonia
- paranoia
- hallucination

attention deficits include:

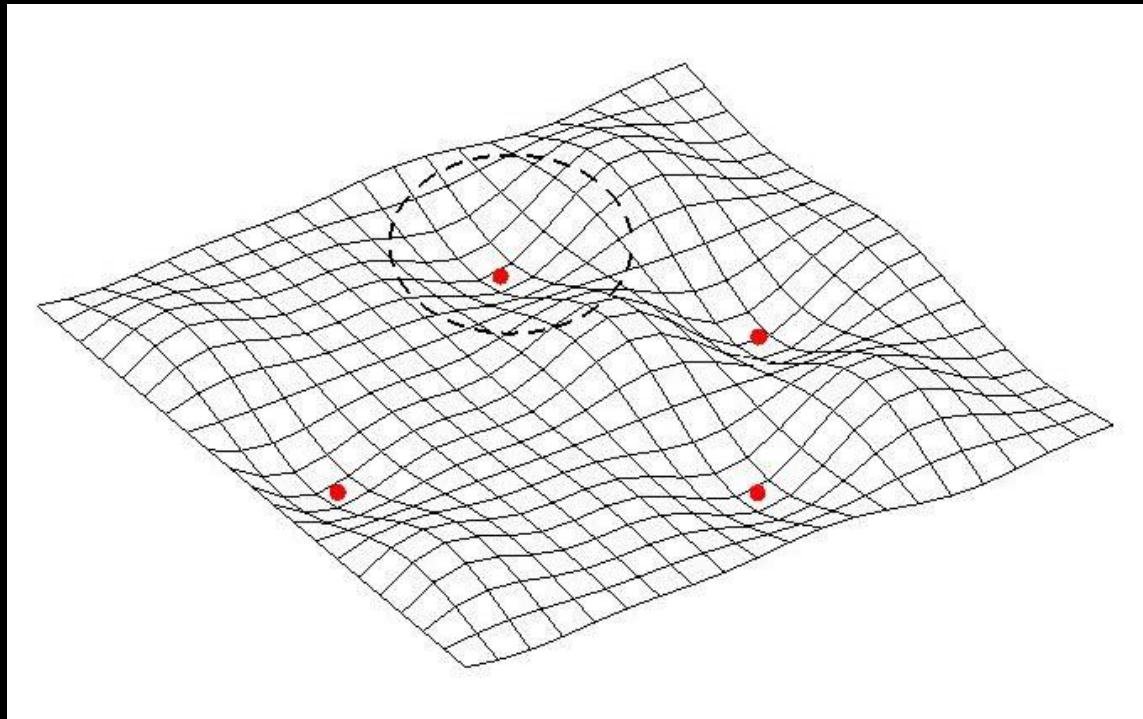
- sustained attention
- set-shifting
- working memory

clues to causes:

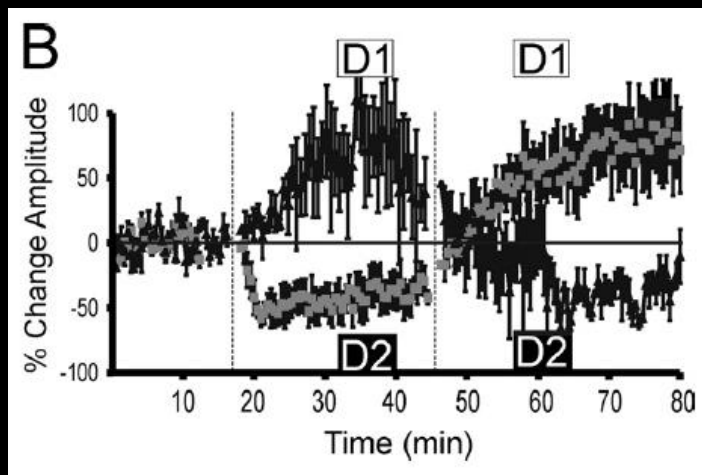
- increased numbers of D2 and D4 dopamine receptors
- antipsychotics are often dopamine receptor antagonists
- diminished numbers of 'parvalbumin' type GABA neurons
- alterations in beta/gamma-frequency LFP rhythms
- smoking/nicotine self-medication in schizophrenics
- 'hypofrontality' – decreased responsiveness of PFC

hallucinations, impairment in sustaining attention, poor working memory, poor intra-dimensional and extra-dimensional set-shifting

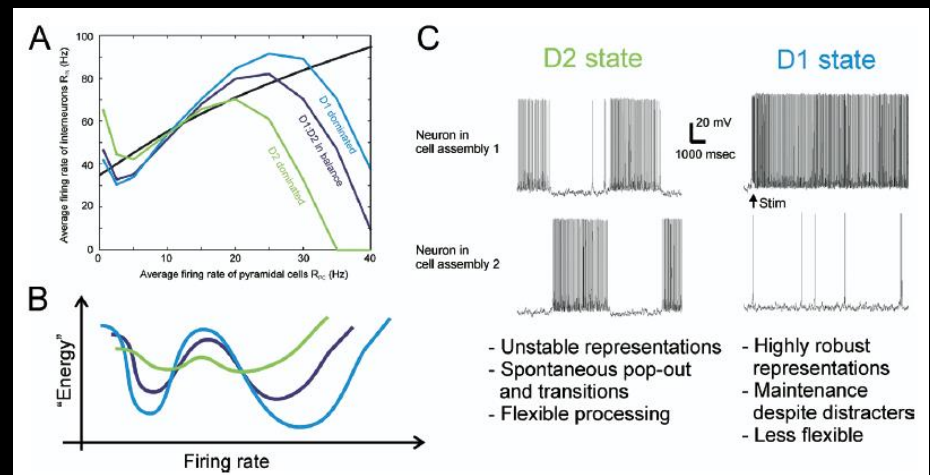
- might all these symptoms be related to instability in the activity patterns produced by prefrontal cortex?



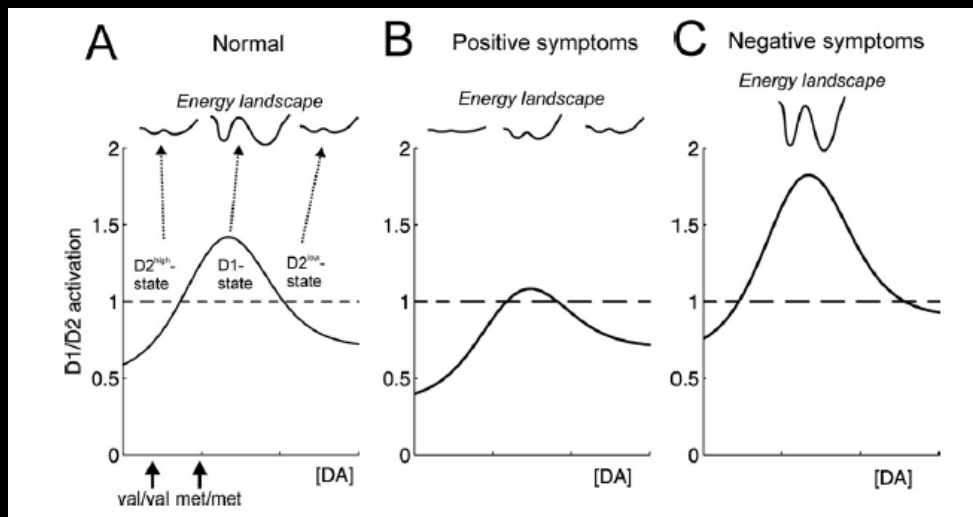
above: schematic of an attractor network where each square corresponds to a specific activity pattern among a population of neurons – red dots denote 'basins' into which activity patterns are more likely to fall – moving out of such attractors demands a 'push' to get over the hills separating different attractors



1. dopamine activation of D1 and D2 receptors produces opposite effects on the responses of PFC neurons to GABAergic inputs



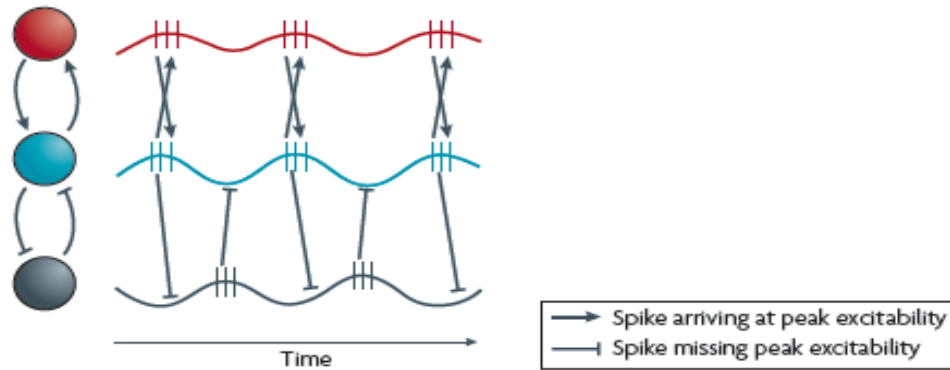
2. -at any given time, D1 or D2 receptors may dominate the response to dopamine (factors include receptor affinity and amount of dopamine release) .
– D1 domination will favor maintenance of current activity patterns while D2 domination favors instability



3. –in normals, the relative influence of D1/D2 receptors varies appropriately according to task demands

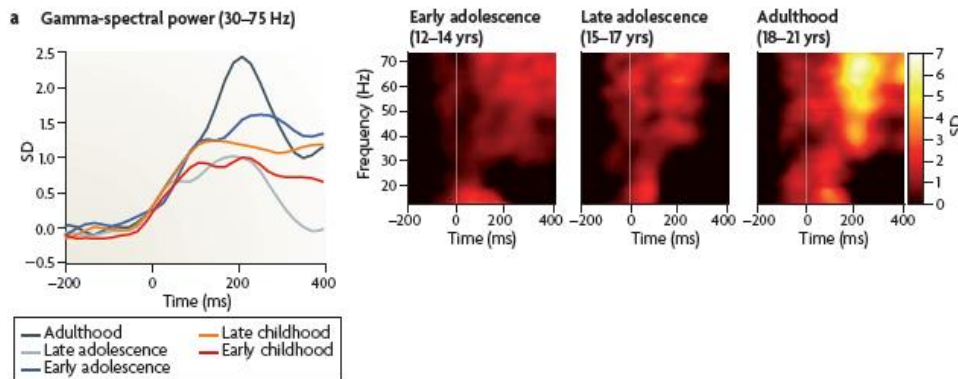
-positive symptoms in schizophrenia result from heightened influence of D2 receptors which reduce the 'energy' barrier between attractor states

-negative symptoms result from over-influence of D1 receptors yielding unchanging patterns



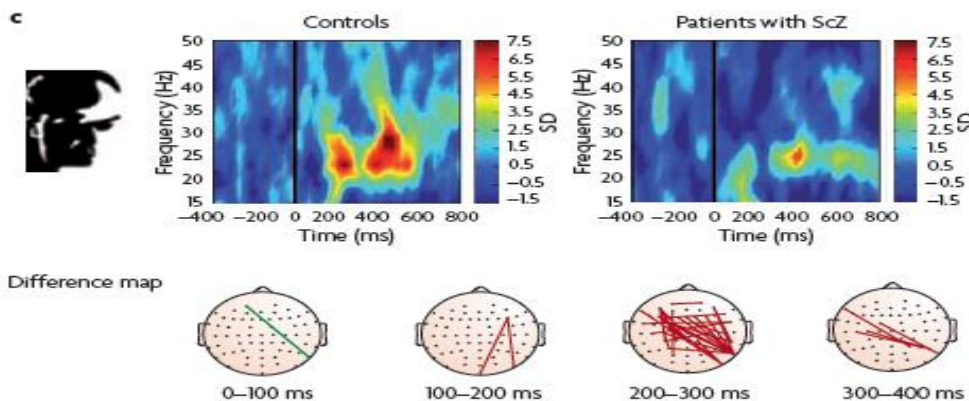
1. neurons that fire in synchrony with respect to gamma LFP rhythms (red-blue) form 'cell assemblies' or 'attractors'

neurons whose activity patterns are not synchronized cannot interact with each other



2. EEG recordings can assess the extent of gamma-synchronization in cortex resulting from presentation of 'Mooney' faces

gamma power peaks ~200ms after presentation – the degree of the response peaks in adulthood



3. schizophrenic patients exhibit depressed responses to 'Mooney' faces

moreover, the coherence of gamma-frequency activity among brain regions is weaker

decreased numbers of GABA neurons could potentially mediate these effects