Too much dopamine can be bad for you:
II. Latent inhibition and schizophrenia

Outline

- Schizophrenia
- Latent inhibition
- Latent inhibition as a model of schizophrenia

PSY/NEU338: Animal learning and decision making: Psychological, computational and neural perspectives

thanks to Ina Weiner for many of the slides in this presentation
First: Schizophrenia

- Schizophrenia = shattered/split mind (note: unrelated to dissociative identity disorder)
- chronic, severe, and disabling brain disorder
- affects about ½-1% of population above age of 18
- symptoms usually appear in men in late teens or early 20s, in women in 20s and early 30s
- significant heritable component, environmental component (urban environment; poverty; stress), also exacerbated/caused by some recreational/prescription drugs (cannabis..)
- no single known organic cause (prenatal neurodevelopmental etiology?)
- co-morbid with major depression and anxiety disorders, substance abuse (40% lifetime occurrence!), higher suicide rate (5%; life expectancy 10-12 yrs shorter)

Bleuler: coined term in 1908 (in plural: the schizophrenias)

positive symptoms

- behaviors not seen in normal people, manifestations of psychosis, such as:
  - hallucinations (most common: auditory, voices)
  - delusions (false unwavering personal beliefs), paranoia
  - thought disorder (disorganized thinking - hard to organize thoughts logically, thought ‘blocking’, garbled speech, neologisms)
  - movement disorder (clumsy, uncoordinated, repetitious movements, catatonia (rare with treatment))
- these symptoms respond well to medical treatment
negative symptoms

• deficits, reductions in normal emotion and behavior
  • flat or blunted affect (immobile expression, monotonous voice)
  • lack of pleasure in everyday life (anhedonia, like depression) & lack of motivation (avolition)
  • decreased ability to initiate and sustain planned activity
  • poverty of speech (alogia) and infrequent speech (even when forced to interact)
  • don’t respond well to medication; are the symptoms that most affect quality of living

Cognitive symptoms

• subtle (detected by neuropsychological tests)
  • problems with executive functions (ability to absorb and interpret information and make decisions based on that information)
  • inability to sustain attention
  • working memory deficits
  • perhaps the most disabling in leading a normal life
diagnosis & treatment

- no lab test currently exists/no neuroscientific criteria
- diagnosed based on behavioral symptom profile (DSM-IV-TR)
  - 2 or more symptoms for most of a month, within a continuous period of 6 months of disturbance; social/vocational disfunction compared to achievements prior to onset
  - bizarre delusions or voice hallucinations on their own are sufficient
- but note: schizotopy - psychotic experiences & mostly non-distressing delusional beliefs, with relatively high prevalence among general public
- dopamine activity consistently higher in patients (PET), amphetamine exacerbates/causes schizophrenia-like symptoms
- treatment: antipsychotics (D₂ blockers; also called neuroleptics) + psychotherapy & vocational and social rehabilitation (also: atypical antipsychotics, which affect serotonin more than dopamine)

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latent inhibition

Repeated exposure to a stimulus in the absence of significant consequences impairs the subsequent capacity of this stimulus to acquire behavioral control when it is subsequently paired with reinforcement.

- LI indexes organisms' capacity to ignore irrelevant stimuli.
- LI is a very prevalent and basic phenomenon; can be demonstrated in many species, including humans.
- Theoretical explanations?
LI: Theory in a nutshell

- **Mackintosh**: learn that the CS is not a good predictor of the US
- **Lubow**: learn association between CS and “no US” (and as a result decrease attention to CS)
- **Wagner**: learn association between CS and context (and as a result decrease attention to CS)
- **Pearce & Hall**: the CS is not accompanied by a prediction error, and thus its associability decreases (less attention to it)
  - Orienting response (OR) as a measure of attention
  - OR decreases when a CS appears without a US; decreases more slowly when there is a US
  - partial reinforcement maintains OR
  - transiently increases in extinction

![Graph showing OR over time]

LI: phenomena

- **Context specific** (pre-expose in context A and then conditioning in context B → no LI when tested in context B) [supports Wagner]
- Can get LI even with pre-exposure with a small US and then training with a large US (Hall & Pearce, 1982) [not specific to no-US preexposure, against Lubow]
- “Spontaneous recovery” - not inhibition of learning, but an inhibition of performance?
food for thought: inhibition of learning or performance?

• All the theories talk about a deficit in learning about the CS
• What if learning was normal, but just does not come to control responding?
• Due to?
  • the association that was learned in preexposure interferes with retrieval of the CS-US association
  • interference as a result of both associations competing to control behavior

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Latent inhibition and SCZ

• LI can be seen as a measure of the ability to ignore irrelevant stimuli (attention phenomenon)
• SCZ as a disorder of attention: can’t focus attention, rapid switching, can’t maintain attention set
• SCZ associated with excess of dopamine; amphetamine disrupts latent inhibition

LI: “window phenomenon”

Pre-exposure

NPRE  PRE

2 or 5 tone-shock pairings

Conditioning

2 pairings

Time to 100 licks

NPRE  PRE

Normal LI

5 pairings

Time to 100 licks

NPRE  PRE

Normal absence of LI
two poles of LI abnormality

Disruption of LI  Persistence of LI

2 pairings

Time to 100 licks

NPRE  PRE
normal LI  disrupted LI

5 pairings

Time to 100 licks

NPRE  PRE
persistent LI  normal absence of LI

1. disrupted LI: model of positive symptoms

amphetamine disrupts LI

2 pairings

amphetamine 1mg/kg

typical & atypical APDs restore amphetamine-induced disruption of LI
disrupted LI: model of positive symptoms

2 pairings  5 pairings

MEAN LOG TIME TO COMPLETE LICKS

and in humans...

- Normal amphetamine-treated humans fail to show LI
- High schizotypal humans fail to show LI
- Normal haloperidol-treated humans show potentiated LI
- LI is disrupted in acute schizophrenia, associated predominantly with positive symptoms and increased DA transmission
disrupted LI: model of positive symptoms

Schizophrenia

Positive symptoms

Dopamine ➔

Disrupted LI

2. persistent LI: model of negative symptoms

2 pairings

5 pairings

MK-801 (NMDA antagonist) causes persistent LI

atypical but not typical APDs counteract MK-801
and in humans...

- Schizophrenia patients exhibit persistent LI; correlates positively with the negative dimension of the illness

"It is quite common for them to lose both inclination and ability ...to keep their attention fixed for any length of time... there is...a kind of irresistible attraction of the attention to a casual external impressions...

On the other hand, the attention is often rigidly fixed for a long time, so the patient stare at the same point, or the same object, continue the same line of thought, or do not let themselves to be interrupted... “ (Kraepelin, 1919/1971, p. 6)
in sum...

• LI models two deficits: failure to ignore irrelevant stimuli (disrupted LI) and a failure to dis-ignore irrelevant stimuli when they become relevant (persistent LI)

• Weiner: These deficits reflect two extremes of deficient cognitive switching, excessive switching between associations (attentional over-switching) and retarded switching between associations (attentional perseveration), both widely documented in schizophrenia

we did not talk about the following slides in class, but in case you are interested: the neural basis of LI
NAC shell/entorhinal lesions: disrupted LI, as in positive symptoms (restored with haloperidol)

NAC core lesions (or lesion its inputs): persistent LI as in negative symptoms (shell and core - antagonistic?)
the neural basis of LI

Hippocampal lesions: LI persists even with context shift [LI was not a result of CS-context association]

in sum: LI as a phenomenon of learning or performance?

- haloperidol, amphetamine exert their effects at the time of conditioning, not preexposure
- idea: two associations learned, compete for expression (dynamic process: “window”)
- manipulations that impact one association or the competition between them move window
why am I teaching you this?

- Great example of the strength & importance of animal learning phenomena to complex neuroscience/psychology questions
- LI: very simple, basic - useful model of basic function (and its disorders)
- Also demonstrates that optimal learning is not always the fastest learning: the normal state is the one with LI intact! (at least in some conditions)
- cautionary note: LI is a learning phenomenon, SCZ (includes) an attention deficit - not everything that impacts on LI is relevant to SCZ!