Getting excited about apathy
When the spark goes out

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Motivation and apathy

Each decision is a hill to climb – or roll down

People differ in how effortful and how rewarding a task seems to them
Pathological apathy

Historically referred to using different terms
The letter
Pathological apathy following *bilateral* basal ganglia stroke

Adam et al (2013) Cortex
Basal ganglia – medial frontal circuits

Implicated in motivation to action in animal models & apathy across human diseases

Haber & Knutson (2010) *Neuropsychopharmacology*

Circuit level dysfunction regardless of pathology?

Dopamine: identified as a key neurotransmitter

Potential circuit level and neurotransmitter targets
Responded to dopamine receptor agonist drug

Adam et al (2013) Cortex
Apathy is common across brain diseases

Both neurological and psychiatric conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence</th>
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</thead>
<tbody>
<tr>
<td>Parkinson’s disease (PD)</td>
<td>17%–70% (likely ~30% in the general population)</td>
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<tr>
<td>Alzheimer’s disease</td>
<td>~50%</td>
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<tr>
<td>Sporadic cerebral small vessel disease (SVD)</td>
<td>15%–30%</td>
</tr>
<tr>
<td>CADASIL</td>
<td>40%</td>
</tr>
<tr>
<td>Stroke (large vessel territory)</td>
<td>~30%</td>
</tr>
<tr>
<td>Frontotemporal dementia (FTD)</td>
<td>&gt;50% (particularly behavioural variant)</td>
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<tr>
<td>Progressive supranuclear palsy (PSP)</td>
<td>Up to 90%</td>
</tr>
<tr>
<td>Corticobasal syndrome</td>
<td>50%–90%</td>
</tr>
<tr>
<td>Amyotrophic lateral sclerosis</td>
<td>40%</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>20%–72%</td>
</tr>
<tr>
<td>HIV infection</td>
<td>25%–40%</td>
</tr>
<tr>
<td>Multiple sclerosis (MS)</td>
<td>22%</td>
</tr>
<tr>
<td>Myotonic dystrophy</td>
<td>40%</td>
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<tr>
<td>Wilson’s disease</td>
<td>24%</td>
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<tr>
<td>Depression</td>
<td>38%</td>
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<tr>
<td>Schizophrenia</td>
<td>47%</td>
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</tbody>
</table>

Le Heron et al (2018) J Neurol Neurosurg Psychiat
Apathy is dissociable from depression

But both can be present within an individual

Study sample $N = 80$ | Consecutive OPD cases
In untreated 175 PD cases: 27% have apathy; 37% depression

Aasland et al. (2009) JNNP

Kirsch-Darrow et al. (2006) Neurology
Why do we do what we do?

Motivation to action
Why do we do what we do?

*A framework for understanding motivation to action – and loss of motivation in apathy*

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**Behavioural components**

- **Option generation**
  - Self-generated or environmentally cued

- **Cost-benefit decision**
  - Valuation of options according to reward, effort, time and risk

- **Option selection**

- **Anticipatory phase**
  - Preparation for action
  - Motivational arousal

- **Initiating action and sustaining effort**
  - Appetitive/approach phase of behaviour
  - Invigoration of action

- **Interacting with behavioural goal**
  - Consummatory phase of behaviour
  - Hedonic impact

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Learning from outcomes

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Husain & Roiser (2018) *Nat Rev Neurosci*
Measuring option generation | fluency

And uniqueness of options

Option generation task

"Draw as many different paths as you can from the bottom red circle to the top red circle in 4 minutes."

Ang et al (2018) Current Biology
Option generation correlates with motivation in controls
And trades-off with uniqueness so more motivated people find fewer novel options

BUT option generation not related to apathy in Parkinson’s disease

Ang et al (2018) Current Biology
Why do we do what we do?

A framework for understanding motivation to action – and loss of motivation in apathy

Husain & Roiser (2018) Nat Rev Neurosci
Basal ganglia and medial frontal regions

*Play a key role in processing reward signals to direct effort*

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Salamone *et al.*
Phases of motivated behaviour

Approach and invigoration vs hedonic phase

Instrumental phase

Accumbens DA DEPENDENT

INVIGORATION

Homeostatic state and salient predictive stimuli invigorate the organism to approach the reinforcer, overcoming work and tolerating delays in flexible ways

GOAL STIMULI:
FOOD, WATER, SEX, DRUGS, PREDATORS, PAIN, DISCOMFORT

Avoidance / Approach Behaviors

Consummatory phase

Accumbens DA INDEPENDENT

Appetite or Preference
Hedonic reaction

Direct interaction with the goal stimulus

Salamone & Correa (2012) Neuron
Is the reward worth the effort?
Cost-benefit decision making in Parkinson’s disease patients with or without apathy

Le Heron et al (2018a) Brain
Is the reward worth the effort?
Cost-benefit decision making in Parkinson’s disease patients with or without apathy

Total number of apples gathered converts to monetary reward at the end of the task
Is the reward worth the effort in Parkinson’s disease?

Is apathy associated with reduced sensitivity to reward or hypersensitivity to effort?

Le Heron et al (2018a) *Brain*
Reduced reward sensitivity or effort hypersensitivity?

This task allows us to map out the space where people are prepared to work.

Proportion of offers accepted

Proportion of offers accepted reduced in apathy

BUT proportion of offers accepted not related to dysphoria

Le Heron et al. (2018a) *Brain*
Apathy: reduced willingness to work for low rewards

But dopamine has a distinctly different effects on choices

Motivated patients accept more low reward offers

Effect of apathy on decision making

Effect of dopamine on decision making

Dopamine's biggest effect at high effort / high reward offers

Le Heron et al (2018a) Brain
Effort-based decision making for reward in SVD
Also altered with apathy in CADASIL* (a form of cerebrovascular small vessel disease)

* Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy
Apathy in CADASIL: also reduced work for low rewards

*CADASIL* is a genetic form of small vessel disease

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Le Heron *et al* (2018b) *Brain*
Apathy in late-onset SVD

Characterised by reduced willingness to work for low rewards and high efforts

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**Apathetic**

**Motivated**

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Saleh *et al* (2021) *Brain*
Brain systems for motivation: Not just reward but also effort

Net value of an action involves evaluation of costs (effort) and benefits (rewards)

Circuit level dysfunction regardless of underlying pathology in apathy?
Apathy related to disruption of specific tracts
Not explained by global severity of disease

Saleh et al (2021) Brain
White matter tract changes related to apathy in CADASIL

Reduced fractional anisotropy compared to non-apathetic CADASIL cases

Le Heron et al (2018b) Brain
Why do we do what we do?

A framework for understanding motivation to action – and loss of motivation in apathy

Husain & Roiser (2018) Nat Rev Neurosci
Reward for saccade task

Magnitude of reward earned depends upon response time

Auditory cue at trial onset tells you maximum reward obtainable

Actual reward obtained depends upon response time

Muhammed et al (2016) Brain
Magnitude of potential reward modulates pupil response

Muhammed et al (2016) Brain
Pupil reward sensitivity and apathy

Apathetic Parkinson’s patients show blunted reward sensitivity

There were no differences in pupil reward sensitivity between the three groups when split into PD patients with higher and lower depression scores. Suggesting that the reward sensitivity metric is specific to apathy rather than other neuropsychiatric disorders.

Muhammed et al (2016) Brain
Reward sensitivity modulated by dopamine

Parkinson patients’ pupil reward sensitivity greater when ON

But effect of dopamine evident in both apathetic and non-apathetic patients

Muhammed et al (2016) Brain
Reward sensitivity blunted in apathy

But dopamine increases sensitivity in apathetic and non-apathetic

Non-apathetic patients ON dopamine are actually hypersensitive to reward

Muhammed et al (2016) Brain
Serotonin and apathy in ‘prodromal’ PD

REM behavioural sleep disorder (RBD)

45% of RBD cases apathetic

N=65


Barber et al (2018) Brain
Getting excited about apathy: When the spark goes out

Neurology of motivation and apathy

Apathy is a common syndrome across brain disorders

*Dysfunction of ventral striatal – medial frontal systems*

Potential systems level targets for therapy

Abnormal effort-based decision making for rewards

*Apathetic patients are less willing to exert effort for low rewards*

*In PD dopamine alters effort-based decision making but dopamine deficiency may not be cause of apathy*

Blunted reward sensitivity in apathy (pupil response)

*In PD dopamine can improve reward sensitivity – but across both apathetic and non-apathetic cases*