Parkinson's blues: Are anxiety, depression and hallucinations holding you back?

Dr Linton Meagher

BA MBBS (Hons) M Psychiatry FRANZCP

Neuropsychiatrist: North Shore Private Hospital - Sydney Parkinson's and Movement Disorders Surgical Clinic.

Consultant Psychiatrist and Assistant Director of the Northside Clinic Mood Disorders Unit

Clinical Associate, University of Sydney

Private practice in Cremorne – The Evesham Consulting Rooms

Conflicts of interest

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No other conflicts of interest

Neuropsychiatric symptoms in Parkinson's disease can be due to:

a) the pathologic brain changes

b) the emotional reactions to the disease process

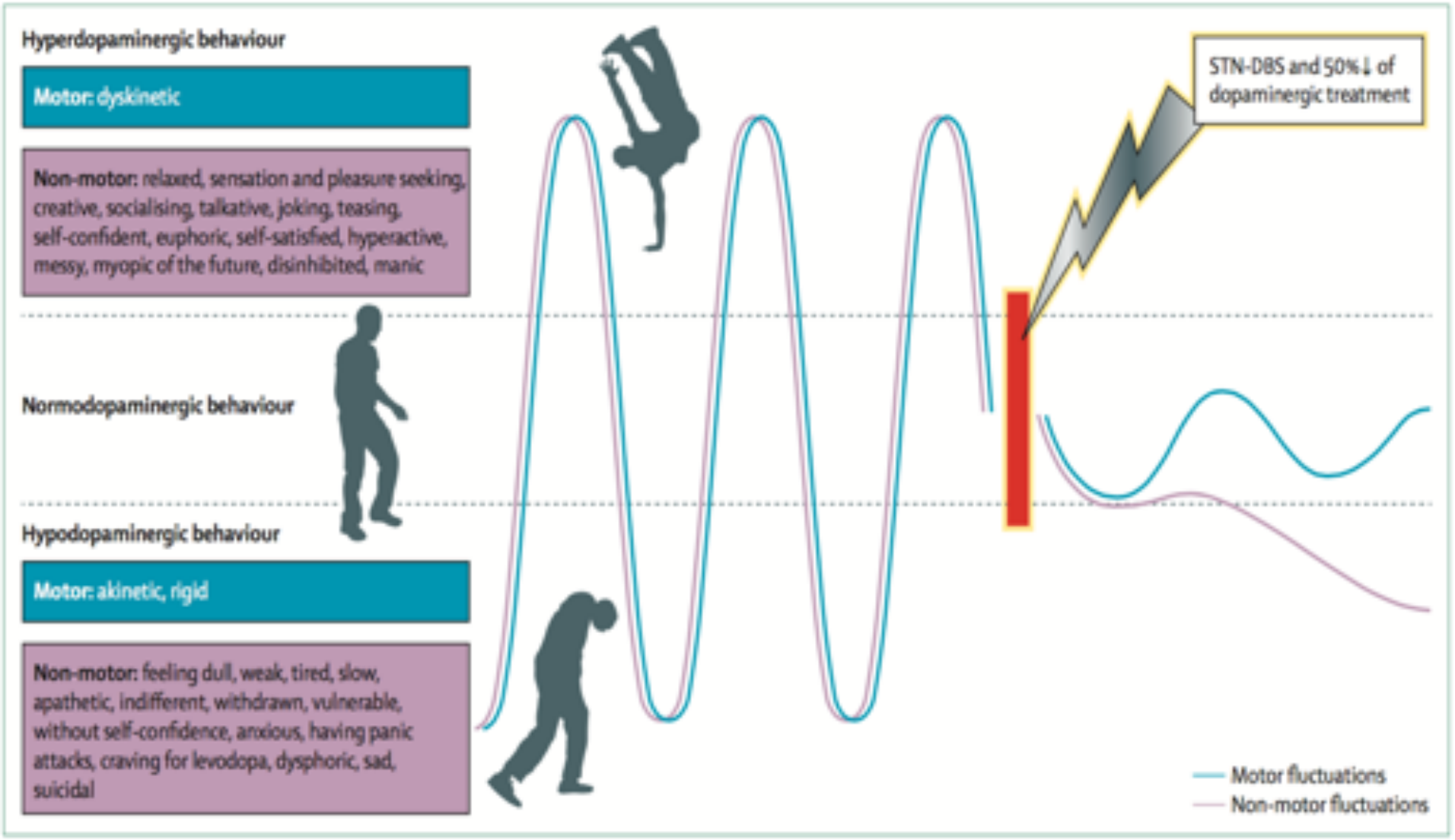
c) treatment-related side effects (eg. medications or deep brain stimulation)

Neuropsychiatric symptoms of PD

- Depression and non-motor fluctuations
- Anxiety disorders
- Hallucinations/psychosis
- Disorders of sleep and wakefulness
- Hypomania/ mania
- Cognitive impairment and dementia
- Apathy
- Impulse control disorders (ICD's), punding and dopamine dysregulation syndrome

- Depressive episodes or panic attacks precede the onset of motor symptoms in up to 30% of patients with PD (Santamaria *Neurology* 1986)

Castrioto et al, Lancet Neurol, 2014



Depression in Parkinson's disease

- Overall prevalence of clinically significant depressive symptoms = 35% (Reijnders et al., *Mov Disord*, 2008)
- Depression in PD → decrease in QAL *independent* of motor deficits (Kuopio et al., *Mov Disord,* 2000)
- Depression commonly occurs along with an anxiety disorder (65%) (Ebmeier, *Advances in Biological Psychiatry* 2012)

DSM-V Major Depression criteria

- Pervasively depressed mood for > 2/52 or
- Anhedonia for > 2/52
- Sleep decrease/increase
- Guilty ruminations/ worthlessness
- Poor energy
- Poor concentration
- Appetite decrease/increase
- Psychomotor retardation or agitation
- Suicidal ideation


MELON COLLIE?

Loss of neurons in PD does not only occur in the basal ganglia…

a) Noradrenergic neurons in the locus coeruleus

b) Serotonergic neurons in the raphe nucleus.

• More marked degeneration in Parkinson's patients with depression *vs* without depression (Ehgoetz et al. *J Neurol Sci* 2017)

Causes of depression and anxiety

1) Biological factors

2) Psychological factors

3) Social factors

4) Lifestyle

- Predisposing, precipitating, perpetuating

Management of depression in PD

Step 1: Ensure safety... then exclude or treat possible physical causes of depression

- Physical examination
- Blood tests, including B12/ folate/ thyroid
- Review medication (? wearing off effect)
- Avoid alcohol

Step 2: Psychological therapy can help to manage depression

- Psychological therapy has been shown to be beneficial, especially Cognitive Behavioural Therapy (CBT). Dobkin et al. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. The American journal of psychiatry 2011

- Combining CBT with an antidepressant may be more effective than medication alone.

Cognitive Behavioural Therapy (CBT)

- A time-limited, structured therapy delivered during weekly 45 minute sessions for around 2-3 months.

- Thoughts/Beliefs → feelings → behaviour

- Learning techniques to challenge automatic negative thoughts and cognitive distortions. Behavioural approaches are also utilised

Behavioural activation strategies

- Scheduling in regular...
  - social activities
  - physical activities
  - pleasurable activities

‘SMART’ *written* goals

- S pecific
- M easurable
- A chievable (eg. >75% likely)
- R elevant
- T imebound

Exercise

- Exercise plays a key role in managing mood and non-motor symptoms.
- If possible, aim for 4 sessions per week with your heart rate between 80-85% of maximum. (Schenkman et al, JAMA Neurology, 2018)
- Consider PD specific exercise programmes.
- Psychologically empowering.
- Exercise can reduce the risk of cognitive decline/dementia (Uc et al. Neurology 2014)

Step 3: Consider a Selective Serotonin Re-uptake Inhibitor (SSRI)

- **SSRI's** are considered to be the first line medication treatment
- Sertraline has been shown to improve quality of life, activities of daily living and mobility (Antonini *Movement Disorders* 2006)
- The *absolute risk* of antidepressants worsening motor symptoms is low (eg. less than 5%). International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Non-Motor Symptoms of Parkinson's Disease. 2018.

- Tricyclic antidepressants (eg.nortriptyline) have been shown to be more effective than SSRI's in PD.
- However, tricyclic's are less well tolerated:
  - impaired cognition, constipation, dry mouth, difficulty passing urine
  - can lower the blood pressure on standing and increase the risk of developing an irregular heart rhythm

- Dopamine agonists (eg. pramipexole) can potentially be helpful. This would require close liaison between your neurologist and psychiatrist.

- Good evidence for other antidepressant classes (eg. venlafaxine) . Richard et al. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurology 2012

Apathy in PD

- Can occur with or *without* depression
- Dopaminergic hypothesis
- 40% of patients (Starkstein et al., *Mov Disord*, 2009)
- However, as in anxiety disorders, apathy can be unresponsive to dopaminergic therapy (Chaduri *Lancet Neurol* 2009)
- Rivastigmine may be helpful. Devos et al. Rivastigmine in apathetic but dementia and depression-free patients with Parkinson's disease: a double-blind, placebo-controlled, randomised clinical trial. *Journal of neurology, neurosurgery, and psychiatry* 2014

Anxiety disorders in PD

- Anxiety Disorders occur in around 20-30% of patients with Parkinson's disease at some stage in their illness.

1. Generalised anxiety Disorder
2. Social anxiety Disorder
3. Specific phobias
4. Panic Disorder

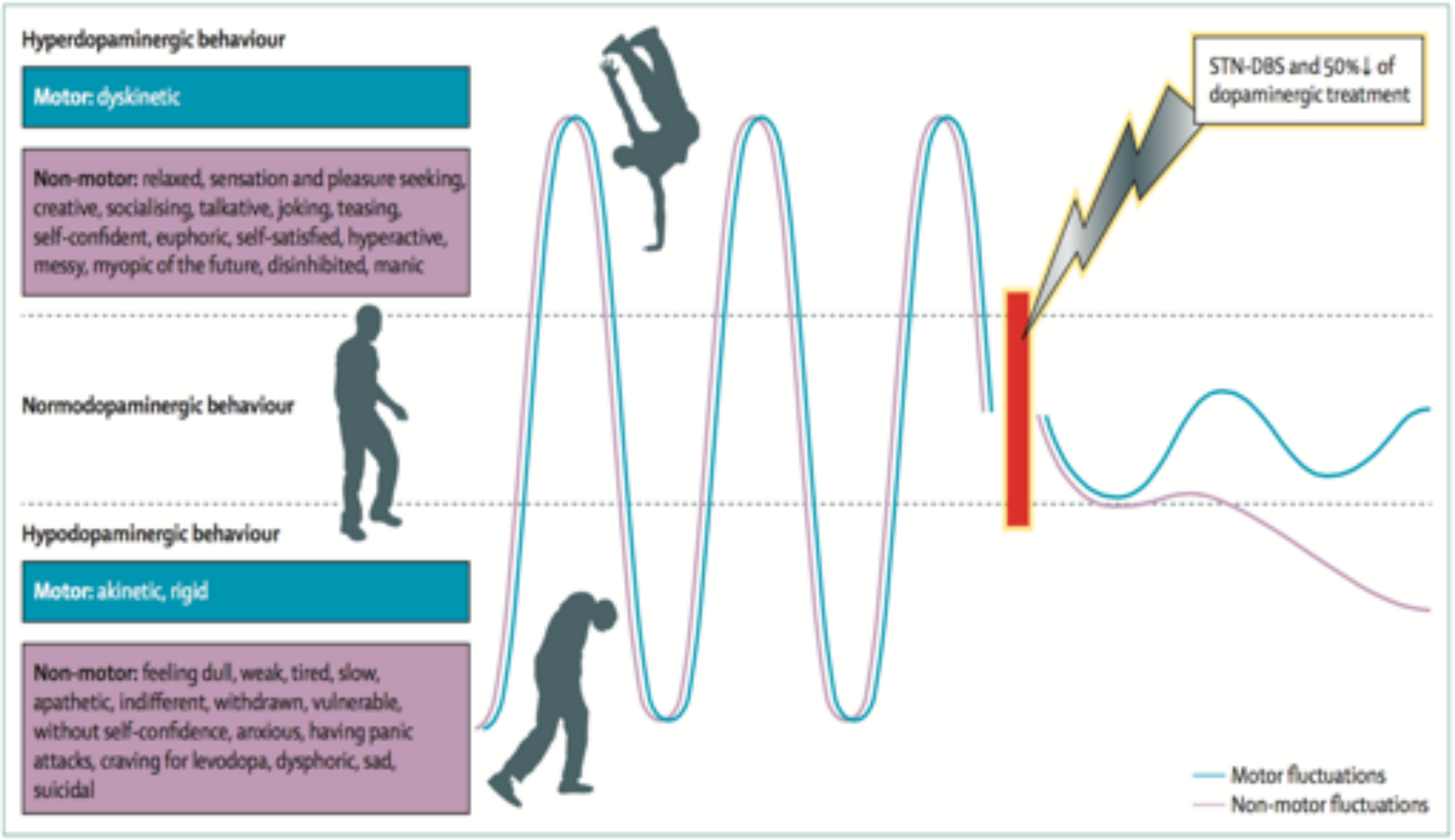
(Broen et al, *Mov Disord.,* 2016)

The “wearing-off hypothesis”

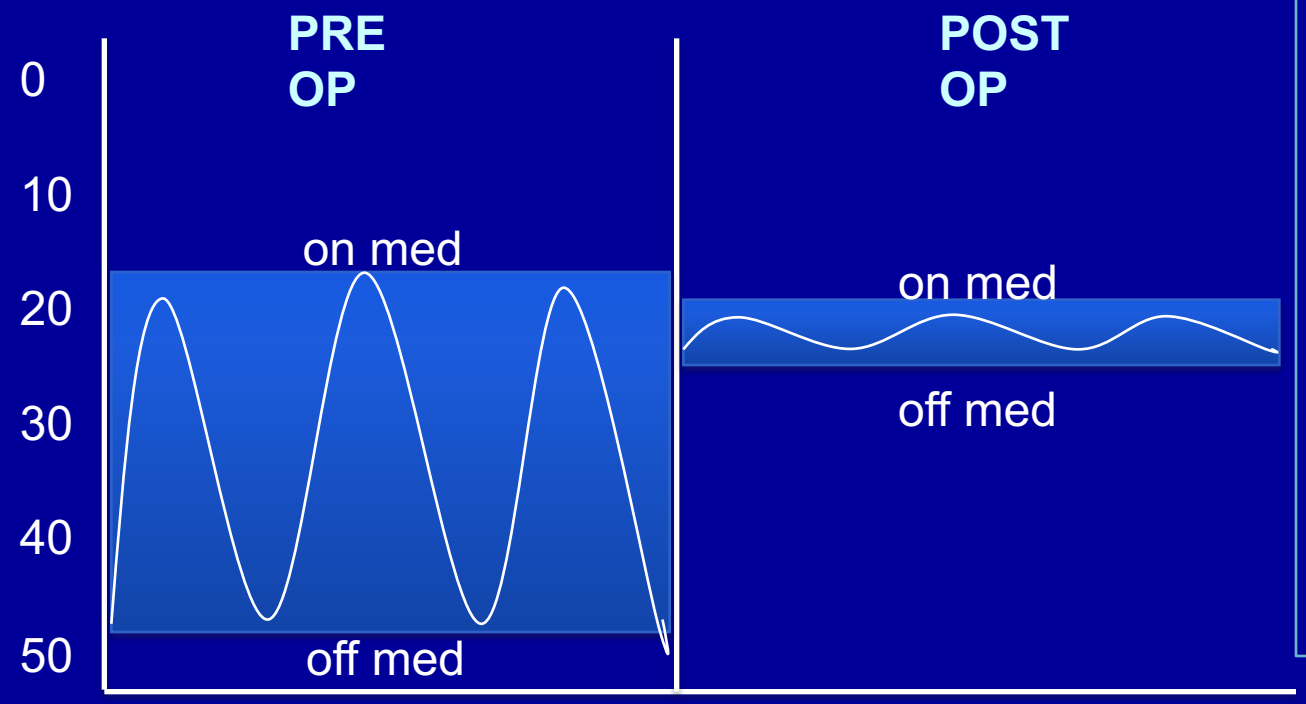
(The dopaminergic striatal deficit hypothesis)

- ‘OFF’ → low mood, anxiety and panic states
- ‘ON’ → mood elevation. Anxiety resolves.

Castrioto et al, Lancet Neurol, 2014



DBS - UPDRS III Motor Impairment



75-80% best most of the time

~75% reduction in dyskinesia

50-75% reduction in medication

Improved quality of life

PDQ-39 improvement 25% - Deuschl et al NEJM 2006

Treatment of Anxiety disorders in PD

1. Exclude physical illness (such as thyroid disease) or a medication effect (eg. wearing off)

2. Address Drug and Alcohol use

3. Cognitive behavioural therapy (CBT) has been shown to be effective.

   'Avoid avoidance' (eg. challenge one's fears)

Treatment of Anxiety disorders in PD (cont.)

4) Increase exercise: aim for daily exercise

5) Mindfulness techniques are helpful

6) Consider commencing an antidepressant

7) If possible, avoid benzodiazepines, since cognitive and motor function can be affected

Mindfulness – another useful tool in the kit bag.

- RCT data in non-PD patients strongly supports mindfulness for managing anxiety.
- There is RCT data for mindfulness training in PD (Pickut et al, *Parkinsons Dis*, 2015). 27 patients randomised to 2.5hrs/wk over 8 weeks → improved motor (5.5 point reduction on UPDRS score).
- Promising qualitative study data for MBCT in PD [Fitzpatrick et al. "A qualitative analysis of mindfulness-based cognitive therapy (MBCT) in Parkinson's disease". *Psychology and Psychotherapy: Theory, Research and Practice*, 2010].

Mindfulness

- Mindfulness is focusing attention on observing oneself or one's immediate context through…

  - describing (*not* judging) experiences
    * external - sounds, sights, environment etc.
    * Internal – sensations, thoughts, urges, and feelings

  - fully participating in the experience (ie. *not* avoiding) and focusing awareness

  - assuming a non-judgmental stance (ie. *not* analysing, reason giving etc. just observing)

1) **Focused attention** involves repeated attention fixation, for example, on the sensation of breath entering the nostril

2) **Open monitoring** trains nonjudgmental awareness of moment-to-moment experience (Kabat-Zinn, 2003).

- MT improves attention and working memory in healthy novices (Tang et al., 2007; Jha et al., 2010; MacLean et al., 2010)

- Allen et al. in a RCT of 61 patients without PD (J. of Neuroscience, 2012) looked at fMRI changes which may account for the positive benefits
- Mindfulness Training → reduced affective Stroop conflict [after 2hrs/week x 6 weeks]
- Greater dorsolateral pre-frontal cortex responses during executive processing

Green Red Blue

Purple Blue Purple

Blue Purple Red

Green Purple Green

The Stroop effect is the finding that naming the color of the first set of words is easier and quicker than the second.

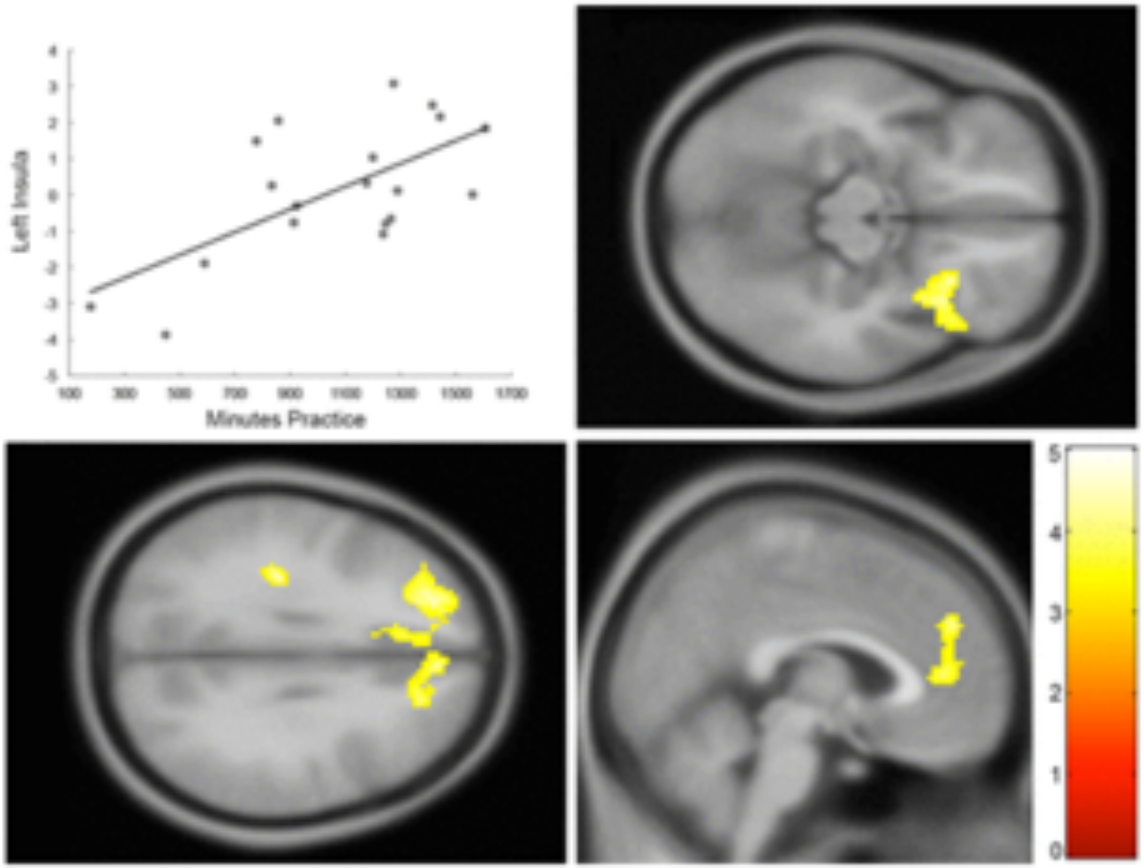


Figure 4.

fMRI results. Greater levels of MT practice predict increased dorsolateral prefrontal (bottom left), right anterior insula (top right), and medial–prefrontal BOLD (bottom right) recruitment during negative emotional processing. *Post hoc* analysis further revealed this effect to be driven by positive correlations in the MT group. Top left, For visualization purposes, BOLD signal was extracted from the peak voxel (left posterior insula) of this contrast and plotted against practice minutes within MT group. The color bar indicates the *t* statistic associated with each voxel. A whole-brain statistical parametric map (in yellow) is displayed superimposed on coronal, sagittal, and axial views of the SPM T1-weighted template, for group by time interaction on the negative > neutral contrast. $p_{FWE} < 0.05$ corrected on cluster level. The voxel selection threshold is $p = 0.001$.

Mindfulness Meditation and Psychological Health Benefits

- Decreased anxiety
- Better pain control (and a possible reduction in tremor)
- Greater self awareness and self-actualisation
- Improved well being
- Better acceptance of Parkinson's and less avoidance of social situations

Fitzpatrick et al. *Psychology and Psychotherapy: Theory, Research and Practice* (2010).

Andrew

- *"A lot of what happens to a Parkinson's patient is exacerbated or can be exacerbated by stress and emotions … So if you can control … control is the wrong word, if you can **ride with them**, then it's … it can be better for you".*

- Fitzpatrick et al. *Psychology and Psychotherapy: Theory, Research and Practice* (2010).

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In summary…

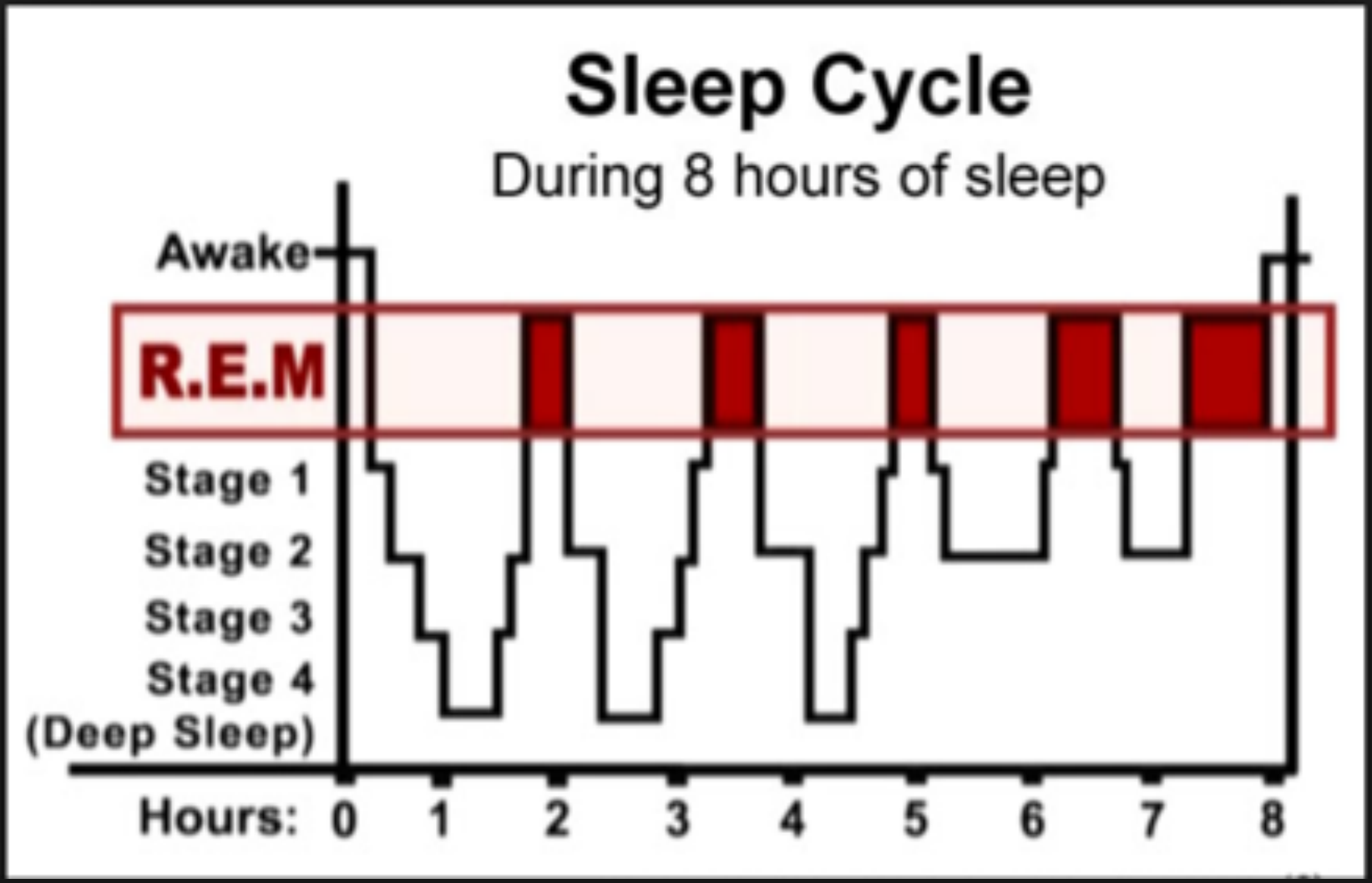
- CBT is the gold standard psychological therapy for managing anxiety and depression in PD…. However, it has its limitations

- Mindfulness based cognitive therapy (MBCT) is increasingly being recognised as a beneficial therapy for managing depression and anxiety

- Consider trialling a mindfulness app (eg. Headspace: www.headspace.com)

Sleep disturbance in PD

- Insomnia and nightmares
- Excessive daytime sleepiness and sleep attacks
- REM sleep behavior disorder (acting out dreams during sleep).
- Restless legs syndrome (RLS).
- Periodic leg movement disorder


Sleep Cycle
During 8 hours of sleep
Awake
R.E.M
Stage 1
Stage 2
Stage 3
Stage 4
(Deep Sleep)
Hours: 0 1 2 3 4 5 6 7 8

REM sleep behavioural disorder

- Loss of paralysis during the REM stage of sleep. Commonly pre-dates the onset of PD
- Education of the partner and harm minimisation approaches
- Medications can be helpful (eg. melatonin or clonazepam for RBD).

Psychosis in PD

- Visual > auditory hallucinations
- Visual illusions → benign hallucinations → paranoid psychosis
- Psychosis and dementia frequently co-exist → having one predicts the development of the other (Factor *Neurology* 2003)
- Sleep disorder → increased risk of psychosis (Reich *Neurologist* 2003. Pachetti, *Mov Disord*, 2005)

Psychosis in PD (cont.)

- Dopaminergic medication plays a key role in causing psychosis, in addition to the illness alone
- Anticholinergics and dopamine agonists are associated with a higher risk of inducing psychosis than levodopa or COMT inhibitors (Ives *Mov Disord* 2004)
- Psychosis → caregiver distress, early death → leading cause for institutionalisation (Aarsland *J Am Geriatr Soc* 2000)

Treatment of Psychosis in PD

- Exclude organic illness (eg delirium)
- Environmental optimisation and caregiver education.
- If patient has insight and hallucinations are infrequent and not distressing, do not treat.
- Consider reducing/stopping anticholinergics and dopamine agonists, if possible, and monitor motor function.

- Review by neurologist to see if PD meds can be rationalised.
- Suggested elimination order for PD patients with psychosis (Olanow *Neurology* 2009)

  Initially cease...

  - anticholinergics.... then...
  - amantadine
  - MAO-B
  - Dopamine agonists
  - Levodopa/Carbidopa

Treatment of psychosis in PD (cont.)

- Low dose Quetiapine is the best tolerated of the atypicals (Prueter *Mov Disord* 2003).
- Clozapine efficacy > quetiapine (Merims *Clin Neuropharmacol* 2006).
- The risks of antipsychotic medication has to be carefully considered.
- Consider a cholinesterase inhibitor, especially if there is co-morbid dementia (Fernandez *Mov Disord* 2005, and Burn et al, *Mov Disord* 2006

Resources for patients

- DASH: promoting a healthy brain and mind in PD (Parkinson's InfoLine 1800 644 189 www.parkinsons.org.au)

- Beyond Blue – Depression and PD
  → free DVD available 1300 22 4636

"The Happiness Trap" by Dr Russ Harris.
www.actmindfully.com.au

- Carers Australia

The end