
The importance of a staging approach to psychiatric illness in understanding the role of biomarkers and treatment response

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Background to presentation

- 28 year follow-up of children exposed to Ash Wednesday disaster in 1983 and a 9 year follow up of 500 firefighters
- 25 year follow-up of lead-exposed cohort with 5 time points of assessment in childhood (Port Pirie Study)
- Longitudinal study of 1,166 trauma victims over 6 years
- Studies of entire Australian Defence Force (n=24,481) and a 5 year follow up
- Pre/post deployment study of MEAO veterans (n=1,690)
- Multiple medico-legal assessments of military /emergency service personnel with access to all medical records

Correspondence

Biological
Psychiatry

It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group

To the Editor:

There is an urgent need to address a critical lack of advancement in the psychopharmacologic treatment of posttraumatic stress disorder (PTSD). The clinical, social, and financial burden of ineffectively treated PTSD is enormous (1–6). The impact of PTSD morbidity and mortality is further magnified by its substantial disruptions in family, workplace, and societal contexts (7). For the

federal funding agencies in research on medical treatment of military personnel and veterans with PTSD have yet to bear fruit in the form of new validated pharmacotherapies for PTSD.

Paradoxically, this is a time of tremendous progress in the basic neuroscience of stress and PTSD that could inform the identification of novel therapeutic targets (14,15). There is a longstanding translational neuroscience tradition in PTSD research (16,17). However, recent developments in the genetics and epigenetics of PTSD (18–20), progress with animal models (21), the emergence of the first molecular analyses of postmortem brain tissue from people with PTSD (22), an expanding number of brain molecular targets probed with positron emission tomography imaging (23), the refinement of

Table 6. Top Therapeutic Targets for PTSD From Expert Group (N = 27)

Target	Score
NMDA Receptor Antagonists	78
Cannabinoid Receptor Modulators	70
Glucocorticoid Receptor Agonists	58
Non-SRI Antidepressants	50
Opioid Receptor Agonists	25
Alpha-1 Adrenergic Receptor Antagonists	21
5HT ₂ -D ₂ Receptor Antagonist (Other Than Risperidone)	20
Riluzole	18
Alpha-2 Adrenergic Receptor Agonists	18
NPY Receptor Modulators	10
Glucocorticoid Low-Activity Partial Agonists And/Or Antagonist	10
Orexin Receptor Antagonists	9
NMDA Receptor Coagonists	9
Anticonvulsants	8
D ₂ Receptor Agonists	8

D₂, dopamine type 2; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; PTSD, posttraumatic stress disorder; SRI, serotonin reuptake inhibitor; 5-HT₂, 5-hydroxytryptamine-2.

Meta Analysis of Treatment in Military Populations

- Mean post treatment scores for CPT and PE remained at or above clinical criteria for PTSD
- Approximately 66% of patients retained their PTSD diagnosis after treatment (range 60-72%)
- Prolonged exposure marginally superior compared to non-trauma focused psychotherapies
- Need to improve existing treatments and test novel evidence based treatments

– Steenkamp et al JAMA 2015, 314;489-500



Contents lists available at ScienceDirect

Clinical Psychology Review



The efficacy of recommended treatments for veterans with PTSD: A metaregression analysis



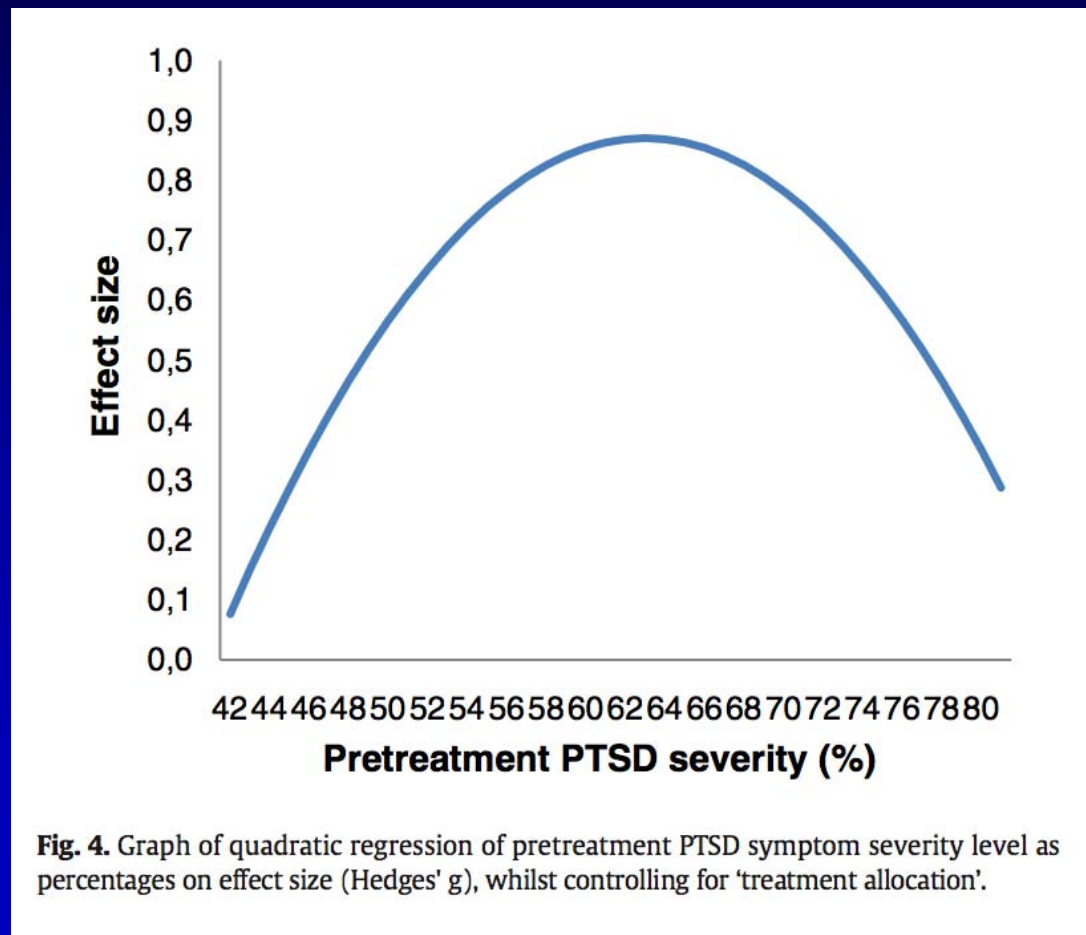
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Curve of effect size versus symptom severity for psychotherapy for PTSD



The need for new biologically based treatment approaches supported by evidence

The chronicity and disability
associated with PTSD

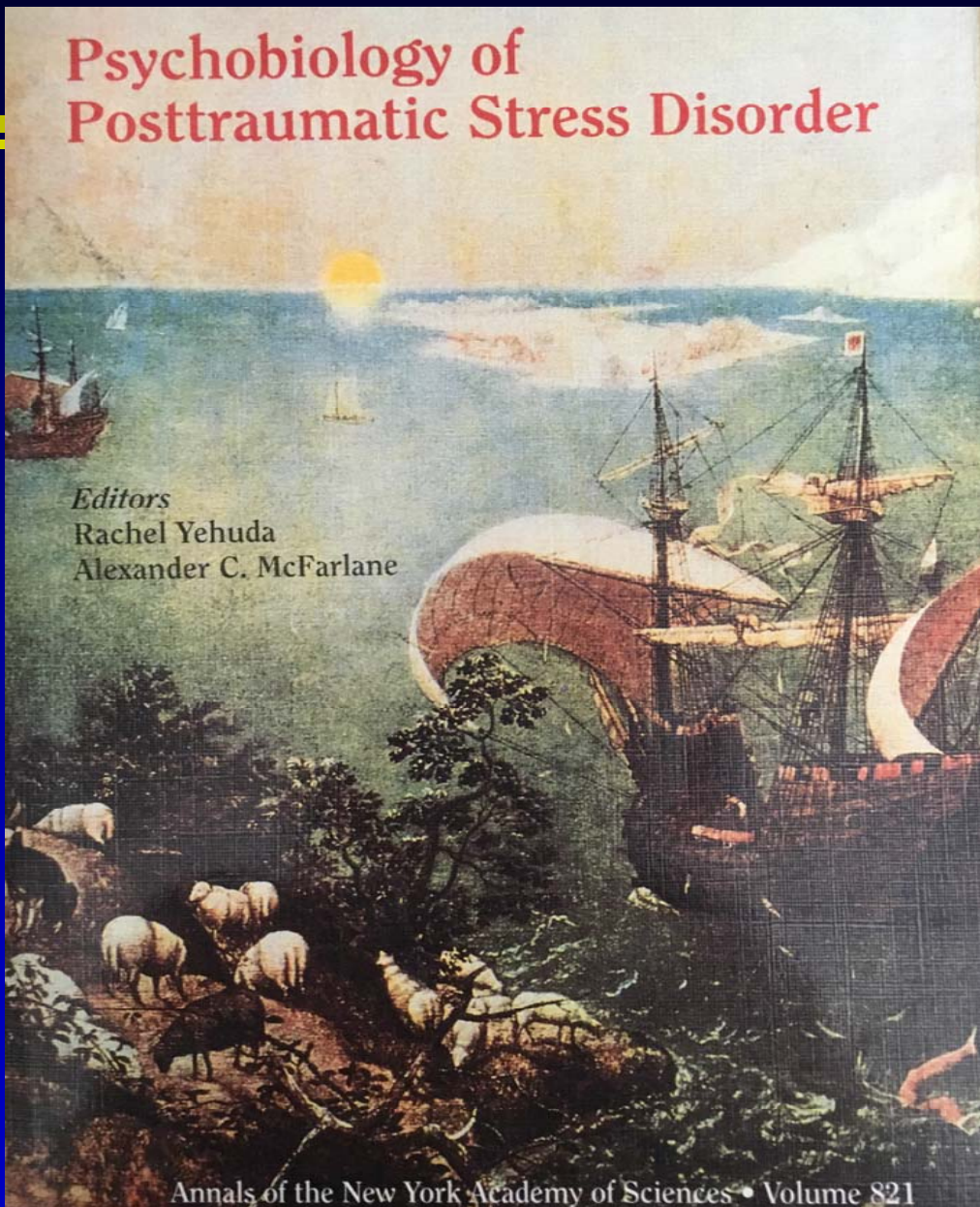
Psychobiology of Posttraumatic Stress Disorder

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Overview of Biological Themes in PTSD^a

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Biology is truly a land of unlimited possibilities. We may expect it to give us the most surprising information and we cannot guess what answers it will return in a few dozen years to the questions we have put to it. They may be of a kind which will blow away the whole of our artificial structure of hypotheses (Sigmund Freud, 1920).

Possible Origins of an association between a Biological Abnormality and PTSD Pitman 1997

1. The abnormality was preexisting and increased the risk of the individual's being exposed to a traumatic event.
2. The abnormality was preexisting and increased the individual's vulnerability to develop PTSD upon the traumatic exposure.
3. The traumatic exposure caused the abnormality, and the abnormality caused the PTSD.
4. The traumatic exposure caused the PTSD, and the PTSD caused the abnormality.
5. The traumatic event independently caused both the abnormality and the PTSD.
6. The traumatic exposure caused PTSD, the PTSD caused a sequel or complication, and the sequel or complication caused the abnormality.

Biomarkers – varying indications

- Causal mechanisms (genetic or neurohormonal)
- The consequences of pathophysiology
 - » Cognitive, structural or physiological
- Both eg inflammation
- May have predictive value and/or indicative of novel therapeutic interventions.

The need for clinical staging in PTSD

What does a biomarker indicate? –
staging is a method for clarifying the
issue of longitudinal course

Staging model of disorder

- Stage 0
 - » Trauma exposed asymptomatic but at risk
- Stage 1a
 - » Undifferentiated symptoms of mild anxiety and distress
- Stage 1 b
 - » Subsyndromal distress with some behavioural and functional decline

Staging model of disorder

- Stage 2

- » First episode of full threshold symptoms that has different trajectories

- Stage 3

- » Persistent symptoms which may fluctuate with ongoing impairment

- Stage 4

- » Severe unremitting illness of increasing chronicity

Biomarkers and clinical staging in psychiatry McGorry et al 2014

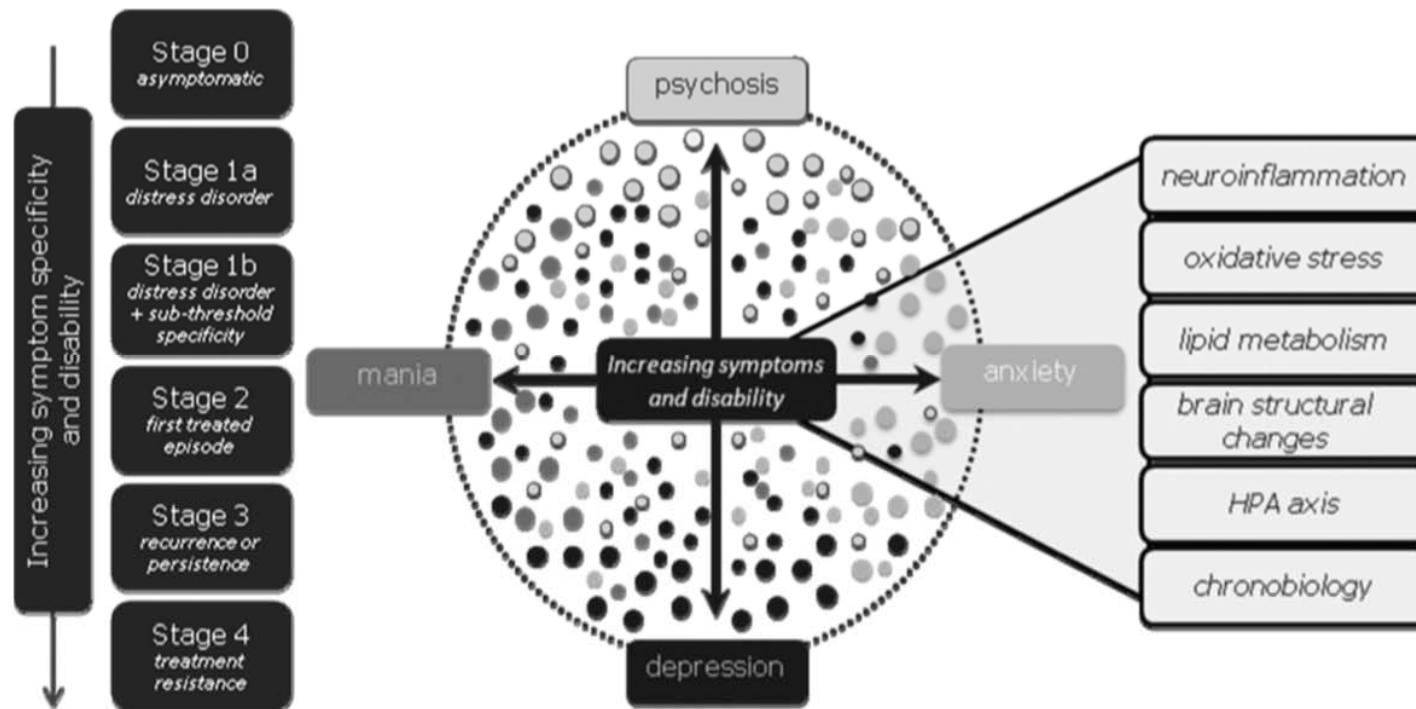


Figure 1 Clinical staging model for mental disorders and putative biomarkers. HPA – hypothalamic-pituitary-adrenal

Staging Model Bipolar Disorder

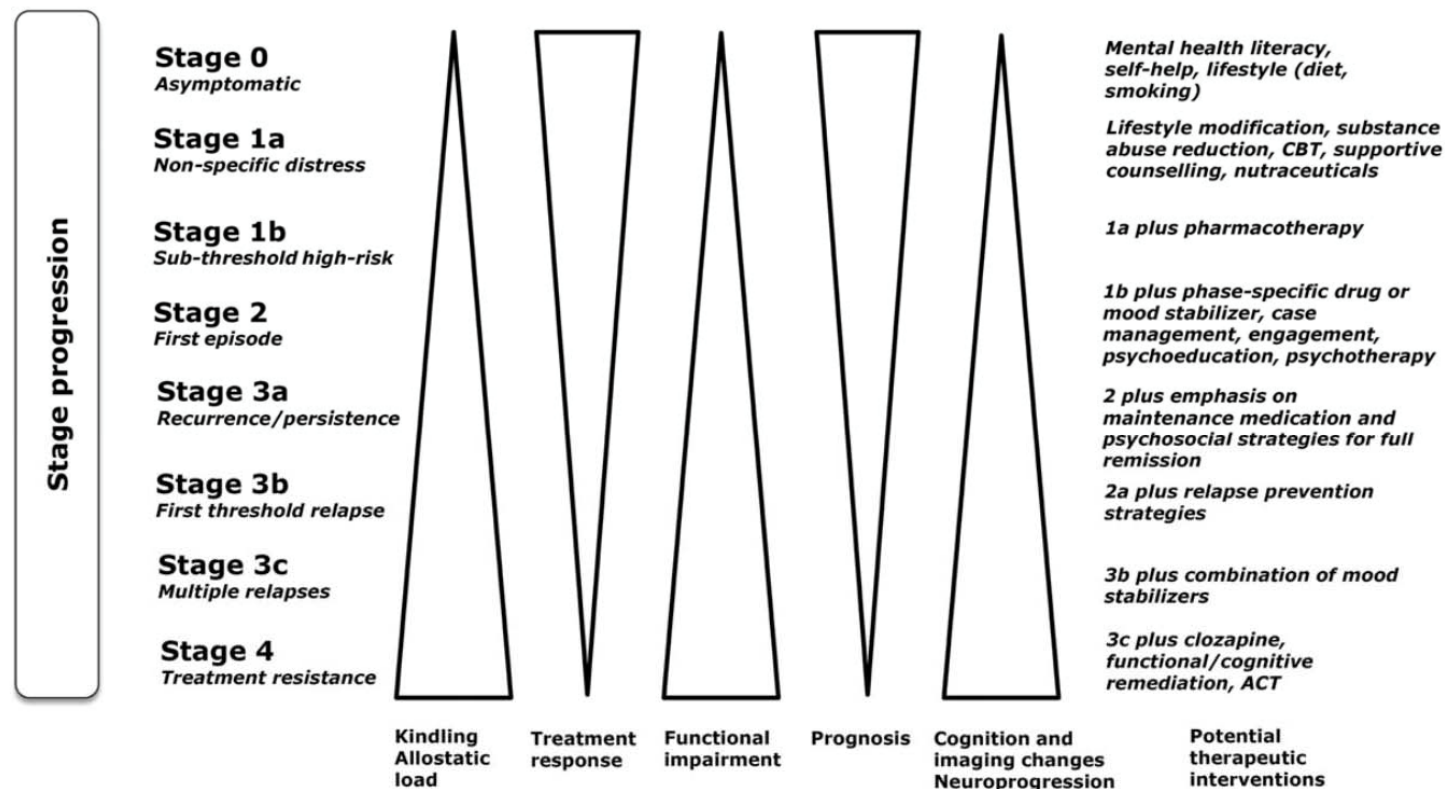


Figure 1 Staging in bipolar disorder. CBT – cognitive behaviour therapy, ACT – assertive community treatment

The importance of the longitudinal course

The changes in reactivity over time is
the critical issue

Predicting PTSD

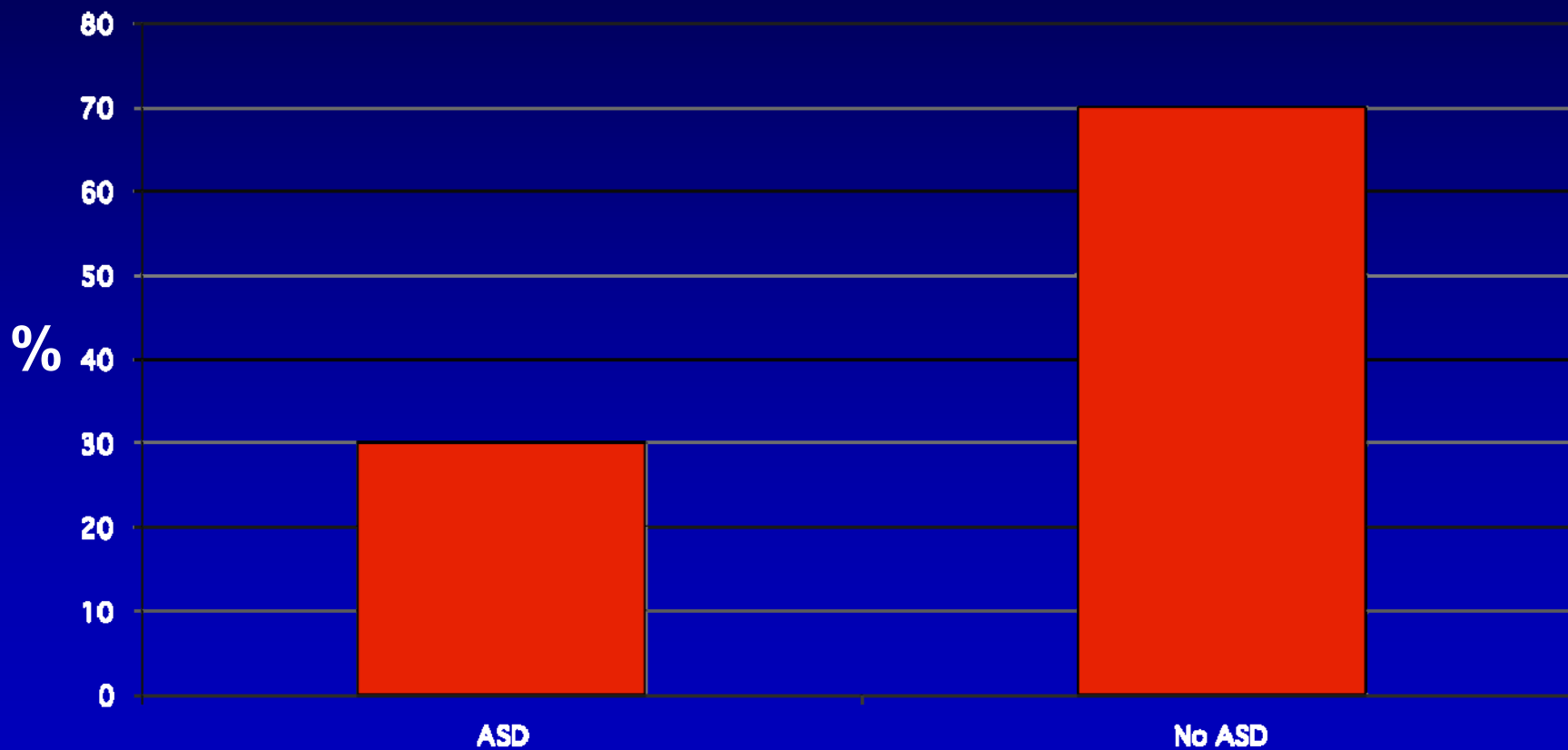
- Patients admitted to hospital after traumatic injury
- N = 1,166
- Sites: Sydney (2 hospitals), Melbourne (2 hospitals), Adelaide (1 hospital)
- Assessments: first week, 3, 12, 24 & 60 month follow up
 - Bryant, Creamer, Silove, McFarlane, O'Donnell, van Hooff

How Many People with ASD Developed PTSD 12 months later?



Bryant et al A multisite study of the capacity of acute stress disorder diagnosis to predict posttraumatic stress disorder, Journal of Clinical Psychiatry, 2008;69(6):923-929.

Rates of PTSD in those with and without an Acute Stress Disorder at 12 months?



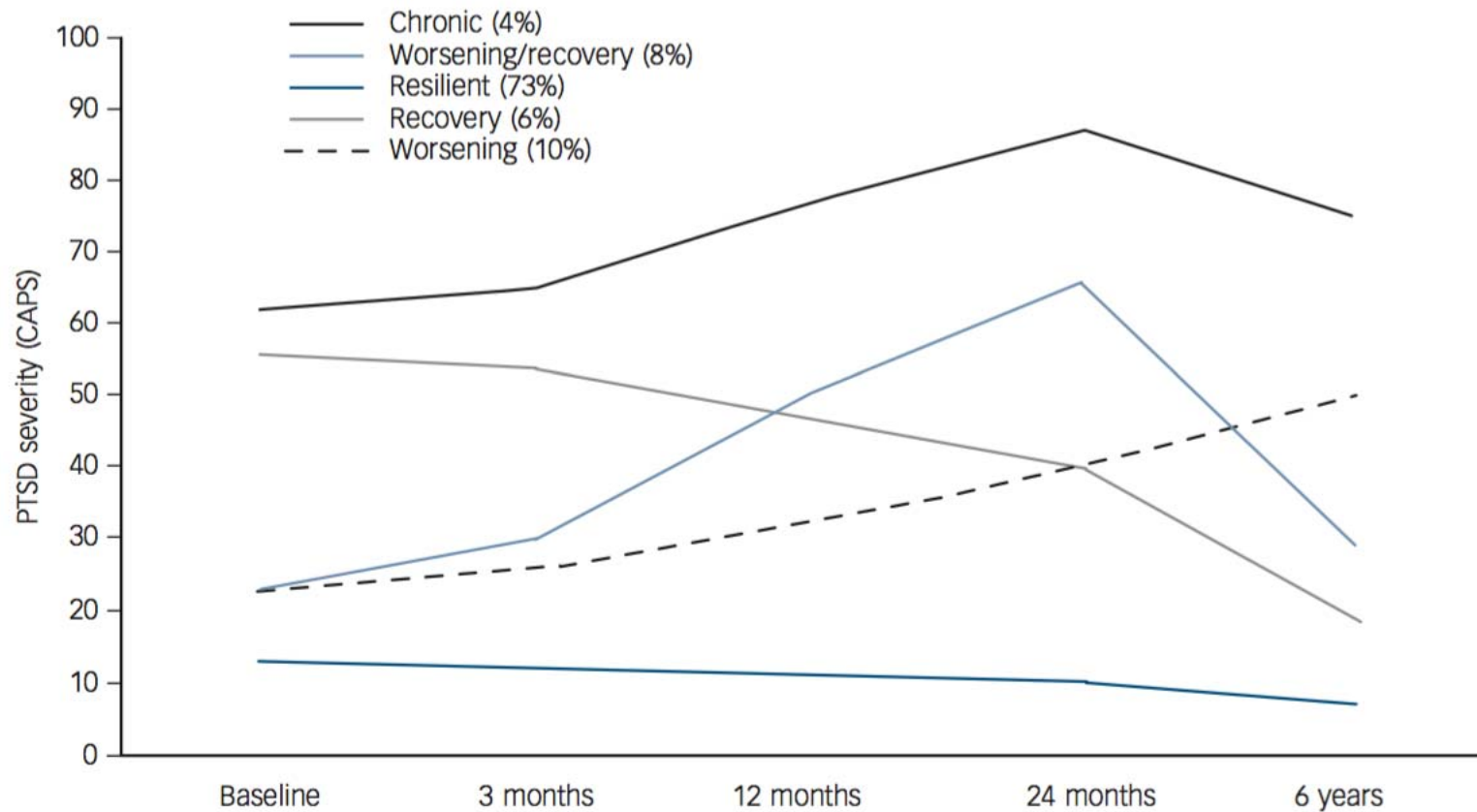
Bryant et al A multisite study of the capacity of acute stress disorder diagnosis to predict posttraumatic stress disorder, Journal of Clinical Psychiatry, 2008;69(6):923-929.

Relationship of PTSD and ASD

- Individuals who develop an acute stress disorder have a much greater risk of chronic PTSD
- The majority of individuals with PTSD do not have an acute disorder
- ASD is not a necessary antecedent for PTSD
 - Bryant et al 2012 J Psychiatric Res

The issue of delayed onset PTSD

Trajectories of PTSD after traumatic injury Bryant et al 2015



Progression of cases at 24 months in accident and work injuries (PTSD Cases n=96)

- At 3 months 35.9% had full diagnosis
 - » 44.1% reported minimal symptoms
- At 12 months 49% had full diagnosis
 - » 26.7% reported minimal symptoms
- There is a progressive emergence of disorder at with time which means there is a need for repeated reassessment -moves through a subsyndromal stage
- Coping in the immediate aftermath does not mean an individual will not develop PTSD or chronic pain later

- O'Donnell et al 2013 Psychological Medicine

Millennium Cohort Study: Pre/Post Deployment Samples

- 3393 with single deployment
- 4394 with multiple deployment
- Predeployment and 3 year follow up
- Latent growth mixture modelling
 - » Banonno et al Brit J Psychiatry 2012

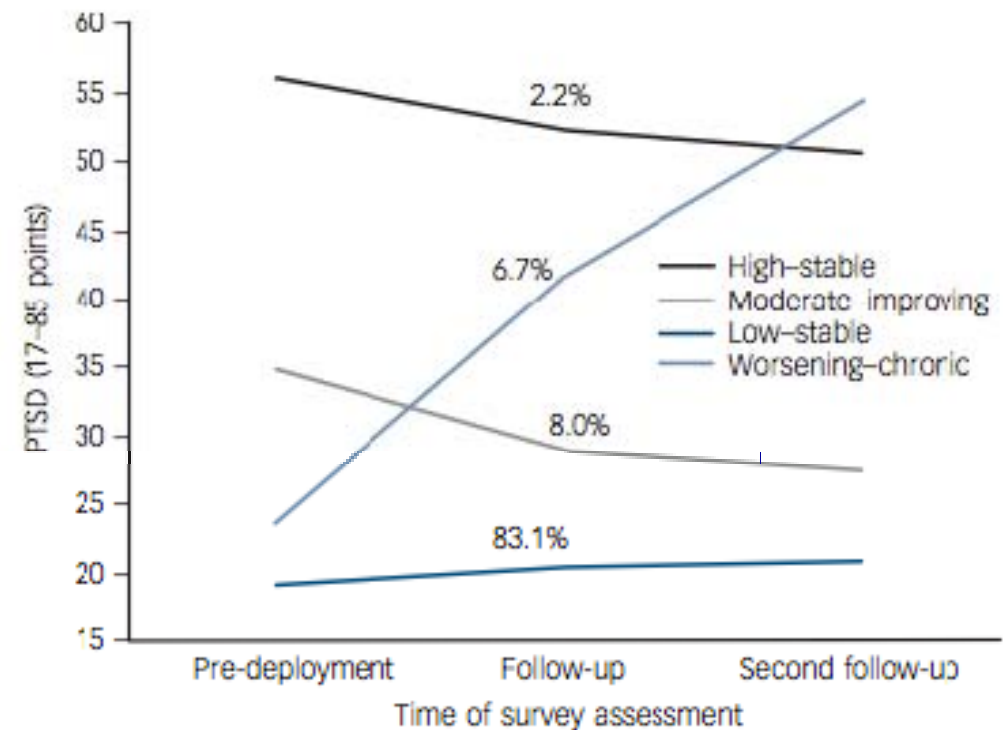


Fig. 1 Conditional model (including covariates) of post-traumatic stress over time among 3393 Millennium Cohort participants with a single deployment between baseline (pre-deployment) and first follow-up.

Post-traumatic stress disorder (PTSD) assessed using the PTSD Checklist – Civilian Version.

The need for clinical staging in PTSD

- Different phenotypes that need to be addressed in treatment
- Staging is a method for clarifying the issue of longitudinal course and the changing neurobiology

McFarlane et al Clinical Psychiatric Reports 2017

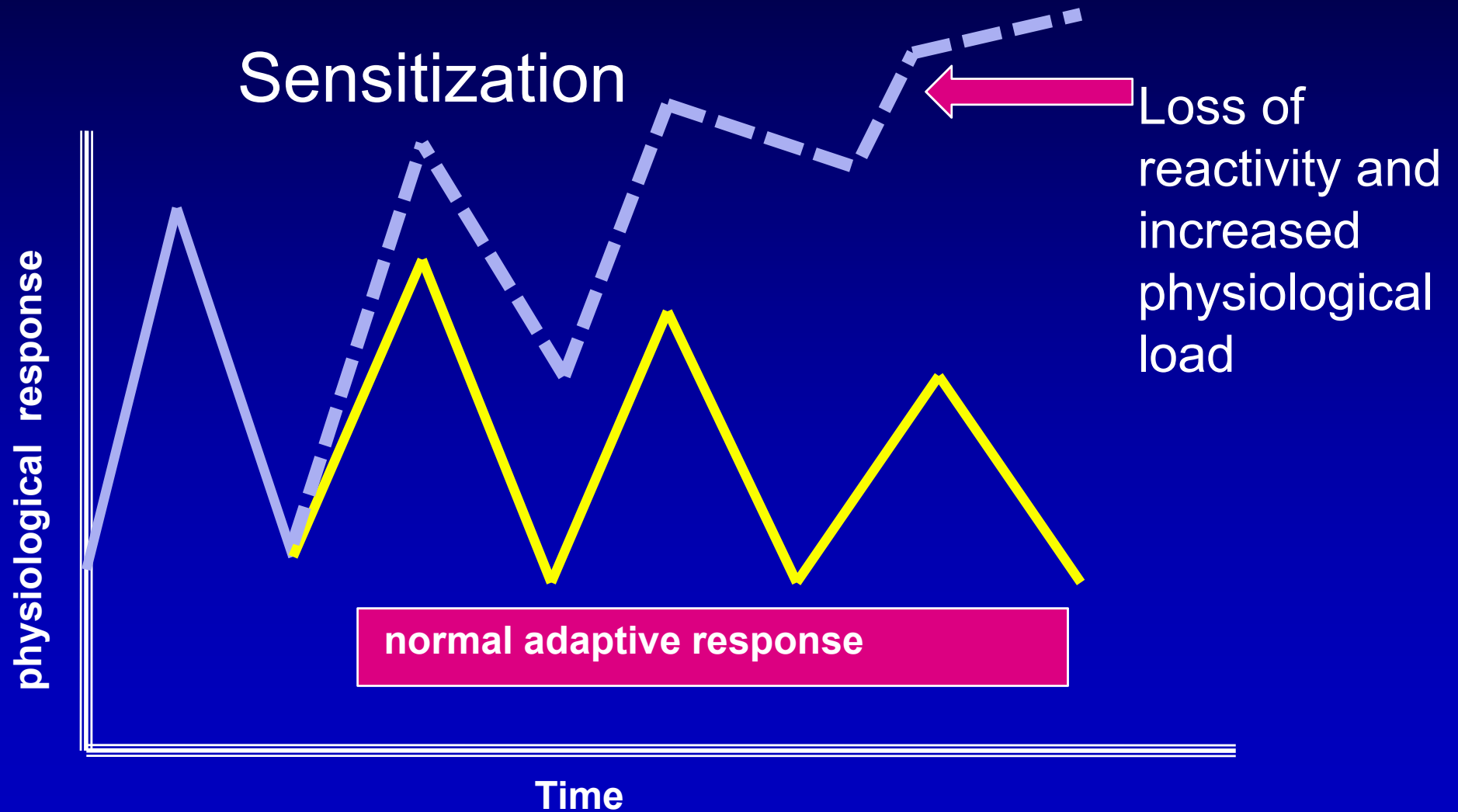
Staging model of PTSD

- 0. Trauma exposed no symptoms but at greater risk with further exposure
 - 1a. Minor symptoms
 - 1b. Subsyndromal PTSD – similar to PTSD
- 2. First episode of brief duration
- 3. More enduring or relapsing disorder following treatment
- 4. Chronic, severe and treatment unresponsive

Staging model of disorder

Stage	Presentation	Example of possible neurobiological changes
Stage 0	Trauma exposed asymptomatic but at risk	Down regulation of glucocorticoid receptor sensitivity, increased amygdala reactivity, 5FKH genotype
Stage 1a	Undifferentiated symptoms of mild anxiety and distress	Inflammatory cytokine activation, decreasing response inhibition in the frontal cognitive systems
Stage 1b	Subsyndromal distress with some behavioural and functional decline	Increased physiological reactivity to trauma related stimuli and startle response, prolonged autonomic arousal on provocation

Repeated hits from multiple stressors



Systems vulnerable to sensitization

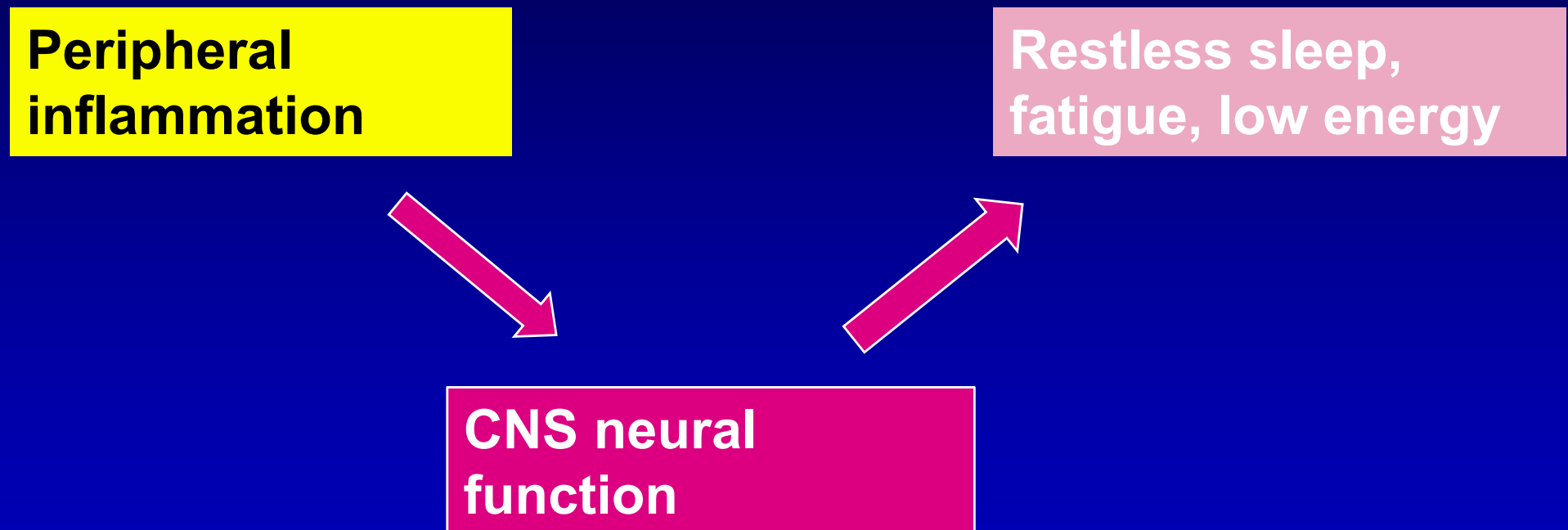
- Hypothalamic pituitary adrenal axis
- Medial prefrontal cortex - amygdala network
- Corticothalamic networks
- Locus coeruleus projections
- Vagal / parasympathetic systems
- Startle response
- Immune / cytokine systems

Staging model of disorder

Stage	Presentation	Example of possible neurobiological changes
Stage 2	First episode of full threshold symptoms that has different trajectories	Early and potentially reversible neurobiological disinhibition of frontolimbic circuitry

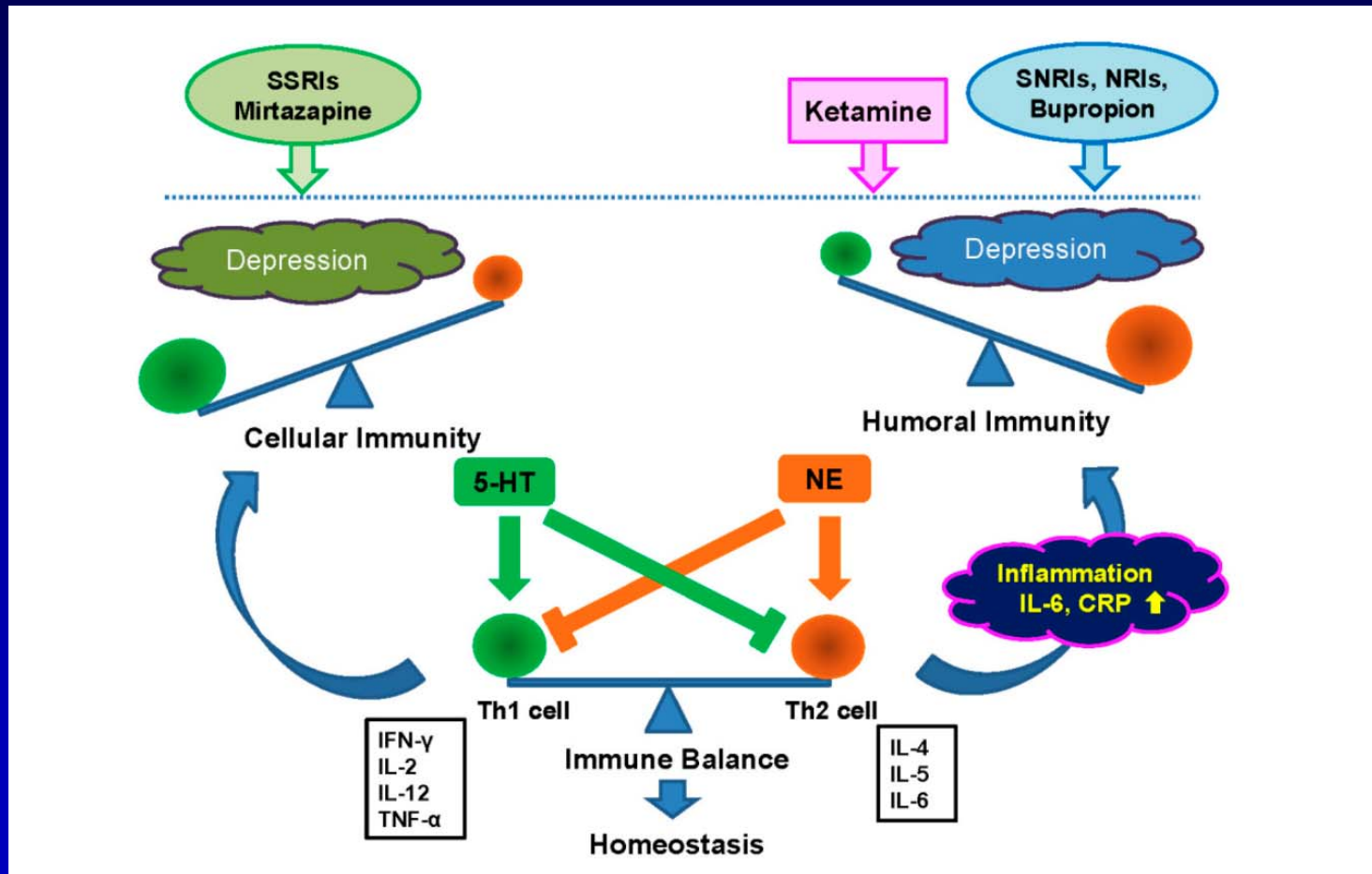
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Role of peripheral inflammation

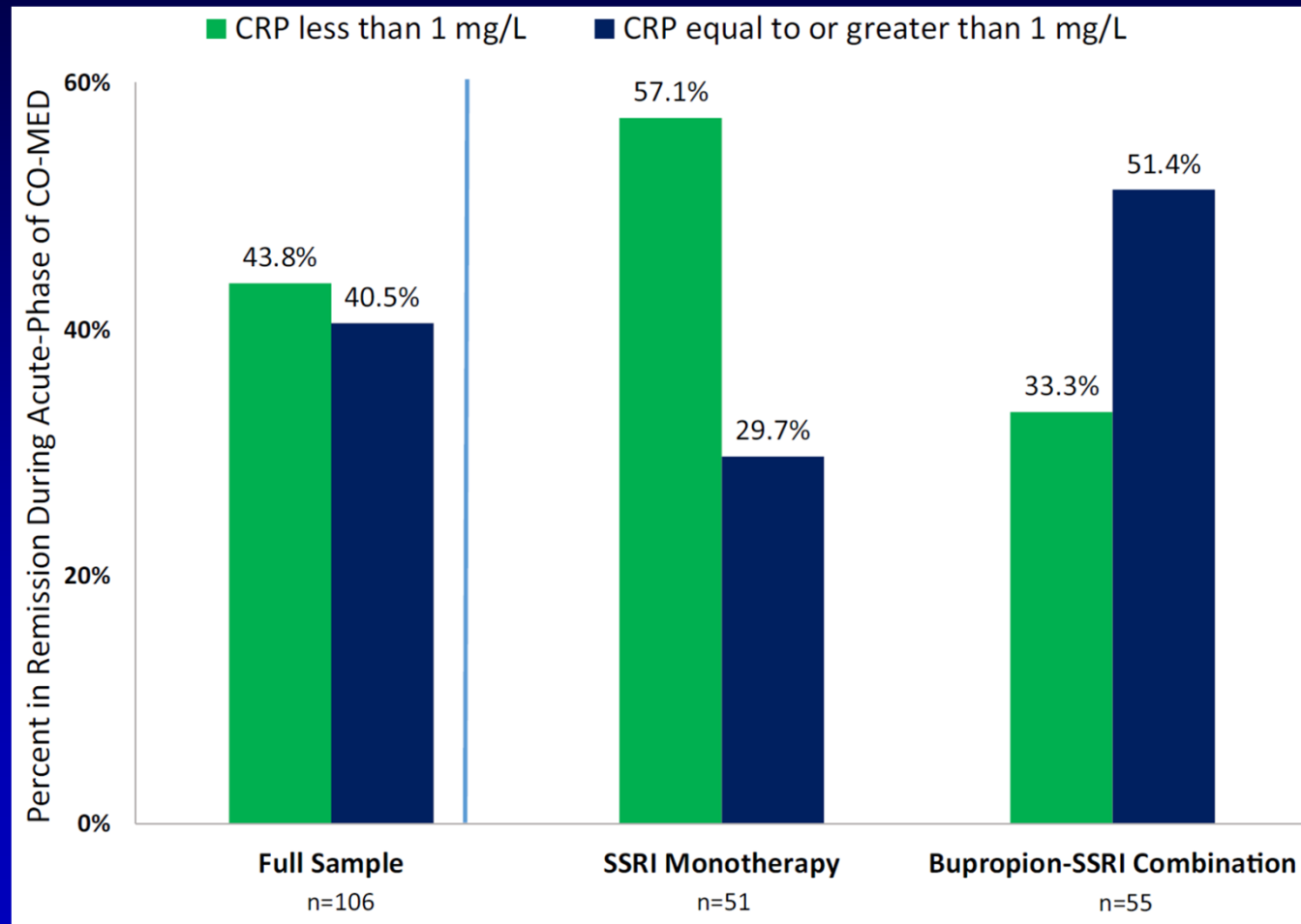


White et al, Brain Behaviour and Immunity, 2016

Antidepressants act on peripheral inflammation



CRP Predicts Differential Response to SSRI vs. SSRI+Bupropion



Jah MK et al. *Psychoneuroendocrinol* 2017; 78: 105-13

Staging model of disorder

Stage	Presentation	Example of possible neurobiological changes
Stage 3	Persistent symptoms which may fluctuate with ongoing impairment	Decreased anterior cingulate and hippocampal volume, hypertension and metabolic syndrome.
3a	Incomplete remission of first episode	
3b	Recurrence or relapse of PTSD and persistent impairments	
3c	Multiple relapses or worsening following incomplete treatment response	

Staging model of disorder

Stage	Presentation	Example of possible neurobiological changes
Stage 4	Severe unremitting illness of increasing chronicity with substantial disability	High allostatic load, high levels of inflammation, medical comorbidities, entrenched sensitization of a range of neurobiological systems

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Therapeutic Stance of Staging

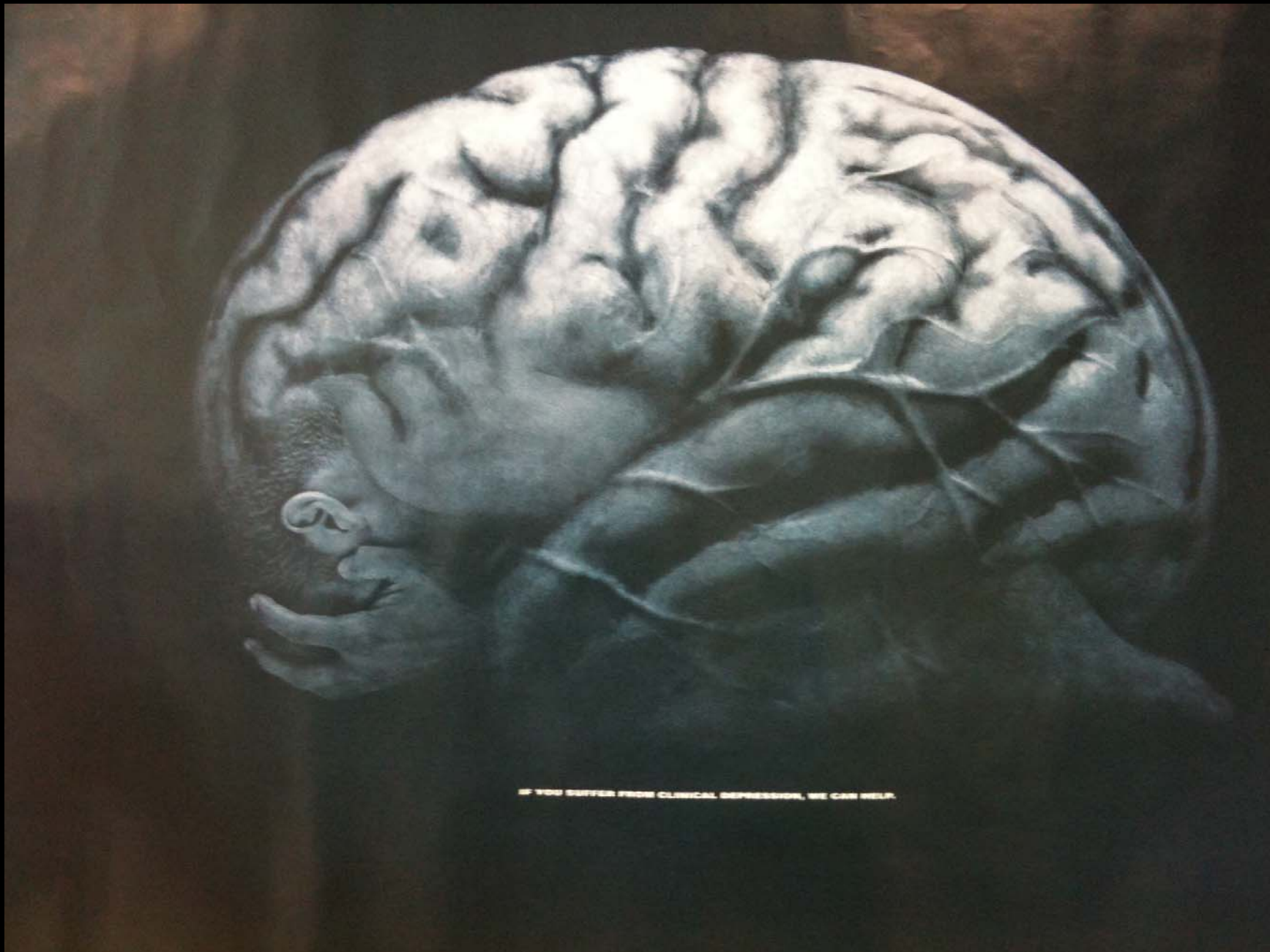
- Emphasis on progression or transition
- Not inevitable
- Earlier stages of treatment have fewer complications and greater tolerability
- Cross sectional and longitudinal biomarkers for the different phenotypes of the disorder
- Different treatment strategies at different stages

The challenge of biomarkers

- Prediction of risk of onset and chronicity
- Potential diagnostic value
- Development of novel treatments on the basis of identified mechanisms of pathology
- Primary question is about the longitudinal course of the patterns of outcome – may have different biomarkers

Conclusion

- PTSD has multiple stages and treatment needs to be based on an assessment of the individual pathology-not one size fits all
- Need for developing more effective biological based treatments that are supported by evidence
- Timing of an intervention may be critical to its effectiveness



IF YOU SUFFER FROM CLINICAL DEPRESSION, WE CAN HELP.



THANK YOU