Grief:
A Multi-Method Approach

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What we will cover

- Theoretical ideas about what happens in grief from the perspective of the human brain
- Neuroimaging findings, heavily curated
- What goes wrong in grief
- Oxytocin study in human grief behavior
- Few studies about cortisol in human grief

Of mice and men

- What is different about grief in humans compared to rodents?
- Both are social, both bond, both have certain goals (mating, rearing), both can learn new information and have memories
- Humans can explicitly draw on memories, humans have counterfactual thinking (imagining a present that is different with different prior events), humans can imagine the future
- Humans can understand the abstract idea of death (and not just separation)

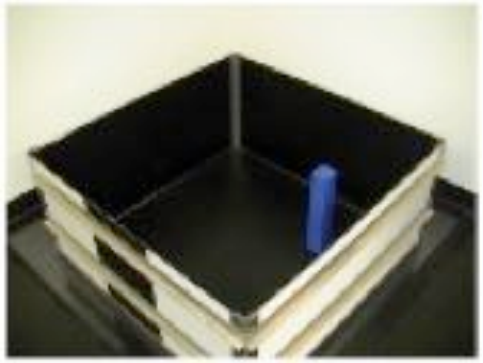
Neurobiology of grief

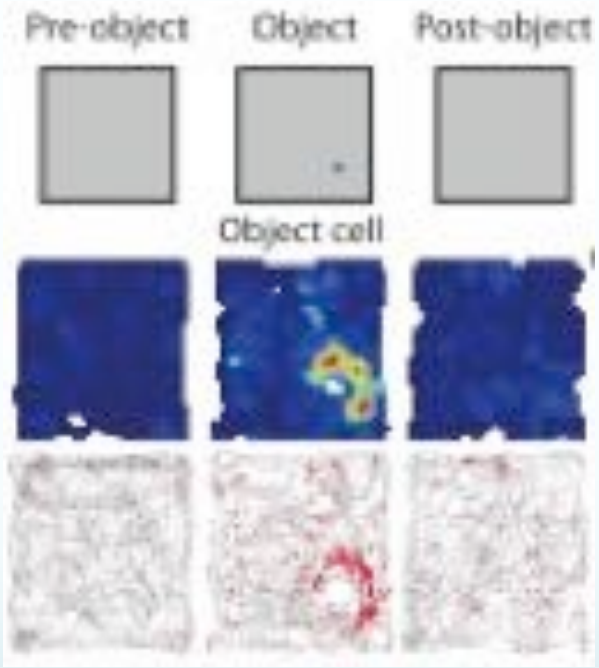
- Why study grief from the perspective of the brain?
- Many variations in grief experience and expression are possible, based on personal, familial, cultural, and historical factors.
- Grief is conserved across evolution—a finding that is the basis of attachment theory.
- Are there aspects of the nervous system that constrain our experience of grief?

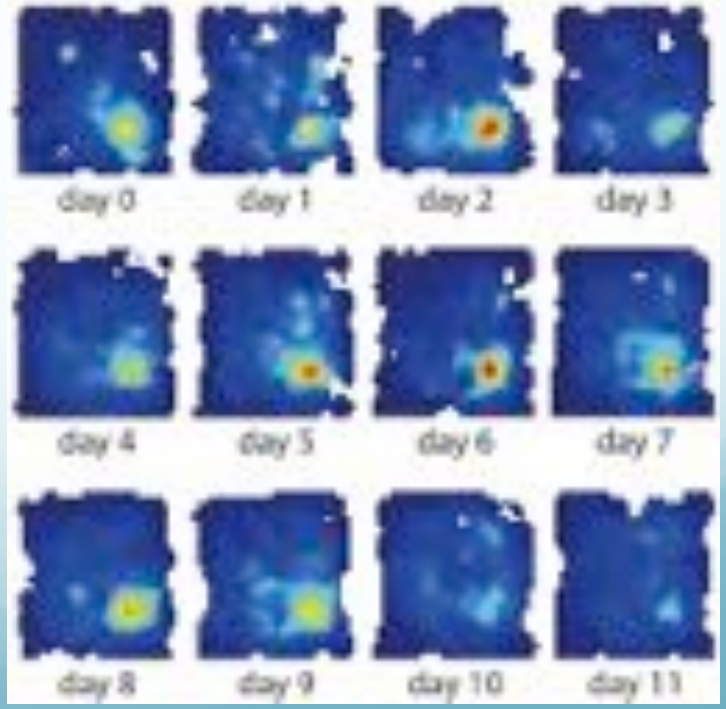
Virtual reality

- We walk around in virtual reality, a representation of our physical world.
- A working model, schema, or representation, stands in for our loved one when they are gone
  - Across distance
  - Across time
- The schema is instantiated in neurons of the brain, particular firing patterns in particular parts of the brain.
- The schema is the virtual reality that includes our loved one.

Object trace cells







Tsao, Moser & Moser, *Curr Biol*, 2013

Learning that they are gone

- So, why does it take so long to learn that they are gone? Why do we grieve and yearn?
- Attachment is a powerful motivational state, and fulfilling this crucial need is rewarding. Yearning might be analogous to hunger or thirst.
- Motivation is maintained through neurobiology, with opioids and dopamine as a reward for being in proximity to our loved ones, and oxytocin and cortisol as an inducer for seeking them.

Magical thinking

- Bonding creates a neural stamp that tells us *this* conspecific is my special one.
- The neurobiology of attachment may encode the belief that they will always be there, that they can always be found.
- Death is a low-likelihood event, unlike separation.
- Magical thinking is reported regularly. “It doesn’t feel like they’re really gone.”

Learning interference

- Why would we *believe* that our loved ones will return, if we *know* that's not true?
- Two streams of information, episodic memory for the death and attachment motivation, are conflictual.
- This conflict may be actively preventing learning, remembering, or accepting the loss.

What goes wrong in grief?

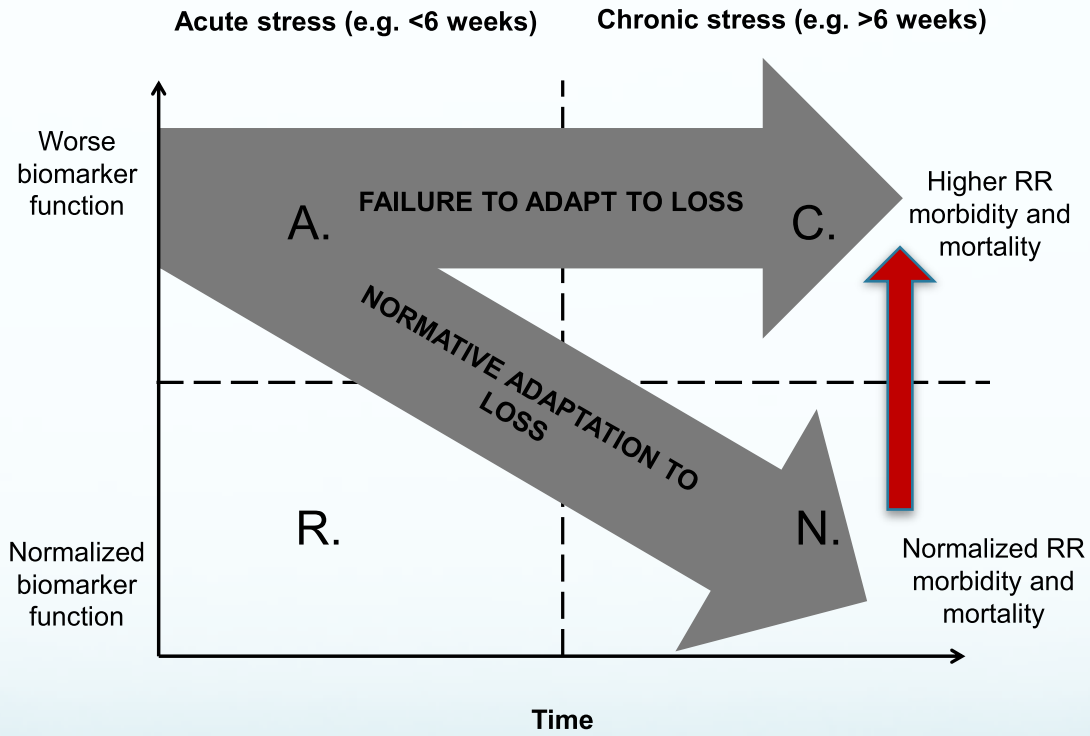


FIGURE 1. Broad model of acute and chronic alterations in immune parameters after bereavement. Quadrants: A = Acute immune dysregulation, R = Resilient to immune changes, C = Chronic immune dysregulation, N = Normalized immune function. The vertical transition line refers to the time point where most individuals show normalization in immune parameters. The horizontal clinical cutoff line refers to the level at which immune parameters affect pathophysiology of disease. RR = relative risk.

Complicated Grief

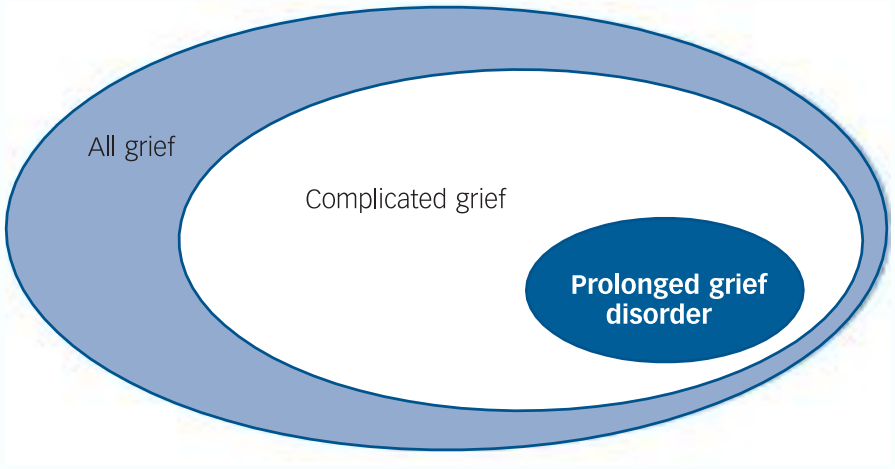
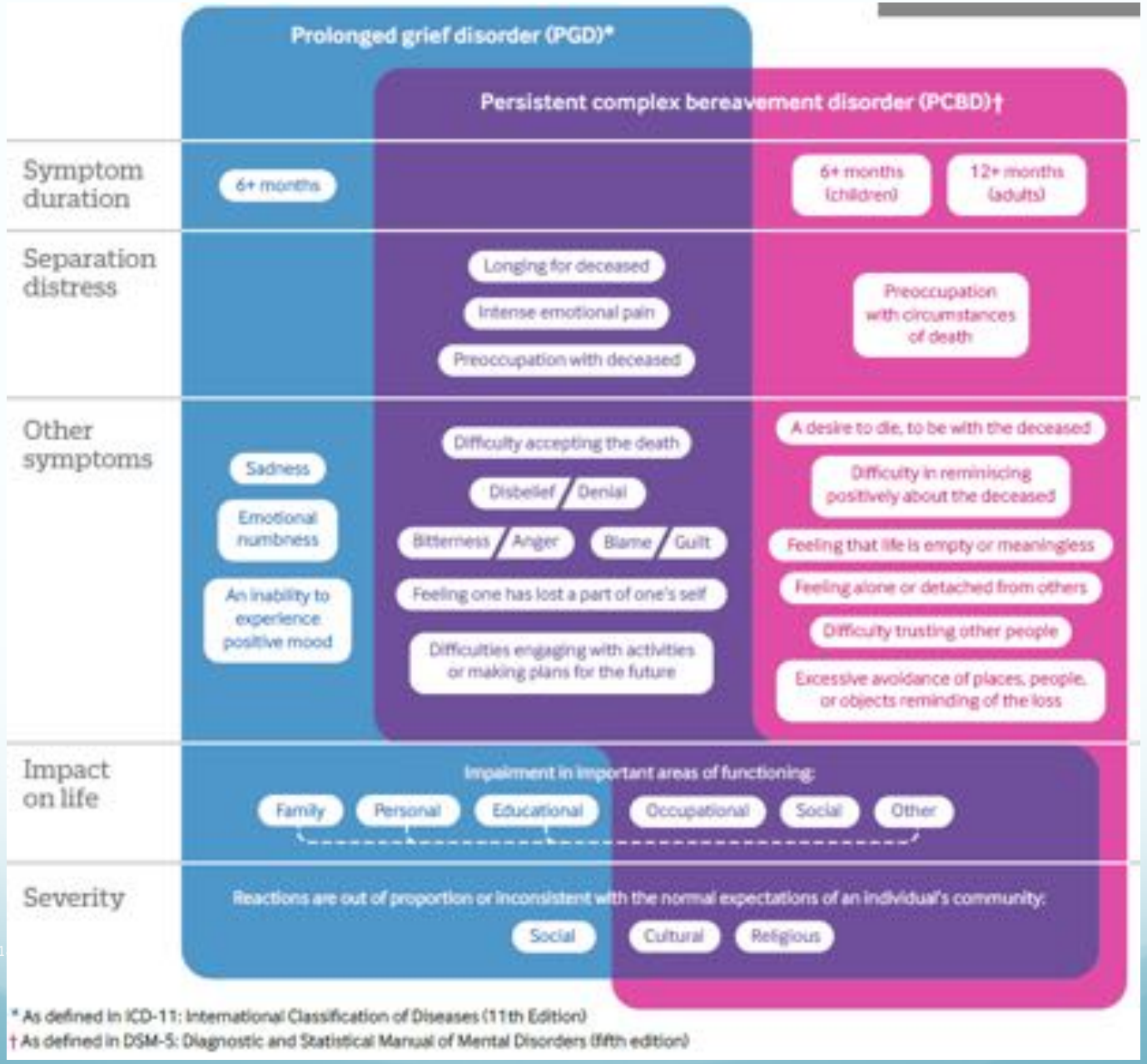


Fig. 1 Relationships between all grief, complicated grief and prolonged grief disorder in the Yale Bereavement Study (YBS) sample.

All grief, 100% of all bereaved individuals in the YBS sample; complicated grief identified using Cozza *et al* symptom threshold, 62% of all bereaved individuals in the YBS sample; prolonged grief disorder using Prigerson *et al* symptom threshold, 12% of all bereaved individuals in the YBS sample.

Maciejewski & Prigerson, *Br J Psychiatry*, 2017



Boelen & Smid, *BMJ* (2017)

Not the same, but often comorbid

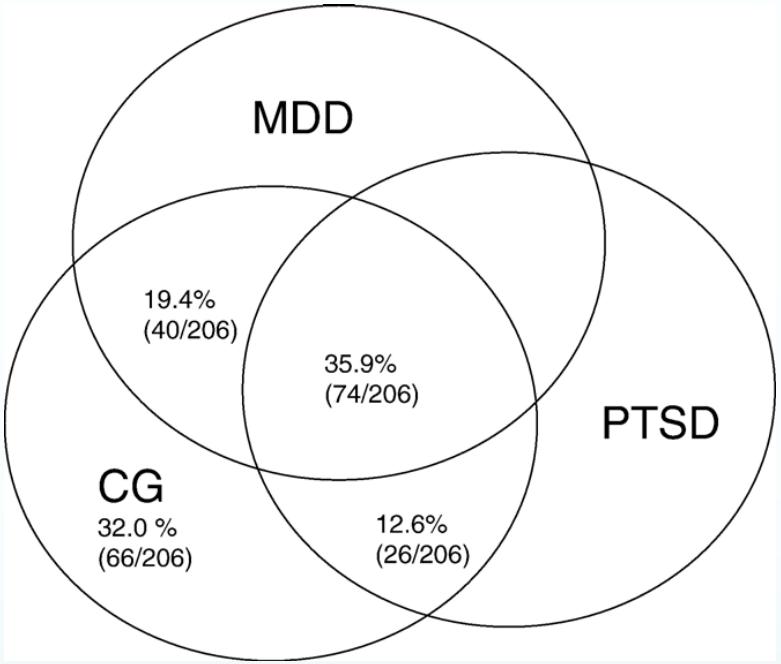
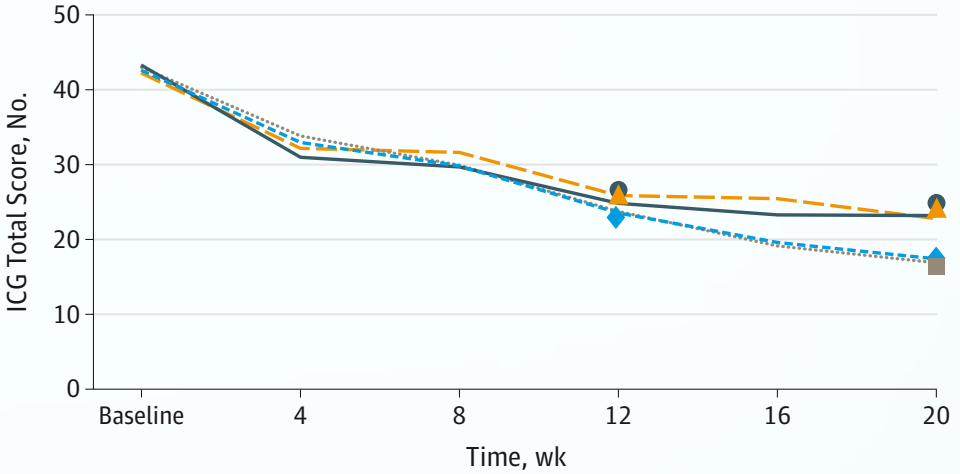


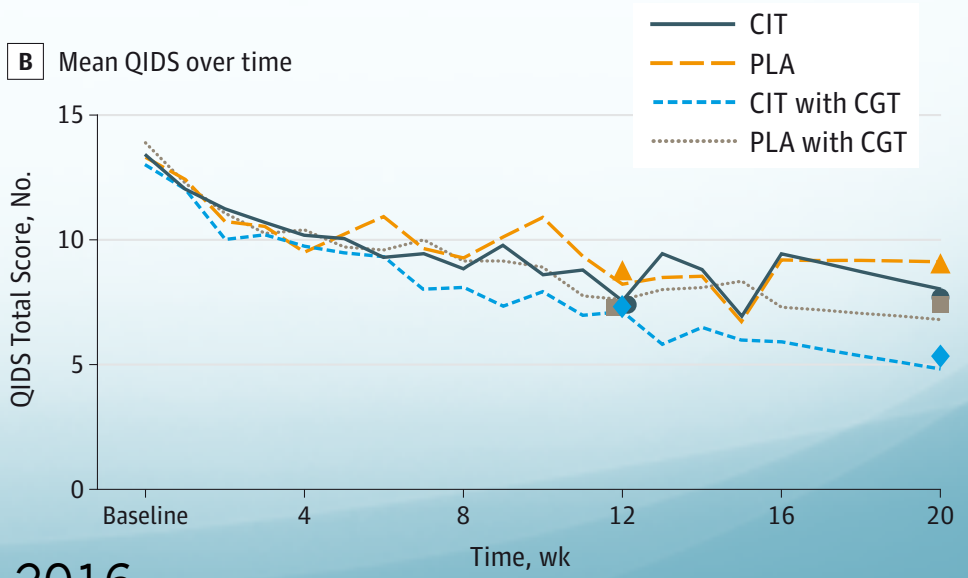
Fig. 1. Current PTSD and MDD comorbidity in treatment-seeking individuals with CG disorder (n = 206).

Simon,et al, *Comprehensive Psychiatry*, 2007

Anti-depressants don't help CG

- A) CG self-ratings
  - improvement in participants randomized to complicated grief treatment (CGT)
  - no specific benefit of citalopram (black line) relative to placebo (orange line)
- B) Depression self-ratings
  - improvement in depression when citalopram is co-administered with CGT (blue line)
  - little improvement in depression with citalopram but no CGT (black line)





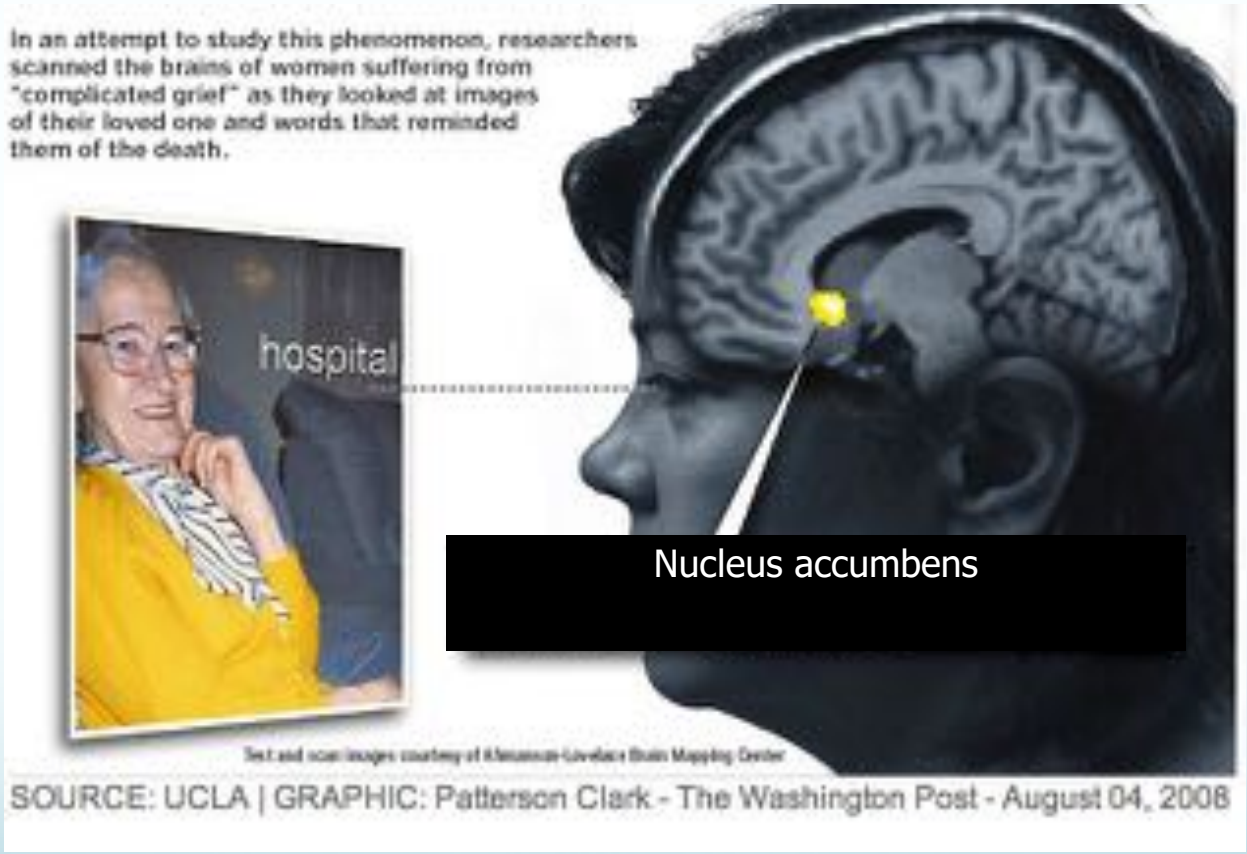
Shear et al, *JAMA Psychiatry,* 2016

What happens in the brain?

Neuroimaging and grief

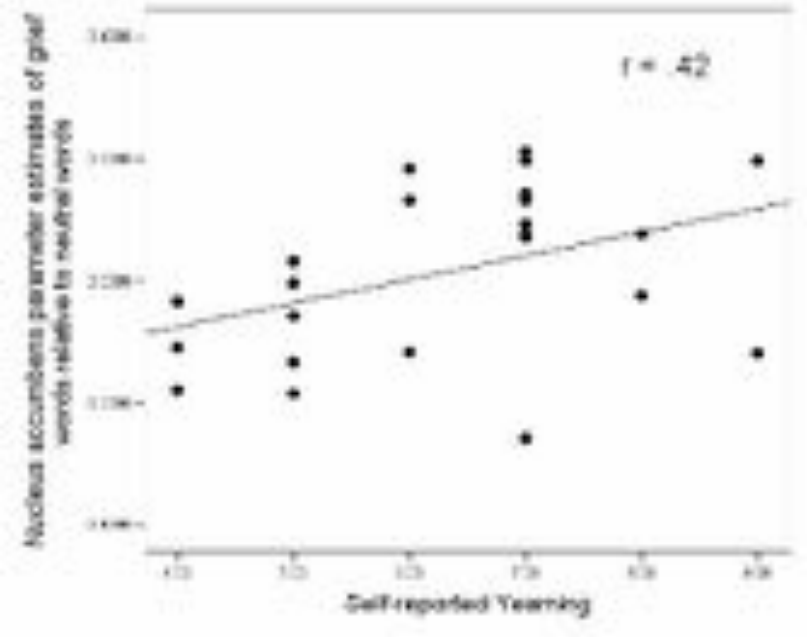
- 23 women
  - 11 Complicated Grief
  - 12 Non-Complicated Grief
- Average time since bereavement was 27 months
- The mean age of participants was 43.7 (SD = 10)
- No psychiatric or medical disorders, no anti-depressants
- Photos and narrative words as reminders of the deceased

Accumbens activation CG > Non-CG



O'Connor et al, *NeuroImage*, 2008

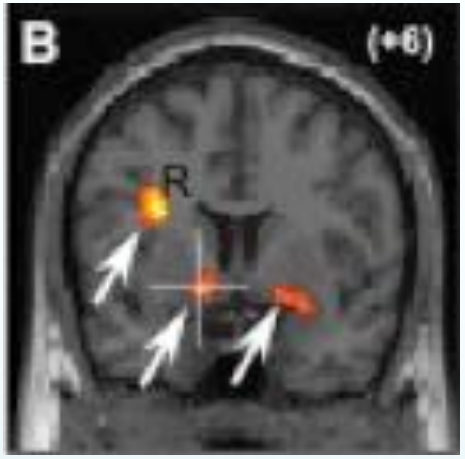
Accumbens with yearning



- In 23 participants, those with CG showed greater activation in nucleus accumbens compared to those with Non-CG.
- Nucleus accumbens activity was correlated with self-reported yearning.
  - not with time since death, positive or negative affect

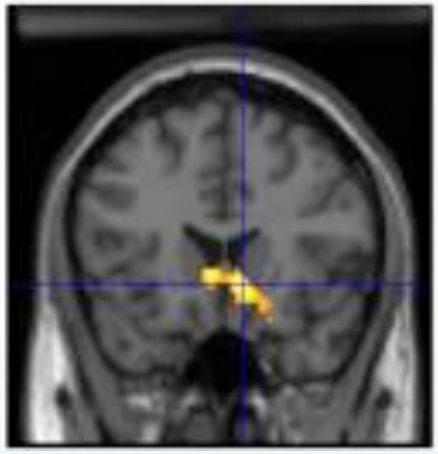
Continuing brain activation after relationship disruptions

- If the disruption remains unresolved



Romantic rejection

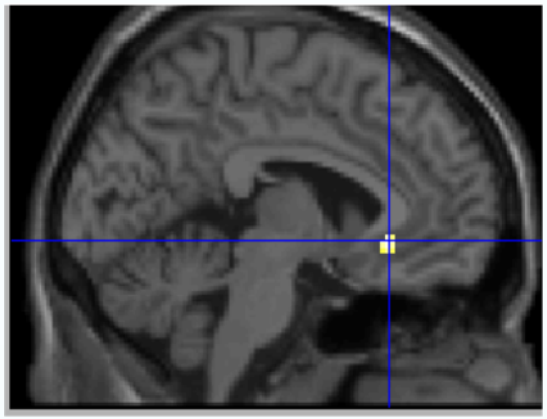
Fisher et al, 2010



Complicated Grief

O'Connor et al, 2008

Another fMRI study



sACC correlated with yearning ($Z = 3.11$, $p < .005$, cluster = 25). $N = 16$

- 25 older adults
  - 9 CG
  - 7 Non-CG
  - 9 Nonbereaved
- Average age was 71.4
- 84% female
- Average time since the death was 21.19 months
- Similar task, but not exactly

McConnell et al, *Heliyon*, 2018

Why no replication?

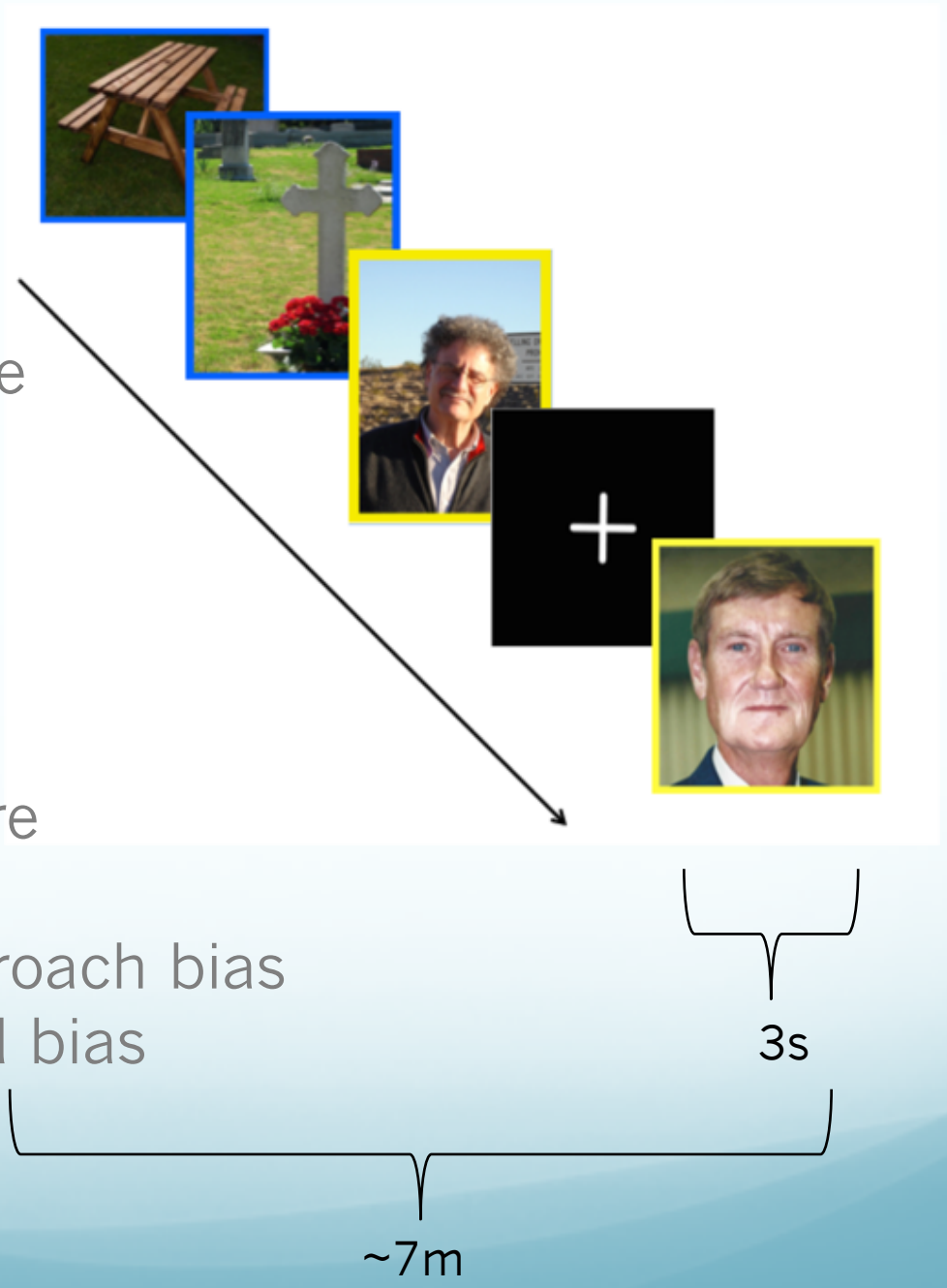
- Our sample was significantly older than in previous work.
- The intensity of absolute nucleus accumbens responsiveness may be lower in this age group.
- Recent studies in older animals have shown changes in nucleus accumbens functioning and behavior (Ruegsegger et al., 2017).

Oxytocin in complicated grief

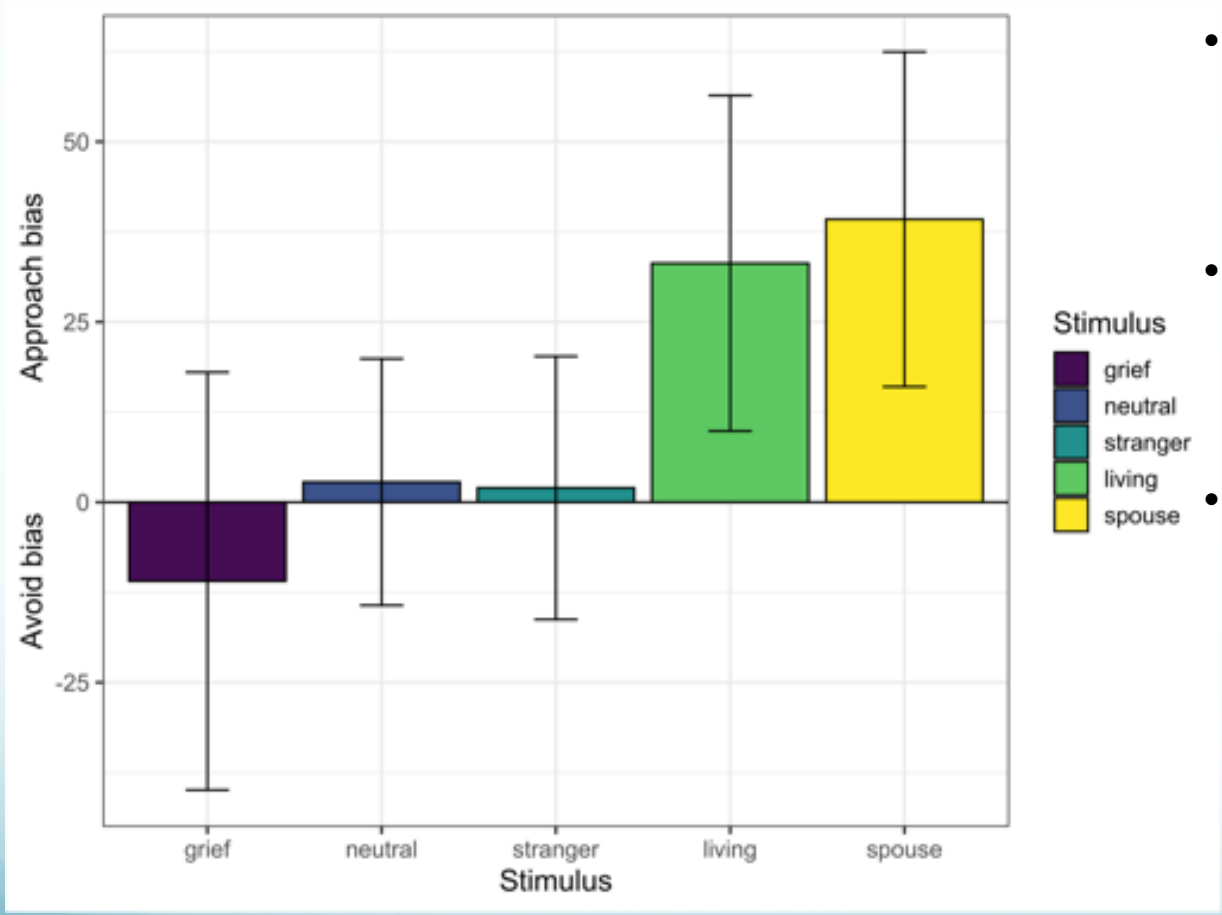
- Nucleus accumbens is rich in oxytocin receptors (Ross et al., 2009; Insel, 2010; Liu & Wang, 2003).
- Pair bonding and maternal bonding are dependent on oxytocin mechanisms (Insel & Young, 2001; Johnson & Young, 2015).
- Approach Avoidance Task
  - Counterbalanced, double-blind, within subject
  - Two visits, one week apart, with oxytocin or placebo administration

- 37 spousally bereaved older adults
- Stimuli
  - Deceased
  - Living loved one
  - Stranger
  - Grief (generic)
  - Neutral

- Calculated raw compatibility score
- Push–Pull
  - (+) score, approach bias
  - (-) score, avoid bias

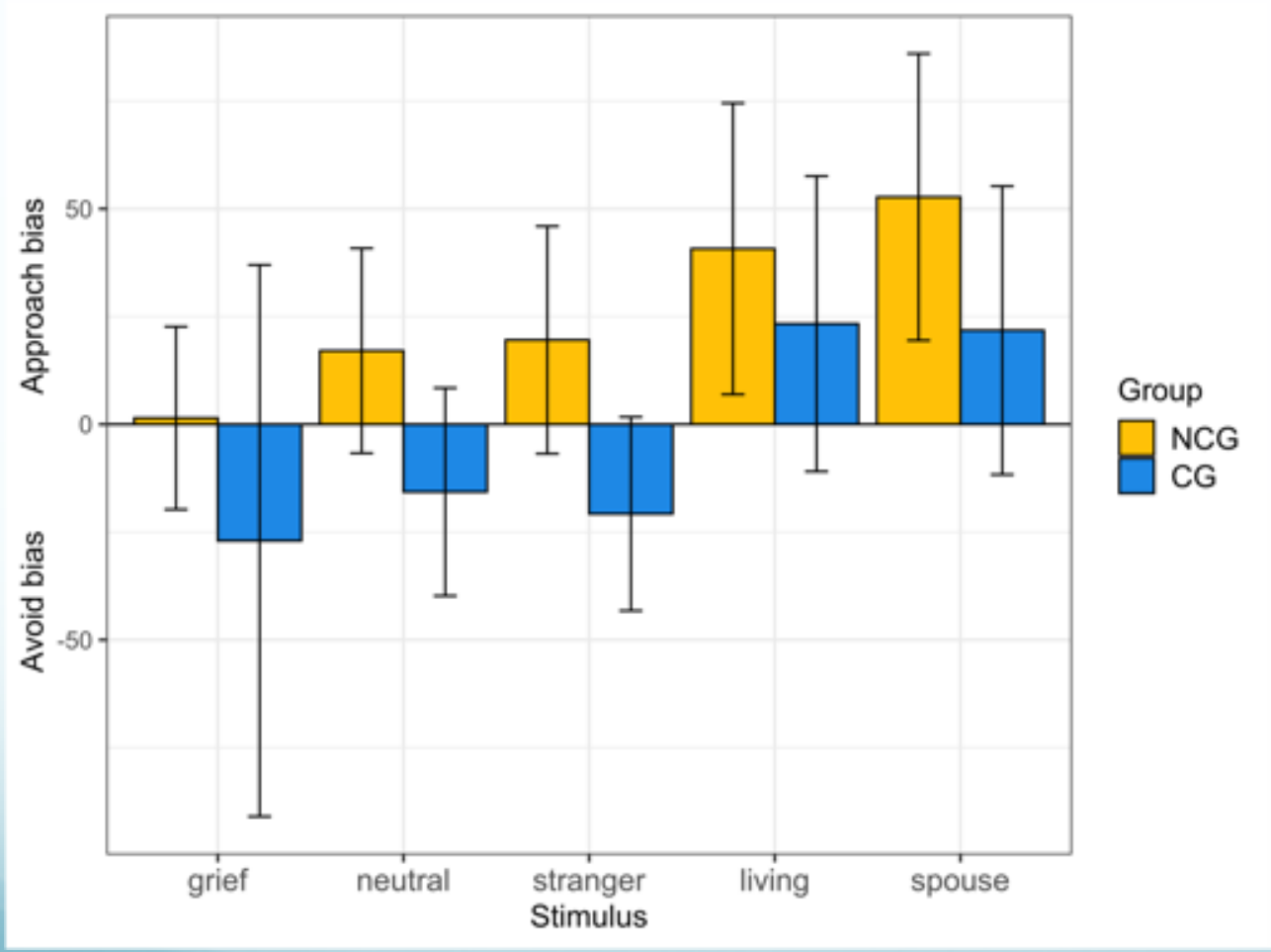


Across bereaved sample



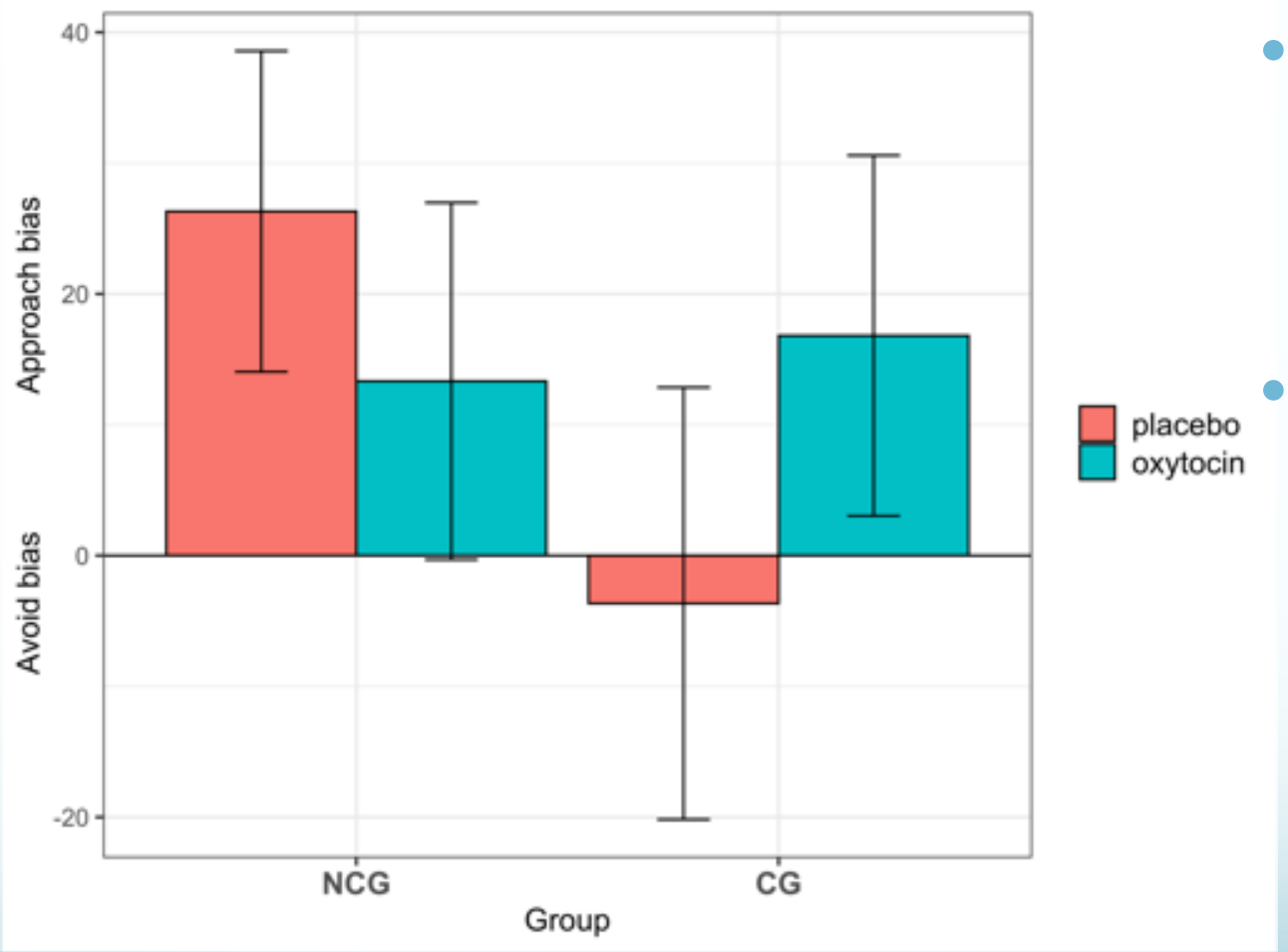
- Approach bias on spouse trials vs. stranger trials (p = .001).
- Bias did not significantly differ in generic grief trials vs. neutral trials
- The statistically significant difference between the two contrast estimates (estimate = 51.0, p = .02) means spouse vs. stranger produced larger differences than grief vs. neutral.

Non-CG shows approach bias



- AAT performance by stimulus category and group, in the placebo condition.
- Overall, the Non-CG group showed greater approach bias regardless of stimulus category (i.e., no group x stimulus interaction).

OT differential impact on CG



- In the placebo condition, across all stimuli, the CG group is significantly more avoidance-biased.
- The CG group becomes significantly more approach-biased under oxytocin
  - while the Non-CG group's behavior does not change significantly from the placebo condition.

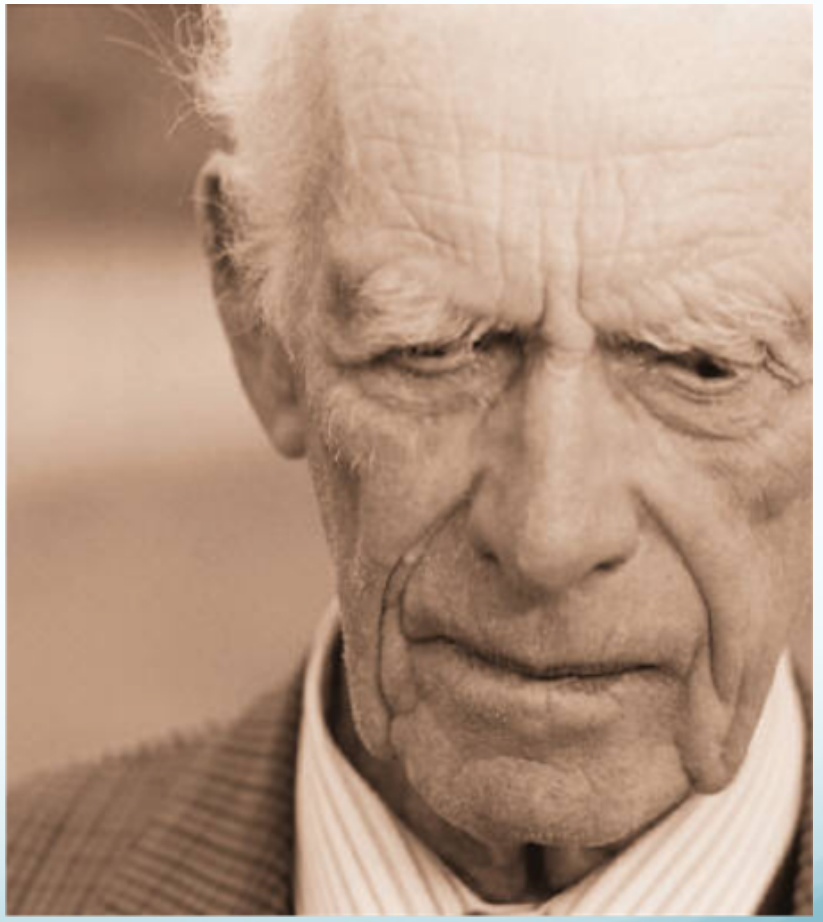
Arizmendi, Seely et al, *under review*

Implications of OT effect

- The oxytocinergic system of those with complicated grief was differentially affected, across types of stimuli.
- Concern that the social salience aspect of oxytocin administration may cause greater rumination about the deceased.
- One possibility is that the density or efficacy of oxytocin receptors is different in complicated grief.
- Variations in oxytocin receptors occur naturally across the population due to single nucleotide polymporphisms (SNPs).

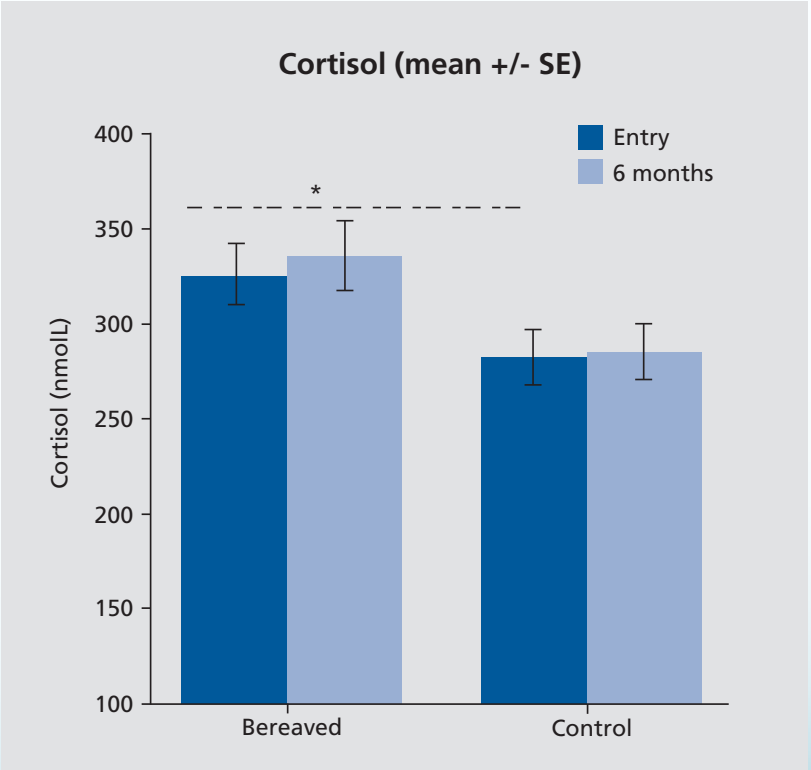
Human grief and cortisol

- Those with acute grief are experiencing one of life's most stressful events.
- Those with complicated grief have a prolonged stress.
- What do we know about cortisol and human bereavement?



Cortisol in human grief

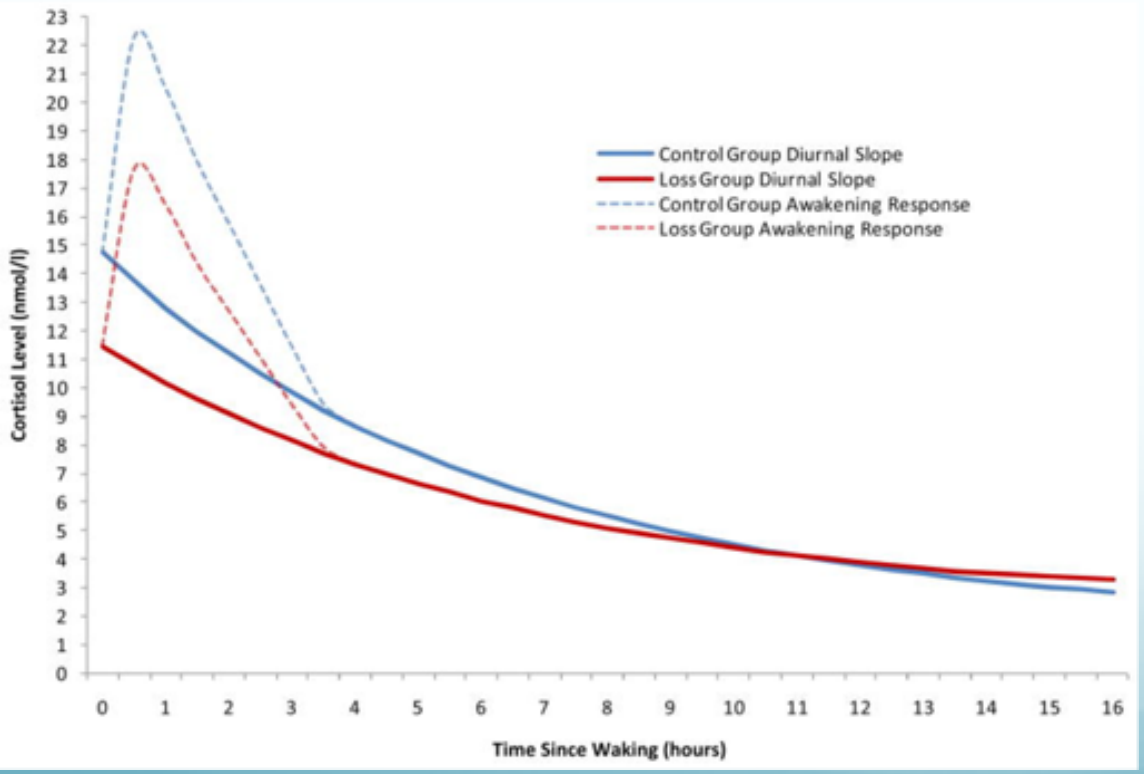
- Increased cortisol in the first 2 weeks after spousal death (Buckley et al, 2009).
- Widow(er)s with prolonged forewarning had higher cortisol levels at 6 months than those whose spouses died suddenly (Richardson, et al, 2013).



Buckley et al, 2009

Outcome Salivary Cortisol Measure 2 years After Loss	No Grief Reference Category *n* = 1922	Grief *n* = 131	Complicated Grief *n* = 31	Comparison Complicated Grief - No Grief		Comparison Complicated Grief - Grief	
	Estimated Mean	Estimated Mean	Estimated Mean	Difference With Reference (95% CI)	*p*	Difference With Reference (95% CI)	*p*
Morning cortisol, nmol/L	14.72	15.51	11.26	−3.46 (−6.78, −0.13)	.042	−4.25 (−7.87, −0.62)	.022
Area under the curve, nmol/L	8.31	8.98	6.89	−1.42 (−2.99, 0.16)	.078	−2.01 (−3.81, −0.37)	.017

Saavedra-Perez et al, *Psychosom Med*, 2017



- Lower morning cortisol in those with complicated grief, and in all bereaved compared to nonbereaved.

O'Connor et al, *PNEC,* 2012

Ong et al, *Health Psychol*, 2011

Cortisol in younger bereaved

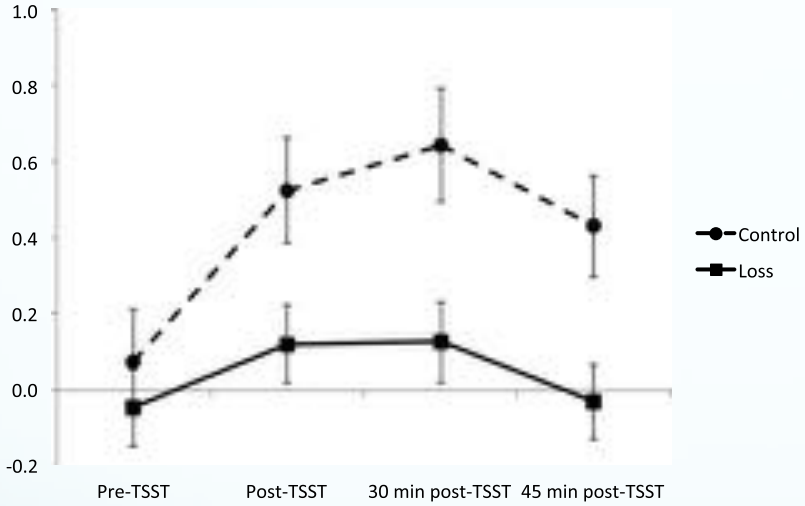
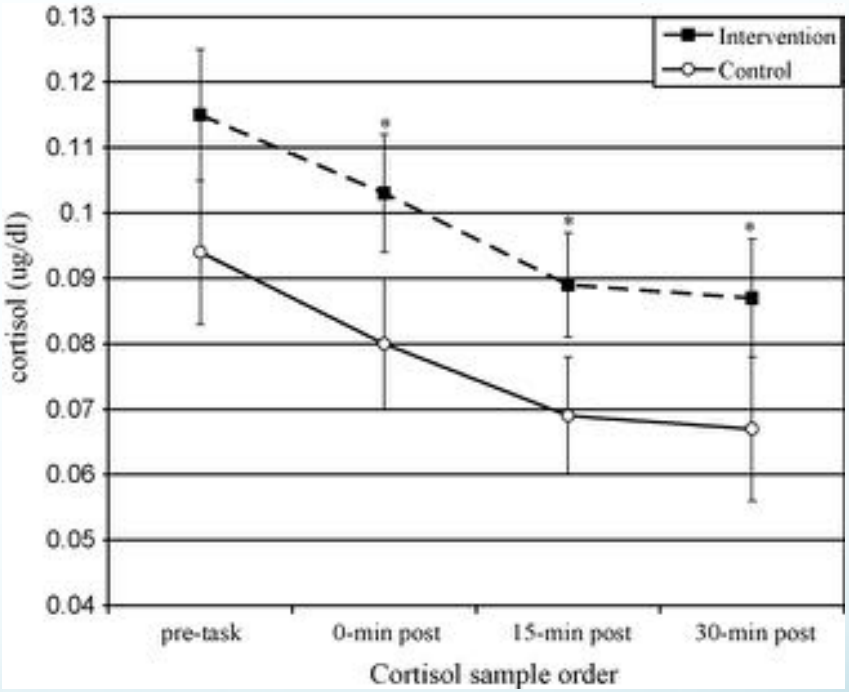


FIGURE 2. Cortisol: model-predicted quadratic trajectories of cortisol (not raw values) over the four time points for the control and loss groups. The quadratic slope of the Loss group is significantly flatter than the control group. TSST = Trier Social Stress Test.



Fallon, et al, 2016

Luecken, et al, 2010

Overlapping reviews help!

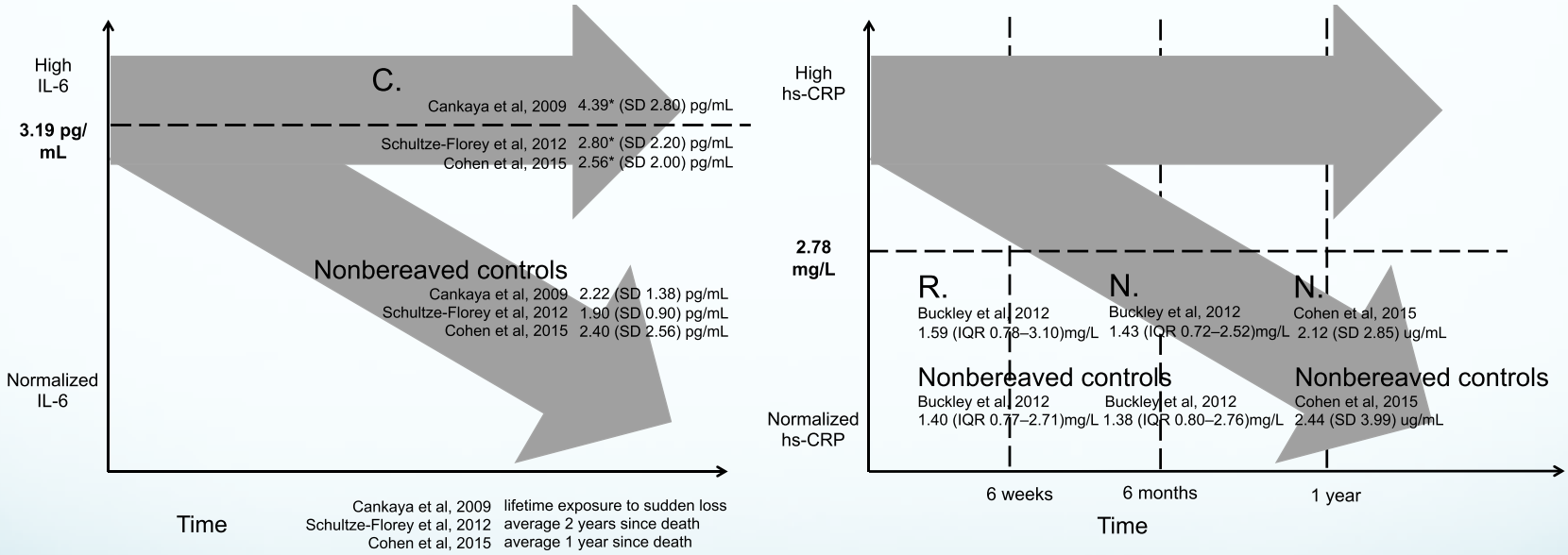


FIGURE 2. Model with IL-6 and CRP results after bereavement. C = Chronic immune dysregulation, R = Resilient to immune changes, N = Normalized immune function. The vertical transition lines refer to various time points postloss. The horizontal clinical cutoff line refers to the level at which immune parameters affect pathophysiology of disease. Asterisks refer to statistically significant group comparisons.

Summary

- Grief is painful (from death and/or separation), and may cause physiological dysregulation.
- Humans may be able to believe that their loved one is just far away (but still alive) AND also that they are dead, slowing the learning and adaptation process.
- Yearning may get in the way of learning, and prevent enjoyment of rewards and opportunities for attachment in the present moment.

Thank you

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