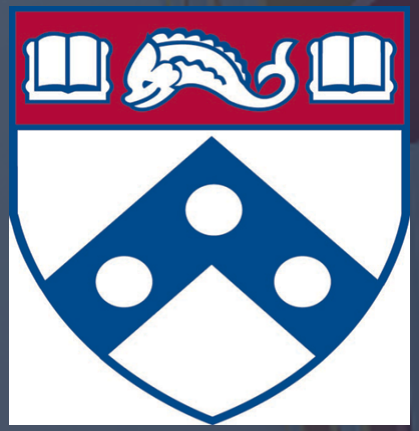
The Neurobiology of Suicide Vulnerability



María A. Oquendo, MD, PhD

Ruth Meltzer Professor and Chairman of Psychiatry

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American Psychiatric Association, Past President

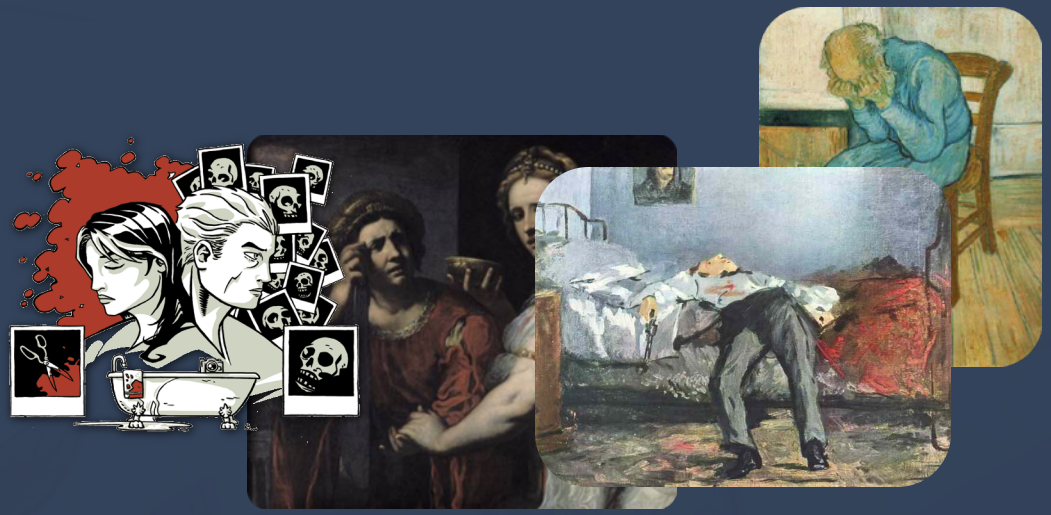
American College of Neuropsychopharmacology, President

DISCLOSURES LAST 36 MONTHS

Dr. Oquendo receives royalties for the commercial use of the Columbia Suicide Severity Rating Scale and owns equity in Mantra, Inc. Her family owns stock in Bristol Myers Squibb.

DEFINITION OF SUICIDAL BEHAVIOR

what is suicidal behavior?



Suicide

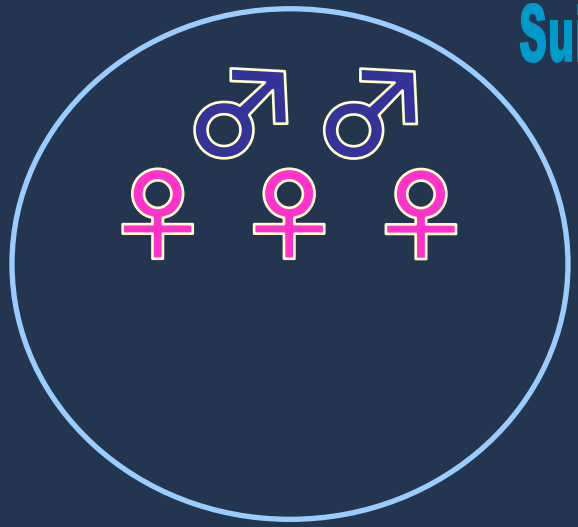
Suicidal attempts

Suicidal ideation

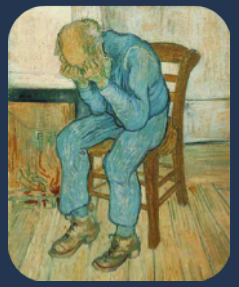
Relationship to non-suicidal self-injury

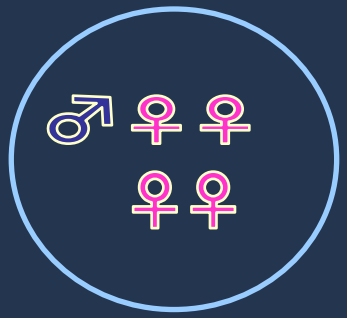
Maria A. Oquendo

EPIDEMIOLOGY OF SUICIDE RELATED CLINICAL PHENOMENA



Suicidal ideation 5-15%



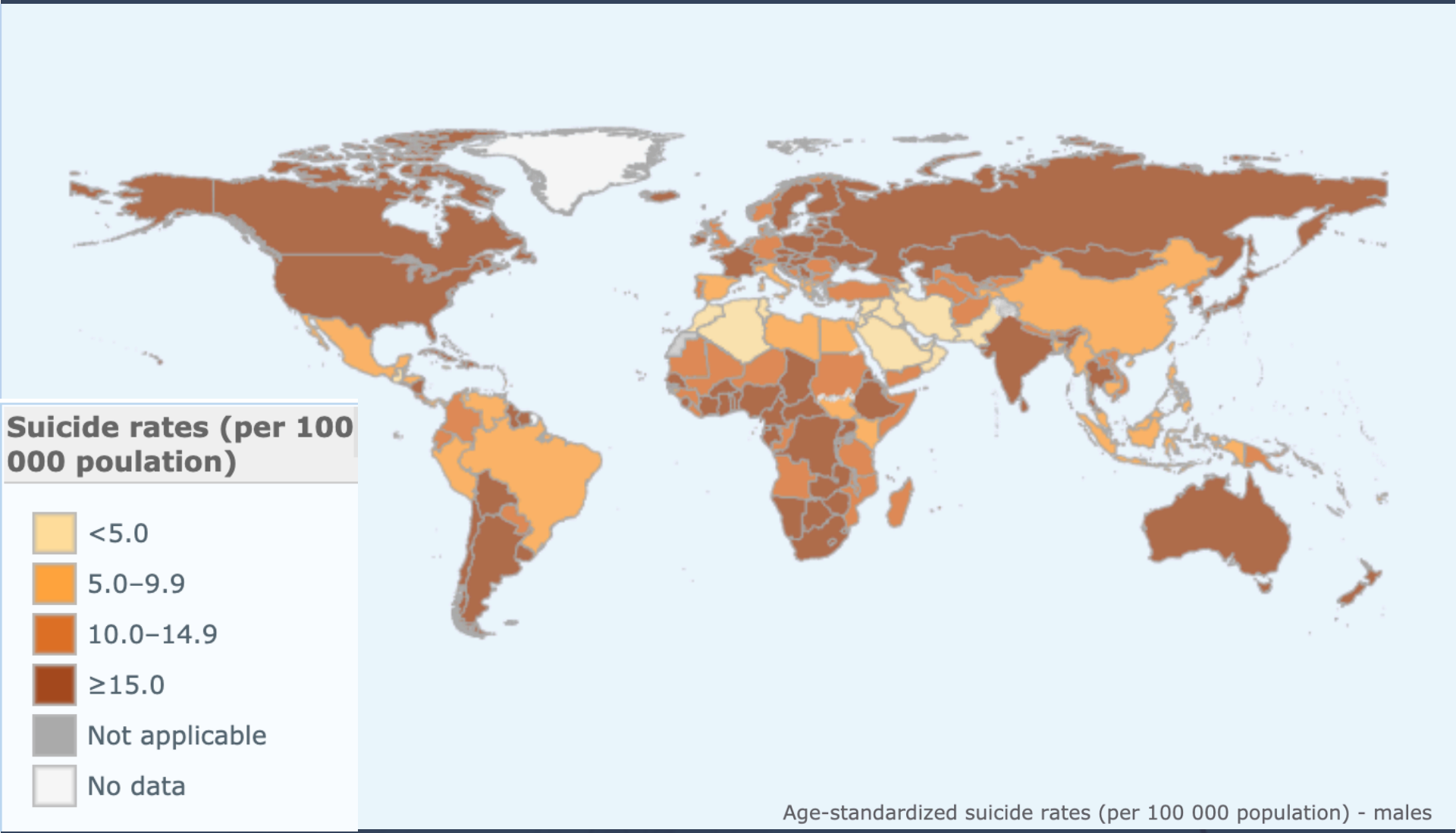


Suicide 6-90/100.000

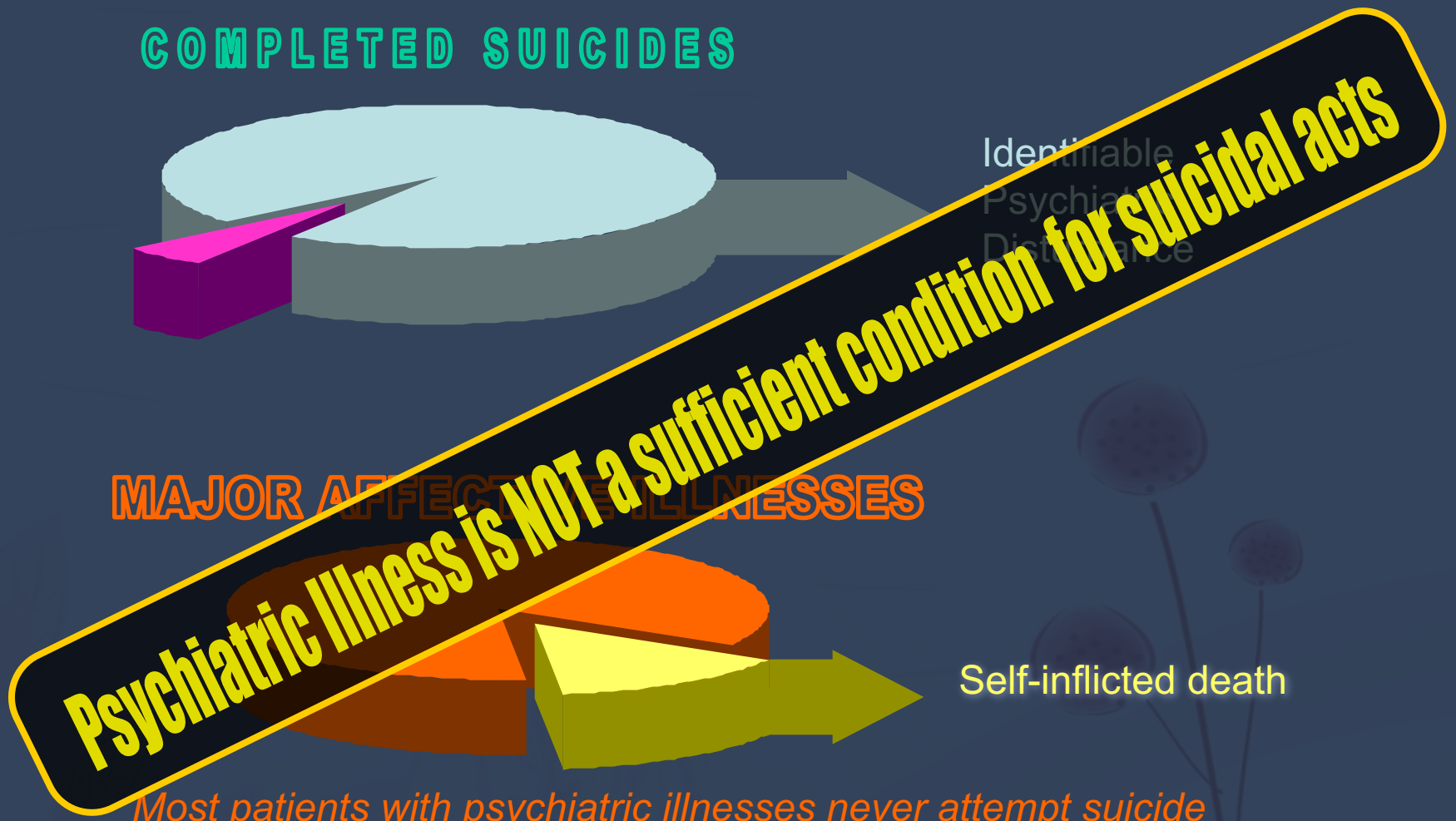
Suicide Attempts

SUICIDE RATES ACROSS THE WORLD (2016)

~800K DEATHS/YR; ~ $1.8 B in lost income; 3rd leading cause of death in youth



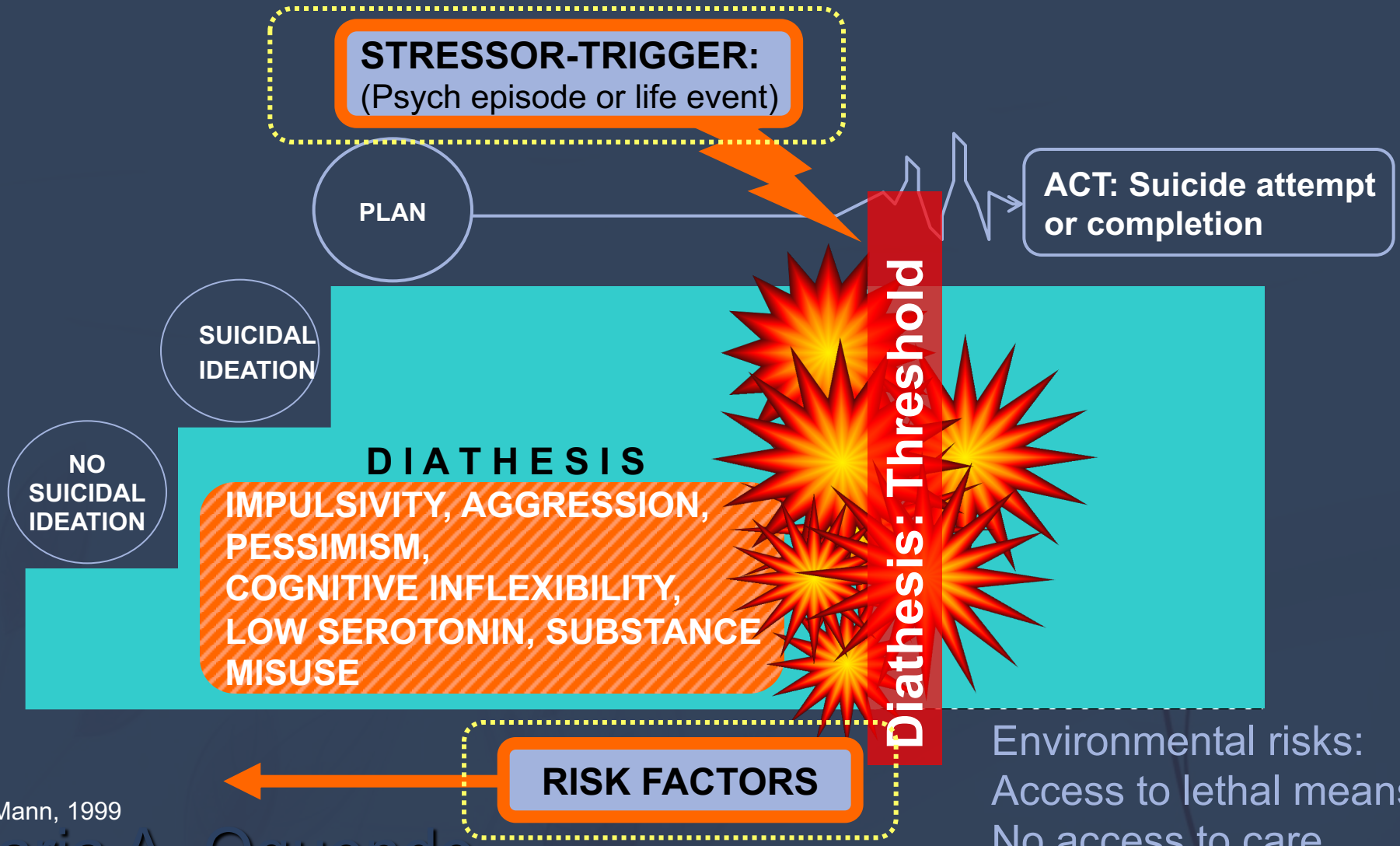
A MODEL FOR UNDERSTANDING SUICIDAL BEHAVIOR



A MODEL FOR UNDERSTANDING SUICIDAL BEHAVIOR

THE STRESS-DIATHESIS MODEL- 1999

Based on cross-sectional data



Mann, 1999

Prospective Study of Clinical Predictors of Suicidal Acts After Major Depression- 2004

SAME SAMPLE USED TO DEVELOP CROSS SECTIONAL MODEL

- 308 depressed patients
- Extensive clinical & biological measures
- Evaluations at 3, 12 and 24 months after enrollment
- Cox Proportional Hazards Regression Analysis

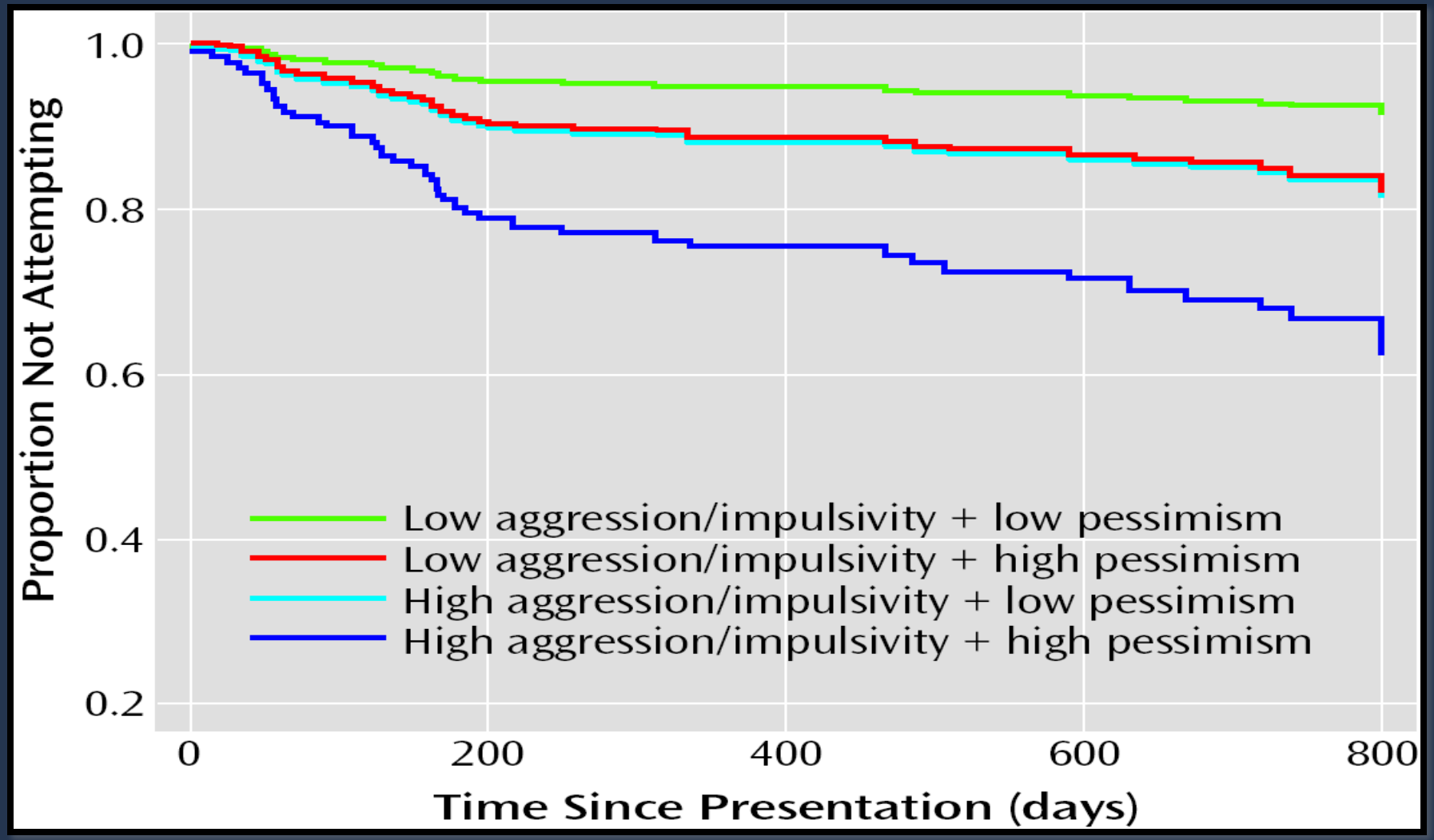
Oquendo, 2004

Prospective Study of Clinical Predictors of Suicidal Acts After Major Depression- 2004

- Four suicides and 38 attempted suicides (14%).
- Most in Yr 1, rate dropped dramatically after 3–6 months.
- Rate in Yr 2 remained elevated but steady.

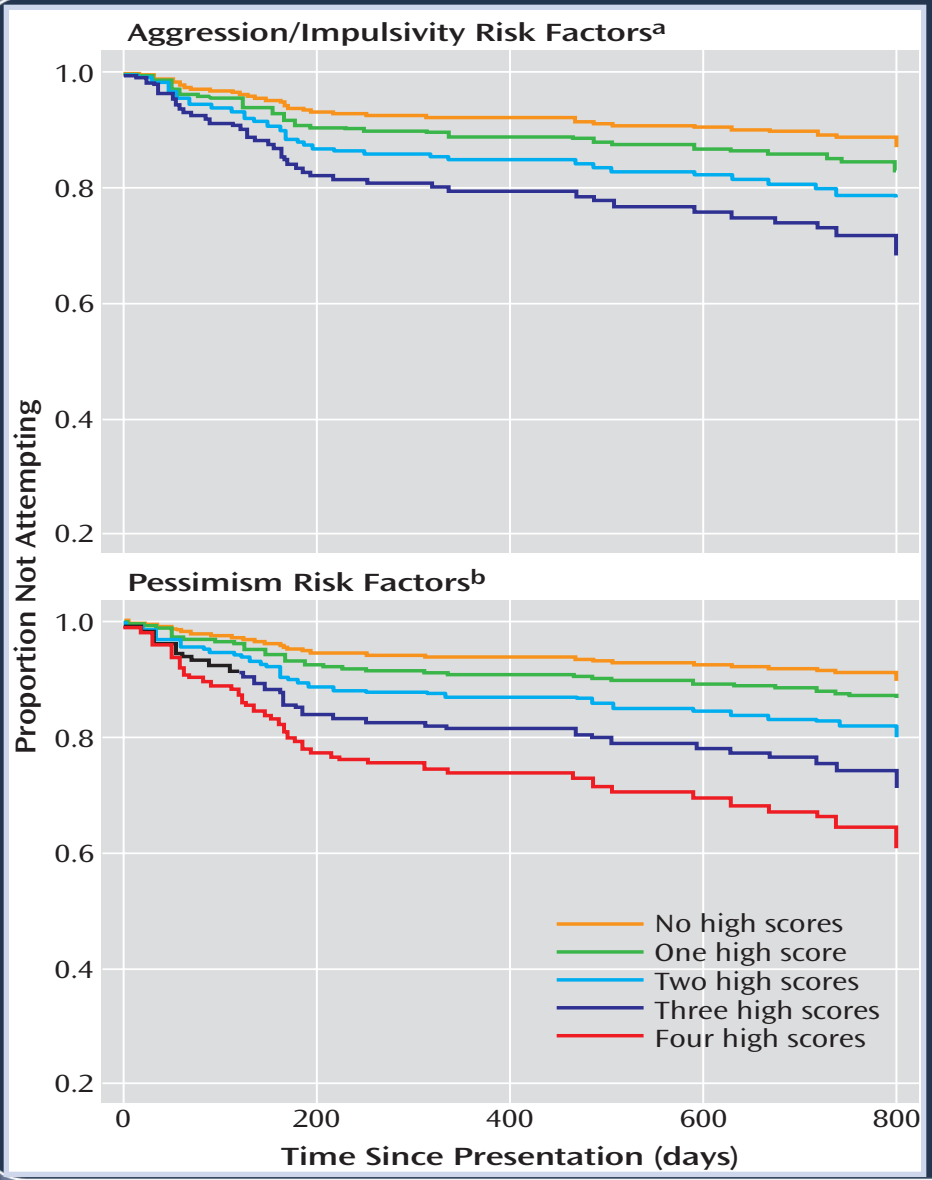
Oquendo, 2004

Prospective Study of Clinical Predictors of Suicidal Acts After Major Depression- 2004



Oquendo, 2004

Prospective Study of Clinical Predictors of Suicidal Acts After Major Depression- 2004



Aggression/ Impulsivity

Brown Goodwin
Barratt Impulsivity
Buss Durkee Hostility

Pessimism Factor

Beck Depression Scale
Beck Hopelessness Scale
Reasons for Living Scale
Scale for Suicidal Ideation

Oquendo, 2004

LIFE EVENTS: a complex role in the timing of suicidal behavior-2013

BASED ON SAMPLE USED FOR CROSS SECTIONAL MODEL AND ENRICHED SINCE LAST PROSPECTIVE STUDY

- 415 MDD patients
- 3, 12 and 24 month follow-up
- Naturalistic treatment
- Longitudinal data in 1-month intervals of MDE (y/n), suicidal behavior (y/n) and life event scores.
- Marginal logistic regression models

LIFE EVENTS: a complex role in the timing of suicidal behavior

Table 1. Baseline descriptive statistics ($n = 415$)

Variables	n	*Percent*
% Female	240/415	57.8%
Childhood abuse (%)	177/384	46.1%
Currently employed (%)	148/415	35.7%
Childhood separation under 15 (%)	145/411	35.3%
Comorbid past substance abuse (%)	171/415	41.2%
Cigarette smoking (%)	141/413	34.1%
Borderline personality disorder	113/414	27.3%
MDD versus bipolar disorder	294/415	70.8%
		Mean ± s.d.
Age (year)	415	38.1 ± 11.8
Number of MDE	395	12.0 ± 24.6
Hamilton Depression Rating Scale	414	19.7 ± 5.7
St Paul Ramsey Questionnaire	405	1.9 ± 0.76
Aggression/impulsivity		
Brown–Goodwin History of Aggression	404	18.8 ± 5.6
Buss–Durkee Hostility Inventory	367	36.0 ± 11.9
Barratt Impulsivity Scale	357	52.8 ± 16.5
Depressive and suicidal cognitions		
Beck Depression Inventory	413	27.1 ± 11.2
Hopelessness Scale	410	12.0 ± 5.8
Scale for Suicidal Ideation	379	12.2 ± 10.4
Reasons for Living Scale	372	155.0 ± 45.3

Oquendo, 2013

LIFE EVENTS: a complex role in the timing of suicidal behavior

Among 7843 person–months:
33% had MDE
73% had life events.

MDE increased risk for suicidal behavior (OR = 4.83, P<0.0001).

Life event scores were unrelated to the timing of suicidal behavior (OR = 1.06 per 100 point increase, p =0.32)

even during MDE (OR = 1.12, p = 0.15)
[no interaction between MDE and life events].

LIFE EVENTS: a complex role in the timing of suicidal behavior

Table 3. Frequency of life events assessed with the recent life changes questionnaire, major depressive episode and suicide or suicide attempt during 2-year follow-up period ($n = 415$ subjects, $n = 7843$ person–months)

	% Subjects with life event during 2-year follow-up		% Person–months with life events			
Life events	*No BPD*	*BPD*	*No BPD*	*BPD*	*T[a] (df = 411)*	*P-value*
Health	75	84	29	37	2.65	**0.0084**
Work-related	64	70	24	29	1.94	0.0527
Home and family	73	84	29	34	1.88	0.0608
Personal/social	85	84	39	48	2.59	**0.0098**
Financial	66	62	25	22	−1.10	0.2723
Any kind of event	97	100	68	75	2.69	**0.0075**
MDE	69	74	30	33	1.23	0.2201
Suicidal behavior	7	18	0.6	1.8	4.52	**<0.0001**

Abbreviations: BPD, borderline personality disorder; MDE, major depressive episode.
[a]Comparisons by BPD diagnosis were tested with marginal logistic regression models.
Values in bold are statistically significant.

Oquendo, 2013

LIFE EVENTS: a complex role in the timing of suicidal behavior

Table 4. Predictors of suicides and suicide attempts during a 2-year follow-up period

	Current month predictors[a]				*Prior month predictors*[a]			
Predictor variables	*OR*	*95% Confidence interval*		*P-value*	*OR*	*95% Confidence interval*		*P-value*
Depressed patients, no BPD								
MDE	13.19[a]	4.52	38.51	**0.0001**	9.39[a]	3.60	24.52	**0.0001**
RLCQ[b]	1.33[a]	1.03	1.72	**0.026**	1.21[a]	1.06	1.38	**0.005**
Aggression/hostility 1	1.15	0.77	1.74	0.493	1.31	0.88	1.96	0.182
Aggression/hostility 2	0.93	0.64	1.35	0.711	0.97	0.68	1.40	0.889
Depressive cognitions	1.20	0.80	1.78	0.380	1.23	0.82	1.84	0.315
Suicide cognitions	1.90	1.20	3.02	**0.006**	1.84	1.17	2.91	**0.009**
Age	0.99	0.95	1.02	0.505	0.98	0.95	1.02	0.394
Female	3.00	1.22	7.69	**0.0178**	2.86	1.18	7.14	**0.0211**
Number of months[c]	1.01	0.96	1.06	0.720	1.01	0.96	1.06	0.694
Depressed patients with BPD								
MDE	3.03[a]	1.46	6.30	**0.004**	1.04[a]	0.49	2.22	0.916
RLCQ total[b]	0.76[a]	0.55	1.06	0.109	0.66[a]	0.46	0.97	**0.035**
Aggression/hostility 1	0.95	0.64	1.42	0.808	0.99	0.68	1.46	0.977
Aggression/hostility 2	1.08	0.74	1.58	0.682	1.10	0.76	1.60	0.606
Depressive cognitions	1.16	0.75	1.80	0.515	1.16	0.74	1.82	0.525
Suicide cognitions	1.06	0.70	1.60	0.793	1.16	0.76	1.76	0.480
Age	0.99	0.95	1.03	0.482	1.00	0.96	1.04	0.859
Female	1.02	0.38	2.70	0.9759	1.18	0.44	3.23	0.747
Number of months[c]	1.00	0.98	1.05	0.933	1.00	0.95	1.05	0.968

Maria A. Oquendo

Oquendo, 2013

LIFE EVENTS: a complex role in the timing of suicidal behavior

Among those without BPD, both health- and work-related life events were key precipitants, as was recurrent MDE, with a 13-fold effect.

The relationship of life events to suicidal behavior among those with BPD was more complex—were we capturing the events with our methods?

Of note, suicidal behavior was not more frequent when life events occurred during MDE recurrence

suggesting there are at least 2 independent paths to suicidal behavior…

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

Suicidal behavior has long been known to not be homogeneous

Jumping gunshot wounds — **VIOLENT** **VS.** **NON-VIOLENT** — overdoses with legal or illegal substances

High — **LETHALITY OR MEDICAL CONSEQUENCES** *medical hospitalization beyond ED visit* — Low

Planning — **PLANNED** **VS.** **NON-PLANNED** — impulsiveness

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

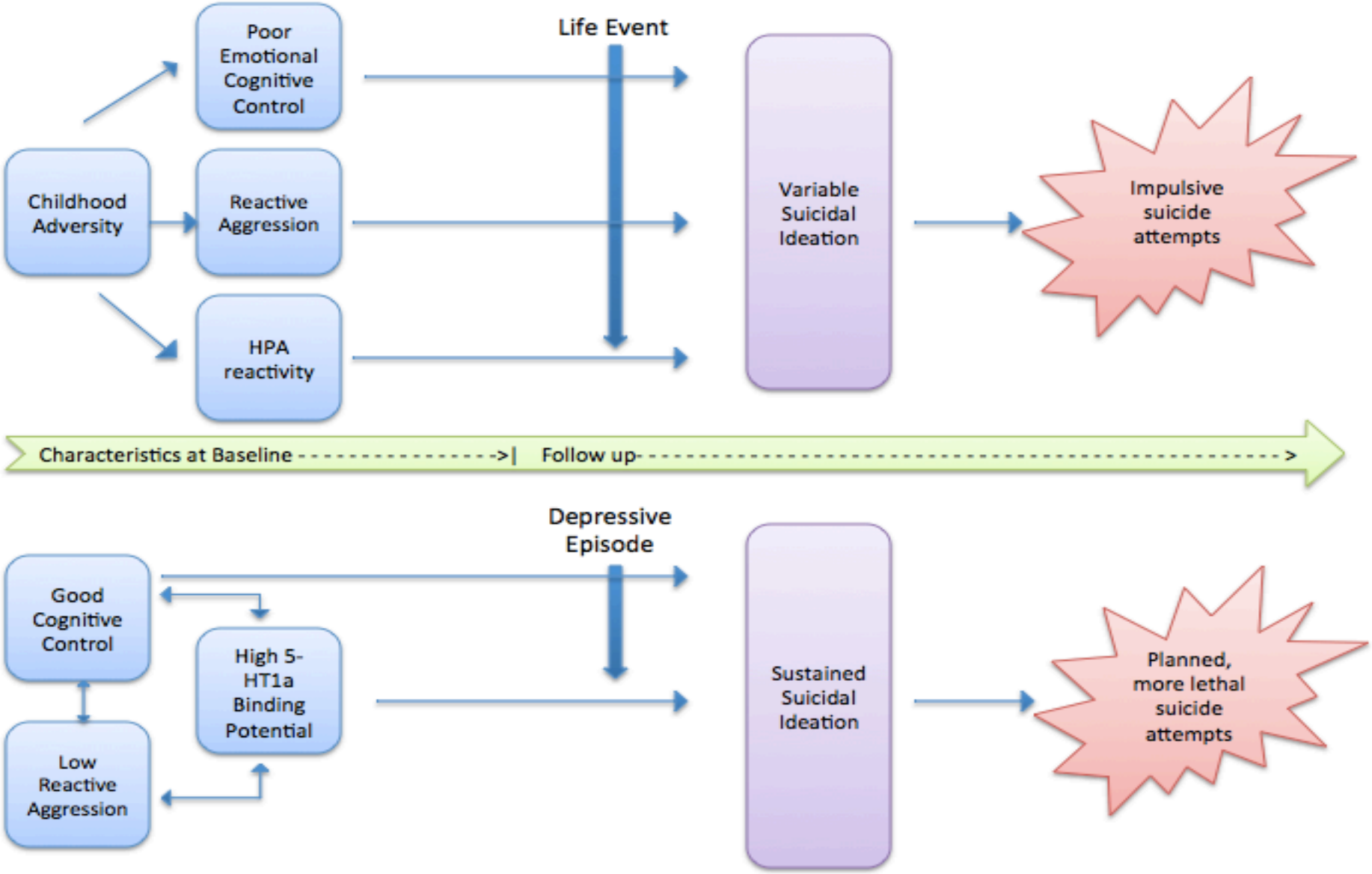


Figure 1. Explanatory Model for Two Subtypes of Suicidal Behavior

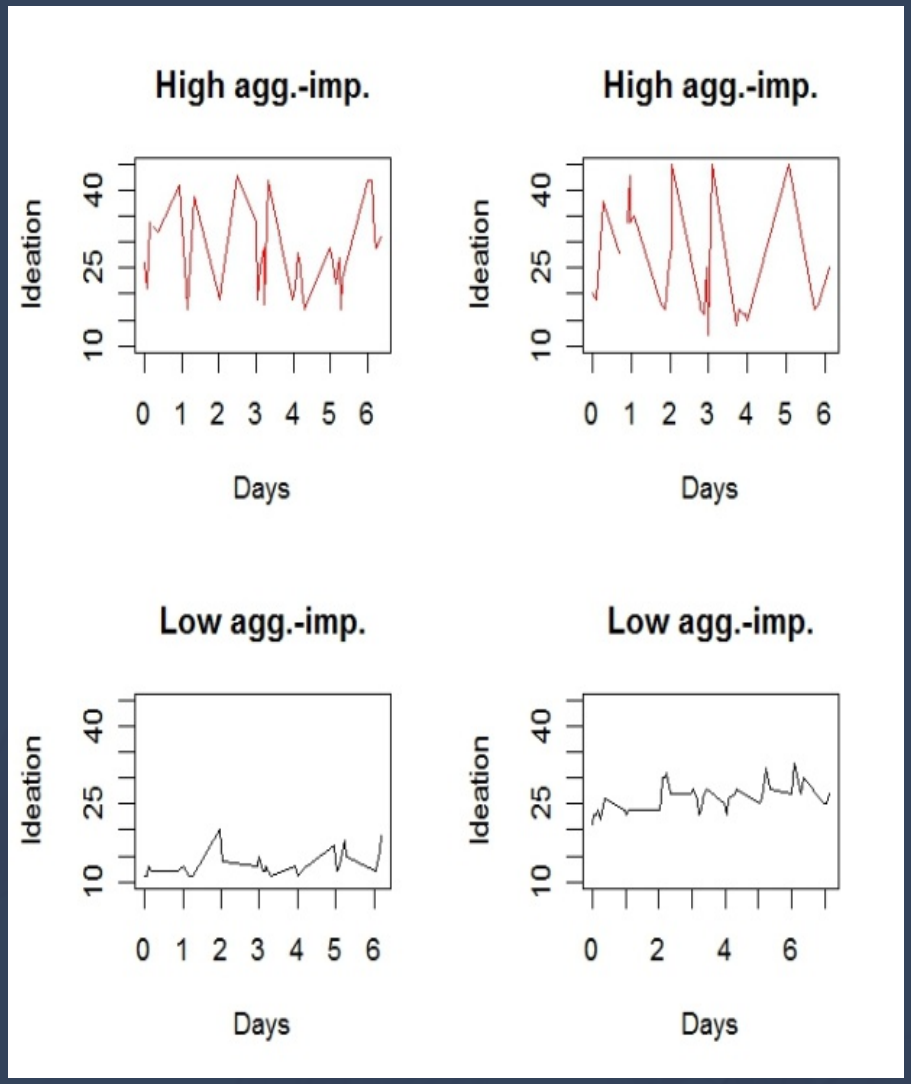
Bernanke JA, Stanley BH, Oquendo MA. 2017 Toward fine-grained phenotyping of suicidal behavior: the role of suicidal subtypes.

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

In two independent cohorts,
childhood trauma → more aggressive BGHA
Mood Disorder: 21.4 vs. 19.1, p<.001;
Borderline Personality + Mood Disorder: 21.3 vs 18.7 p=0.04).

In the latter sample, those with **childhood trauma** have greater SI variability (0.24 vs. 0.19 on SI variability coefficient, p=0.04) and react to events such as disagreements (p=0.006) or rejections by others (p=0.02) with higher SI increases.
(B. Stanley data)

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES



Subjects with high aggression and impulsivity scores (BGAH≥20, BIS≥ 55) had higher SI variability (mean=27% vs. 21%, p=0.05).

EMA analyses showed all 9 life events (e.g. had a disappointment) had effects on SI ($p<0.0001$ for 8/9 life event types).

(B. Stanley data)

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

BPD attempters may be less able to harness neural pathways to manage negative, distressing affect.
(B. Stanley data)

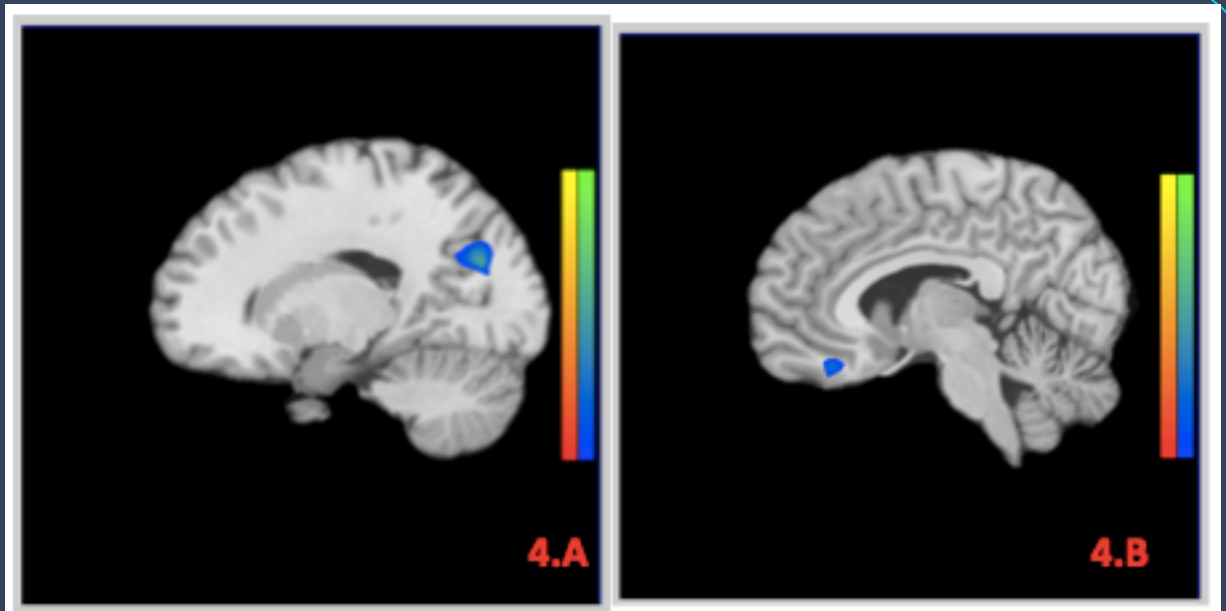
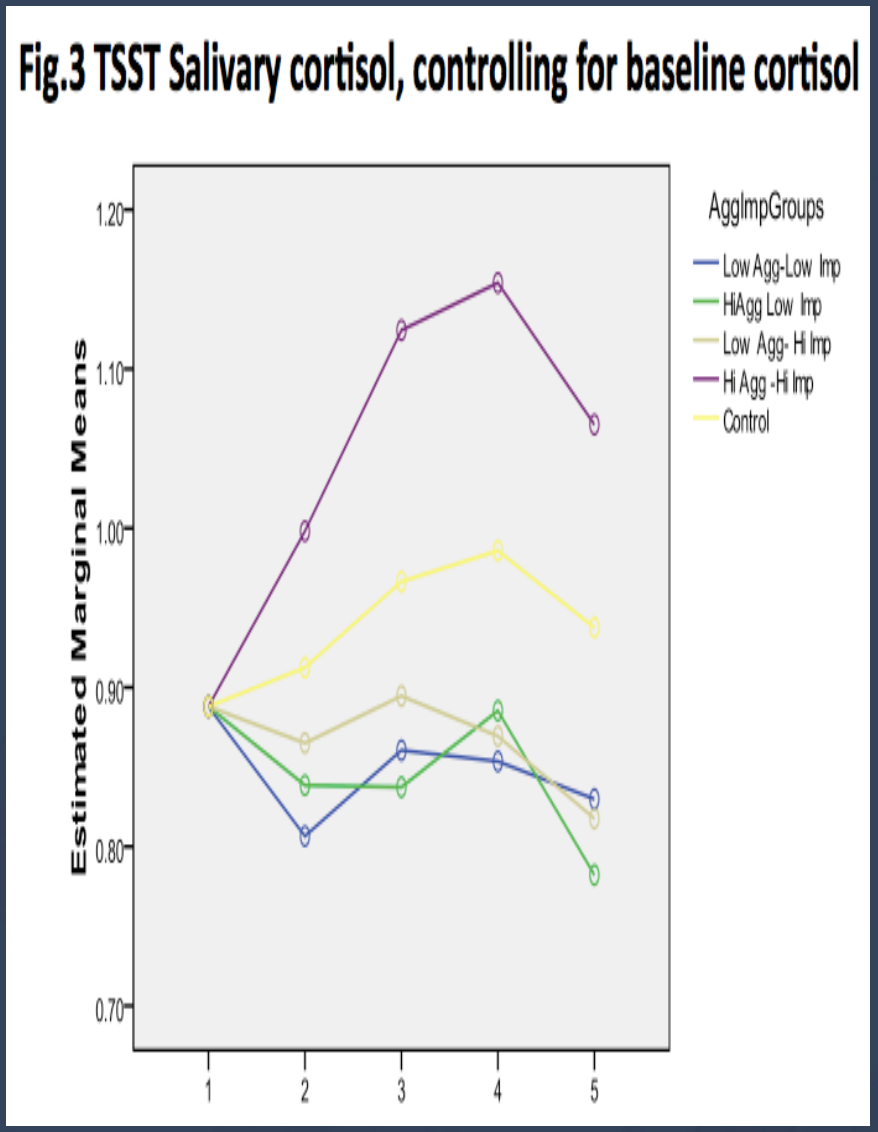


Fig. 4. Blood oxygen-level dependent (BOLD) fMRI in high RA subjects during cognitive emotion regulation. Instructed to emotionally distance themselves from distressing memories, attempters compared to nonattempters show lower activation in A) precuneus and B) oPFC .

Attempters (n=46) and non-attempters (n=14) recalled aversive personal memories. in the MRI. Then instructed to immerse or distance from the memory.

When distancing, NA showed more recruitment of precuneus (self awareness, perspective taking) and oPFC (integrating information about potential rewards and punishments to select appropriate and inhibit inappropriate affective responses;)

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

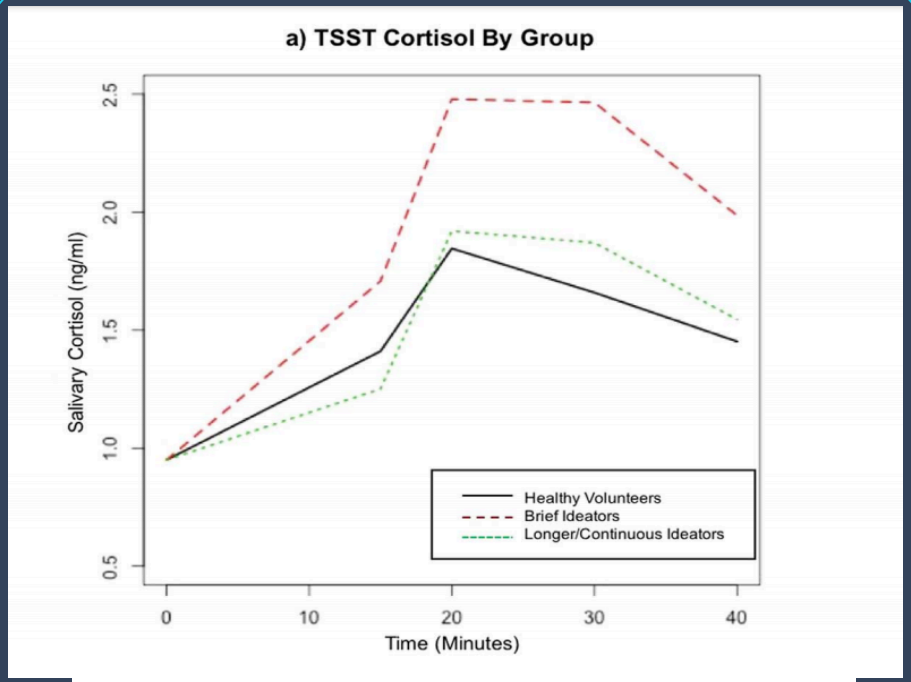


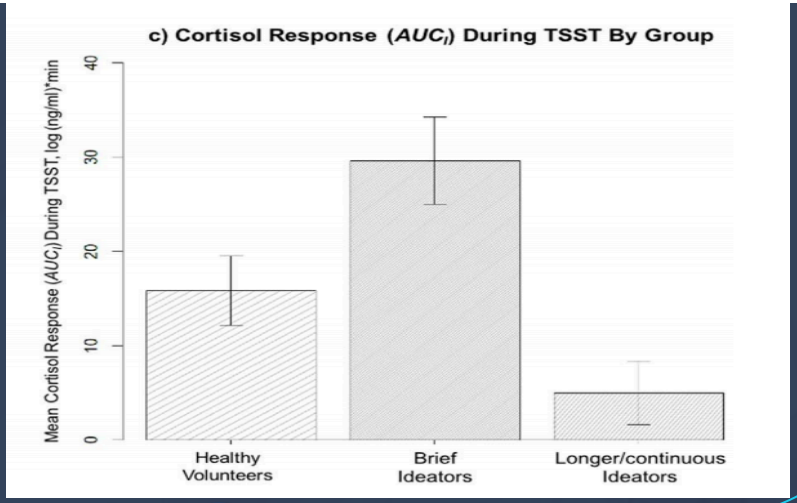
Hi Agg-Hi Imp subjects had the greatest cortisol reactivity (p=.01); not attributable to depression or SB.

Greater cortisol response to TSST (AUC), adjusted for baseline, **predicted a ≥5-point increase in SI during follow-up** (cortisol response for those with and without ≥5 point increment: -5.41 vs. 4.81, t=2.02, df=65, p<0.05).

(B. Stanley data)

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES





Brief suicidal ideators (N = 18), longer/continuous ideators (N = 17) and HV (N=23) aged 18–65 years.

Salivary cortisol during TSST was measured at 6 time-points. SI severity and duration assessed with Beck Scale for Suicidal Ideation. Brief ideators had greater cortisol response controlling for relevant covariates. Total SSI score was unrelated to cortisol response.

Toward subtyping of suicidality: brief suicidal ideation is associated with greater stress response. Rizk et. al 2018

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

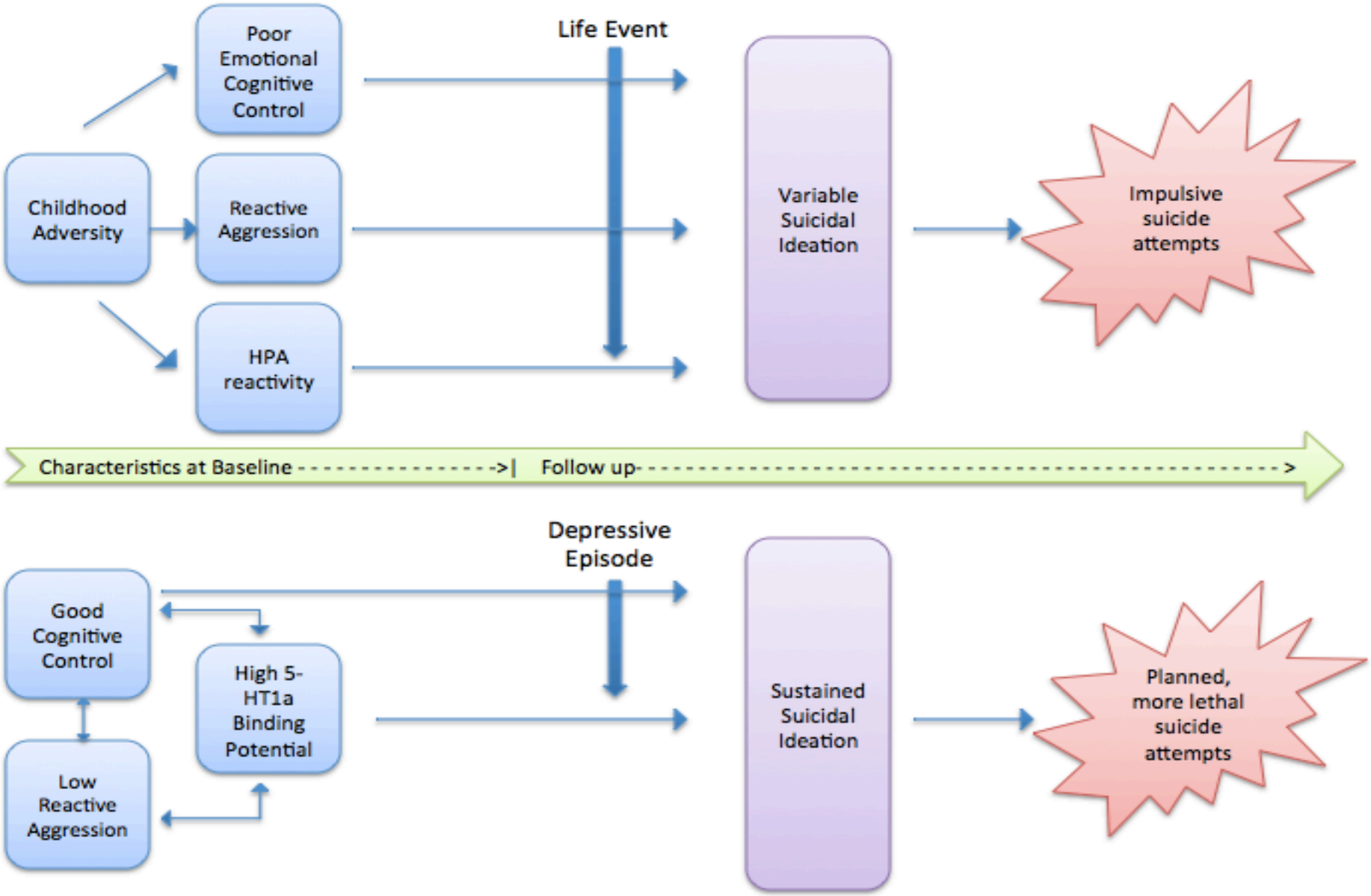
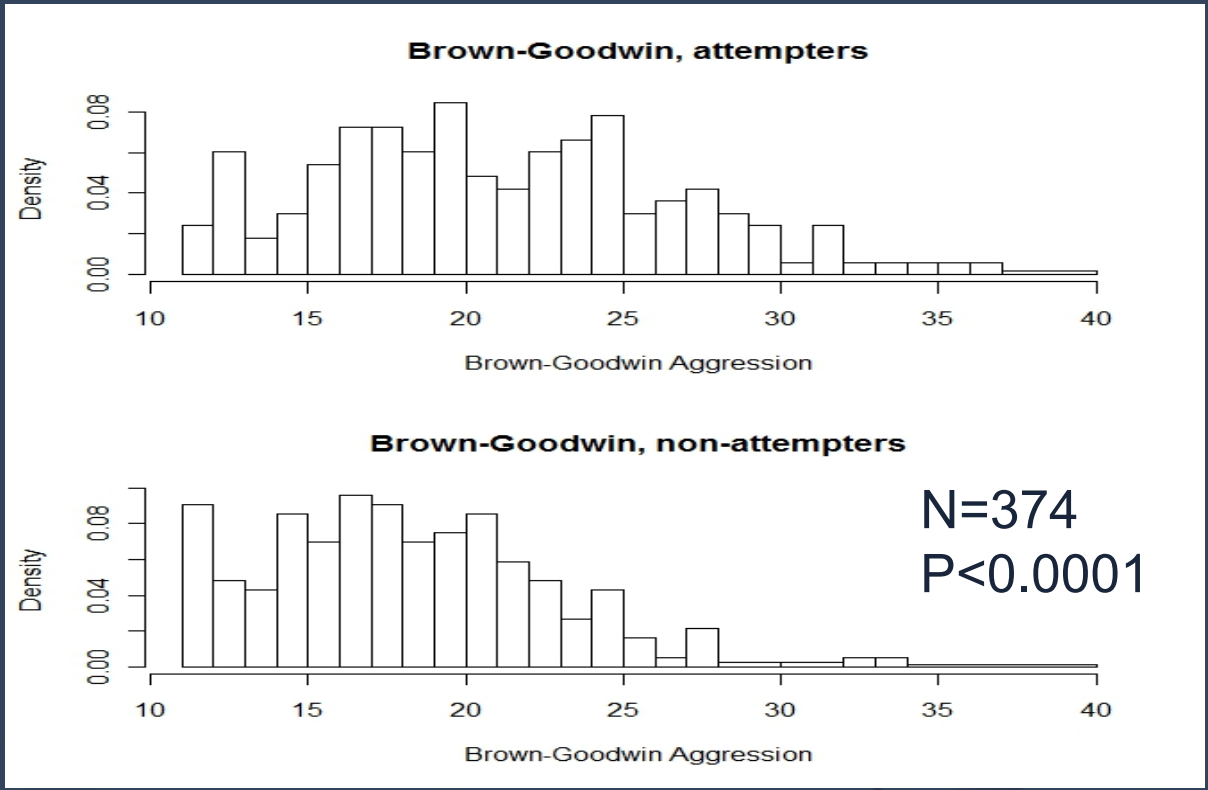


Figure 1. Explanatory Model for Two Subtypes of Suicidal Behavior

Bernanke et al 2017

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

Those with low aggression may make higher lethality attempts and have more severe depressive episodes, putting them at risk for SB. (CCNMD data)



Low aggression attempters (BGAH<17; 25 pctl) had fewer past attempts (p=0.045), less impulsivity (p=0.002), less hostility (p< 0.0001), less likely to have childhood trauma.

Attempts were just as frequent during follow-up as high aggression attempters (p=0.73), but of higher lethality (6 vs. 3, p=0.02) and their 3 months HDRS score was higher (p=0.001). They also had fewer life events during follow-up (p=0.005).

Measuring 5-HT_{1A} with [^{11}C]-WAY100635

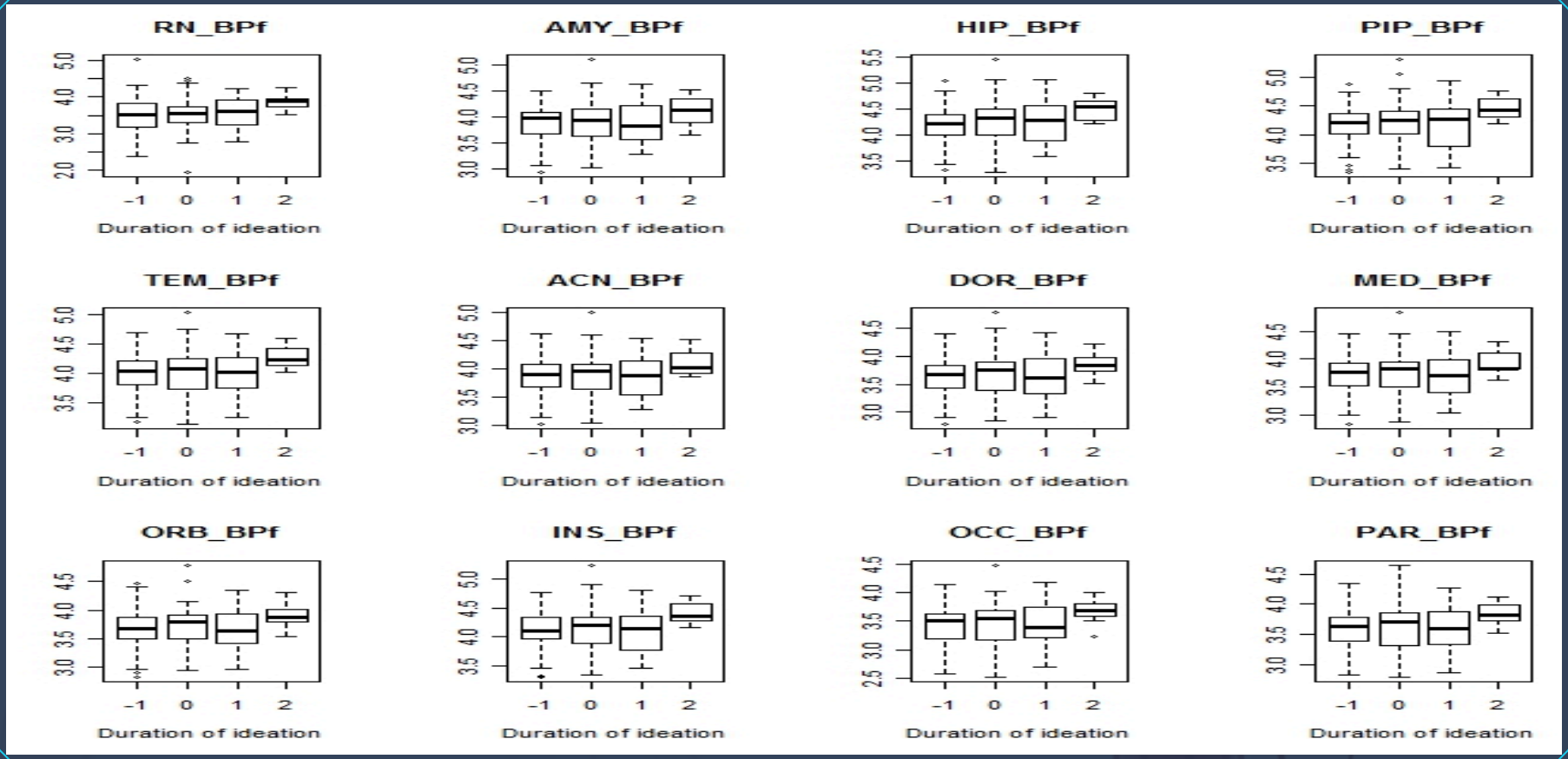
(^{11}Carbon-labeled N-(2-(1-(4-(2-methoxyphenyl)-1-piperazinyl) ethyl))-N-(2-pyridyl)-cyclohexanecarboxamide

- serotonin antagonist
- arterial input function, radioligand metabolites (first 60 mins), and plasma free-fraction (f_P)
- ROIs: RN, amygdala, hippocampus, parahippocampal gyrus, anterior cingulate, medial and dorsolateral PFC, and insular, parietal, temporal, orbital, and occipital cortices.
- ROIs hand drawn on MRI based on brain atlases and published reports. Fixed-volume elliptical ROI (2 cm^3) placed on RN in the dorsal midbrain on a mean PET image. Cylindrical ROI in the cerebellar white matter (reference region)
- ROI contours were processed using the segmented MRI to confine analyses in cortical regions to gray matter voxels.

Measuring 5-HT_{1A} with [^{11}C]-WAY100635

- (ECAT EXACT HR+; Siemens/CTI)
- Emission data collected for 110 minutes as 20 successive frames of increasing duration.
- Image analysis used graphics software (MATLAB 2006b; MathWorks) with extensions to the fMRI of the Brain's Linear Image Registration Tool (FLIRT);
- Brain Extraction Tool
- Statistical Parametric Mapping normalization and segmentation routines
- Motion correction: denoising filter techniques were applied to all PET images starting at frame 5.
- Frames were aligned using rigid-body FLIRT to frame 8.
- A mean of motion-corrected frames 8 through 18 was registered to the MRI using FLIRT.

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES



MDD subjects (n=134) had PET with [11C]-WAY100635
Continuous SI (item 7; SSI) had higher 5-HT1A BPF (0.01<p<0.002, except amygdala p=0.06) than those who had none or intermittent SI.

Sullivan et al 2014

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

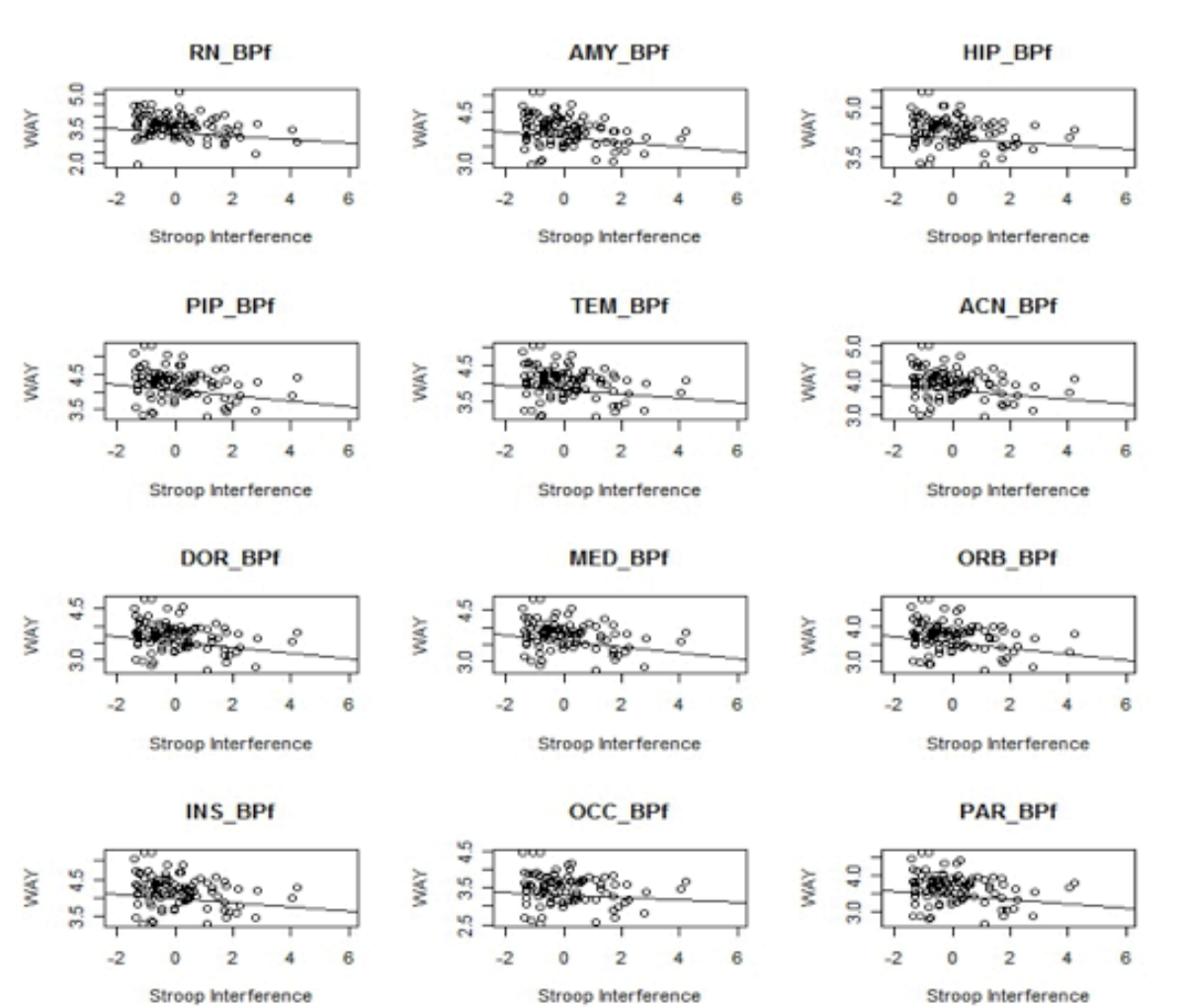


Fig. 7. 5-HT$_{1A}$ BP$_F$ in cortical regions and DRN and Stroop Interference

In MDD (n=95), controlling for sex, lower Stroop Interference scores -> higher 5HT1A BPF in 12 regions ($0.01<p<0.04$). Conservative Continuous Performance Task response bias, possibly indicating attempts to manage interference also negatively associated with 5HT1A BPF.

Maria A. Oquendo

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

134 depressed patients: 13 suicide attempts; 2 suicides.
Planning SI (SSI items 12-18); Beck Lethality: 0 - 8

Higher $5HT_{1A}$ BP_F in orbital cortex predicted higher suicide planning scores (p=0.04).

Higher DRN $5HT_{1A}$ BP_F predicted recent attempt lethality (p=0.003) and intent (p<0.01).

Higher DRN $5HT_{1A}$ BP_F was associated with higher future attempt lethality (p=0.03).

Sullivan, 2014. Oquendo, 2016

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

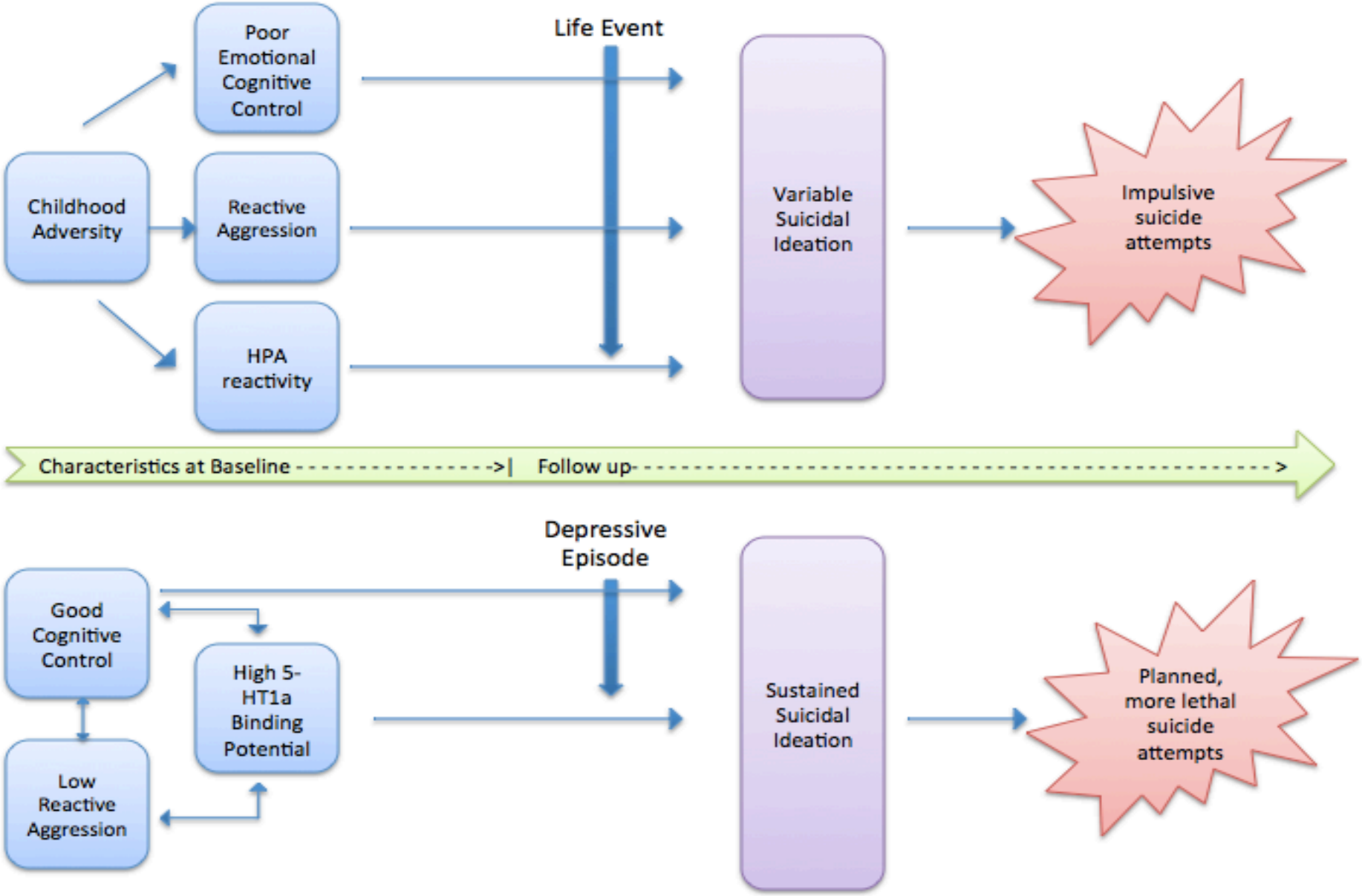


Figure 1. Explanatory Model for Two Subtypes of Suicidal Behavior

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

Opioid Pilot Project 2: Kappa opioid receptor availability in a comorbid pain and opioid use disorder population at suicidal risk. (Oquendo, Cheatle, Kampman, Regier)

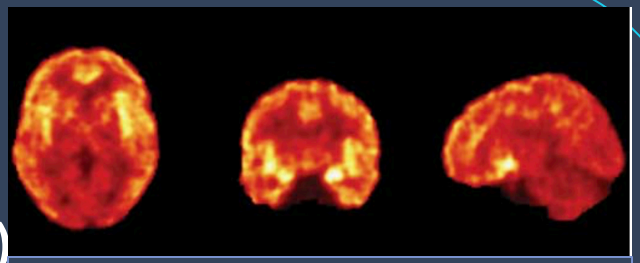


Figure 3. Kappa opioid receptor image in a single subject with [^{11}C] LY2795050 (adapted from Naganawa, et al. 2015).

Subgroup with variable SI:

- reactive to environmental stressors
- brain substrates are unknown
- kappa receptor: down regulated in child abuse and trauma-induced dysphoria, with effects mediated by cortisol secretion
- dynorphin/kappa-opioid receptor (dyn/KOR) system?

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

Opioid Pilot Project 2: Kappa opioid receptor availability in a comorbid pain and opioid use disorder population at suicidal risk. (Oquendo, Cheatle, Kampman, Regier)

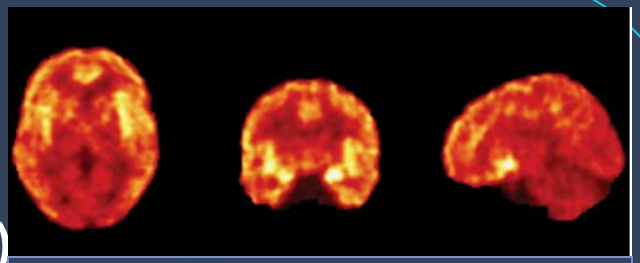


Figure 3. Kappa opioid receptor image in a single subject with [^{11}C] LY2795050 (adapted from Naganawa, et al. 2015).

- KOR radiotracer (Figure 3): a negative relationship between dysphoric post traumatic symptoms and KOR binding
- preclinical research: dyn/KOR dysfunctions in addiction, pain
- prolonged kappa signaling that can lead to persistent behaviors characteristic of depression in humans.

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

Opioid Pilot Project 2: Kappa opioid receptor availability in a comorbid pain and opioid use disorder population at suicidal risk. (Oquendo, Cheatle, Kampman, Regier)

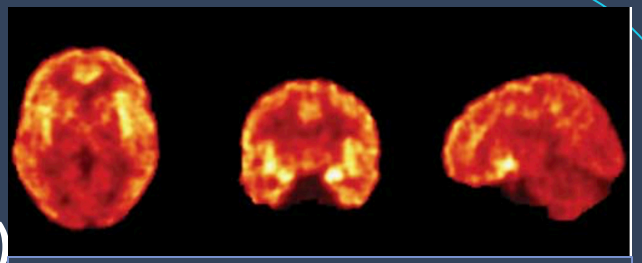


Figure 3. Kappa opioid receptor image in a single subject with [^{11}C] LY2795050 (adapted from Naganawa, et al. 2015).

Aim 1: To characterize baseline KOR availability in individuals with co-morbid pain and OUD, initially stratified by suicidal subgroup (sustained vs. variable SI), using a competitive KOR antagonist, [^{18}F]LY2459989 or [^{11}C]LY2795050. As endogenous dynorphin competes with the antagonist for KOR binding, greater endogenous dynorphin activity results in lower KOR availability. *Hypothesis: dyn/KOR receptor availability will be lower in "variable" SI than in "sustained" SI subgroup.*

Aim 2: To assess continuous measures of SI, drug use severity, pain severity, and prior trauma as a function of KOR availability. *Hypothesis: Individuals with (greater) SI, drug use, and pain will have lower KOR receptor availability in the amygdala and interconnected limbic regions, brain regions implicated in the processing of negative affect, a relevant dimension for each of the conditions under study.*

DELINEATING DIFFERENT SUICIDAL PHENOTYPES WITH DISTINCT BIOSIGNATURES

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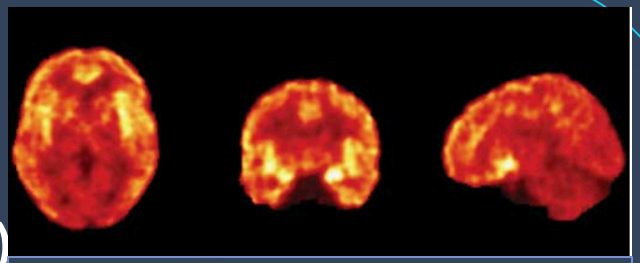

Figure 3. Kappa opioid receptor image in a single subject with [^{11}C] LY2795050 (adapted from Naganawa, et al. 2015).

Study Design:

- Individuals with co-morbid pain, OUD and a range of suicidal risk (n=24)
- 90-min PET scan with arterial blood sampling after bolus IV of radiotracer.
- KOR availability: regional brain distribution volumes (V_T), (ligand uptake in tissue relative to plasma concentration of parent ligand)
- Compare BP between the two SI subgroups
- Correlate BP with Beck SSI, Addiction Severity Index, Brief Pain, and CTQ

Innovations and Deliverables: Parsing the kappa effects by examining suicide subtypes may provide a basis for subsequent treatment trials with KOR antagonist drugs (e.g., buprenorphine) to reduce SI in OUD/pain patients.

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Thank you!