The Neurobiology of Suicide Vulnerability

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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.
what is suicidal behavior?

Suicide
Suicidal attempts
Suicidal ideation
Relationship to non-suicidal self-injury
EPIEMIOLOGY 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

COMPLETED SUICIDES

Identifiable Psychiatric Disturbance

MAJOR AFFECTED ILLNESSES

Self-inflicted death

Most patients with psychiatric illnesses never attempt suicide

Psychiatric Illness is NOT a sufficient condition for suicidal acts

Most patients with psychiatric illnesses never attempt suicide
A MODEL FOR UNDERSTANDING SUICIDAL BEHAVIOR

THE STRESS-DIATHESIS MODEL - 1999
Based on cross-sectional data

Diathesis: Threshold

Stressor-Trigger: (Psych episode or life event)

Plan

Act: Suicide attempt or completion

Suicidal Ideation

No Suicidal Ideation

Diathesis: Impulsivity, Aggression, Pessimism, Cognitive Inflexibility, Low Serotonin, Substance Misuse

Risk Factors

Environmental risks: Access to lethal means
No access to care

Mann, 1999
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
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.
Prospектив Study of Clinical Predictors of Suicidal Acts After Major Depression - 2004
Prospective Study of Clinical Predictors of Suicidal Acts After Major Depression - 2004

Aggression/Impulsivity Risk Factors
- Brown Goodwin
- Barratt Impulsivity
- Buss Durkee Hostility

Pessimism Risk Factors
- Beck Depression Scale
- Beck Hopelessness Scale
- Reasons for Living Scale
- Scale for Suicidal Ideation

Graph:
- X-axis: Time Since Presentation (days)
- Y-axis: Proportion Not Attempting
- Lines represent:
  - No high scores
  - One high score
  - Two high scores
  - Three high scores
  - Four high scores

Oquendo, 2004
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)

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

<table>
<thead>
<tr>
<th>Life events</th>
<th>% Subjects with life event during 2-year follow-up</th>
<th>% Person-months with life events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No BPD</td>
<td>BPD</td>
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<tr>
<td>Health</td>
<td>75</td>
<td>84</td>
</tr>
<tr>
<td>Work-related</td>
<td>64</td>
<td>70</td>
</tr>
<tr>
<td>Home and family</td>
<td>73</td>
<td>84</td>
</tr>
<tr>
<td>Personal/social</td>
<td>85</td>
<td>84</td>
</tr>
<tr>
<td>Financial</td>
<td>66</td>
<td>62</td>
</tr>
<tr>
<td>Any kind of event</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>MDE</td>
<td>69</td>
<td>74</td>
</tr>
<tr>
<td>Suicidal behavior</td>
<td>7</td>
<td>18</td>
</tr>
</tbody>
</table>

Abbreviations: BPD, borderline personality disorder; MDE, major depressive episode.

*Comparisons by BPD diagnosis were tested with marginal logistic regression models. Values in bold are statistically significant.*
# 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

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

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

Figure 1. Explanatory Model for Two Subtypes of Suicidal Behavior
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)
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)
BPD attempters may be less able to harness neural pathways to manage negative, distressing affect. (B. Stanley data)

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;)

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.
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)
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
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 $[^{11}\text{C}]-\text{WAY100635}$

($^{11}$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 $[^{11}\text{C}]-\text{WAY100635}$

- (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.
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.
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.
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 ($p=0.03$).

Figure 1. Explanatory Model for Two Subtypes of Suicidal Behavior
Opioid Pilot Project 2: Kappa opioid receptor availability in a comorbid pain and opioid use disorder population at suicidal risk. (Oquendo, Cheatle, Kampman, Regier)

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

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

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

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.
Thank you!