White Matter Integrity, Suicidal Ideation, and Cognitive Dysfunction in Combat-Exposed Iraq and Afghanistan Veterans

HSR&D Cyberseminar

Presented by Delaney Davey

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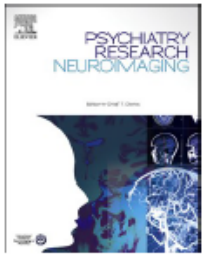

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White matter integrity, suicidal ideation, and cognitive dysfunction in combat-exposed Iraq and Afghanistan Veterans

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Overview

01 Introduction

02 Background

03 Methods

04 Results

05 Discussion

06 Clinical Implications & Future Directions

Suicide

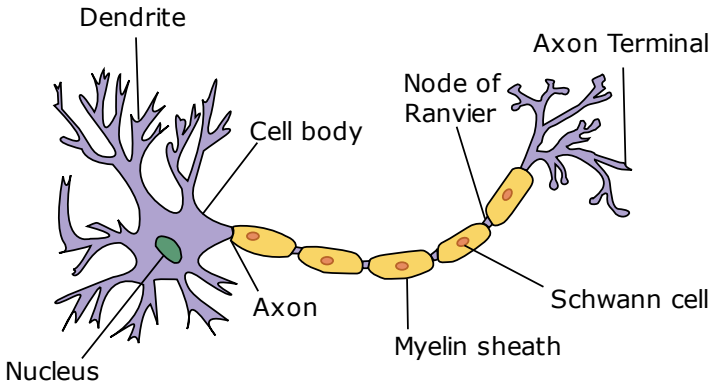
- Suicide prevention is a major public health priority for civilians and Veterans
- Veterans are at a particularly high risk for suicide relative to the general population
  - ➢ Traumatic brain injury (TBI) and psychiatric conditions such as PTSD and depression confer increased suicide risk

Bahraini et al., 2013, Bullman et al., 2018, Center for Disease Control and Prevention, 2019, Kang et al. 2015, Pietrzak et al., 2010, Pompili et al., 2013, VA Office of Mental Health and Suicide Prevention, 2018

Suicide prevalence emphasizes the need to characterize the neurobiological underpinnings of suicidality among Veterans

White Matter

- Millions of axon bundles (nerve fibers) that connect neurons from different brain regions
- Responsible for communication between gray matter regions



Fields, 2010, US National Cancer Institute's Surveillance, 2019

Diffusion Tensor Imaging (DTI)

- MRI-based technique often used to study white matter architecture and integrity
- Utilizes the diffusion of water molecules to characterize the biological microstructure of tissue

Le Bihan et al., 2001, Soares et al., 2017

Fractional Anisotropy (FA)

- Most commonly-used DTI measure of neuronal fiber integrity
- Scalar value between 0 and 1 that describes the degree of anisotropy of a diffusion process

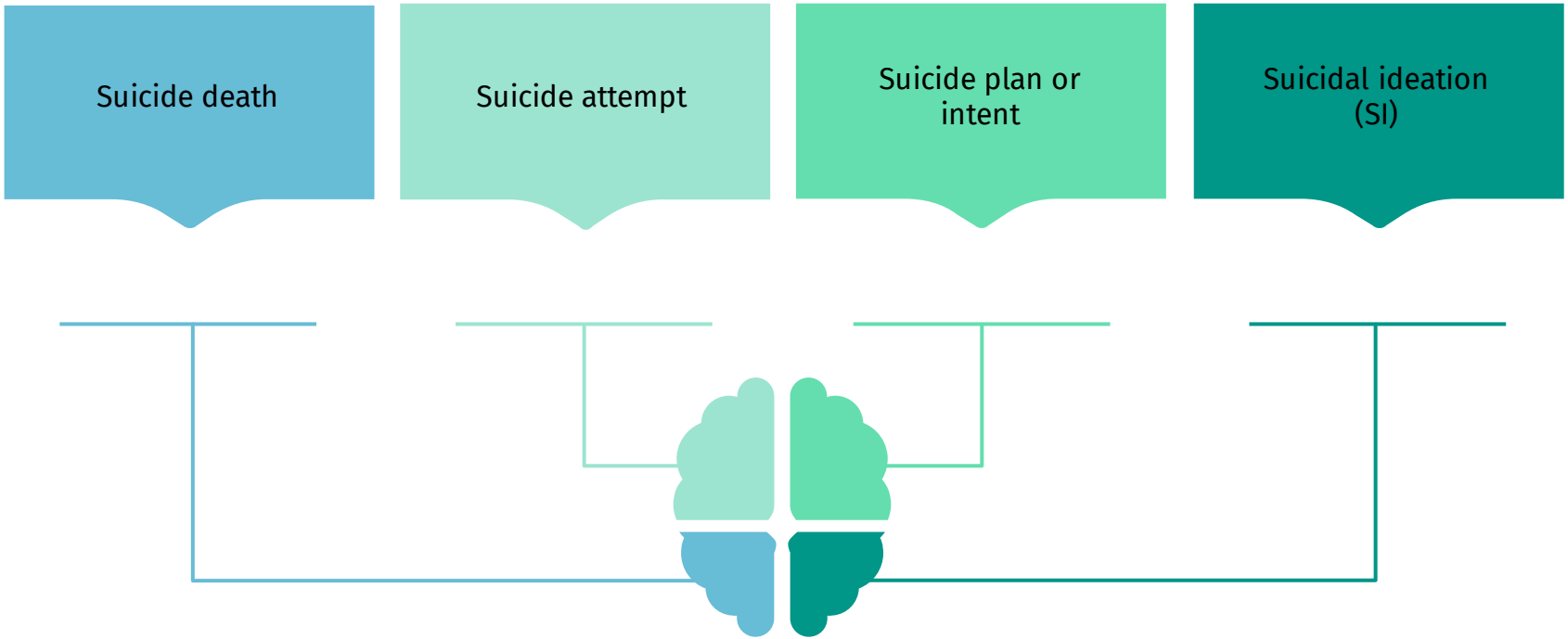
Suicidality & DTI

White matter alterations among individuals with suicidal thoughts and behaviors found across numerous psychiatric conditions

Inconsistent FA findings, with both increased and decreased FA associated with suicidality

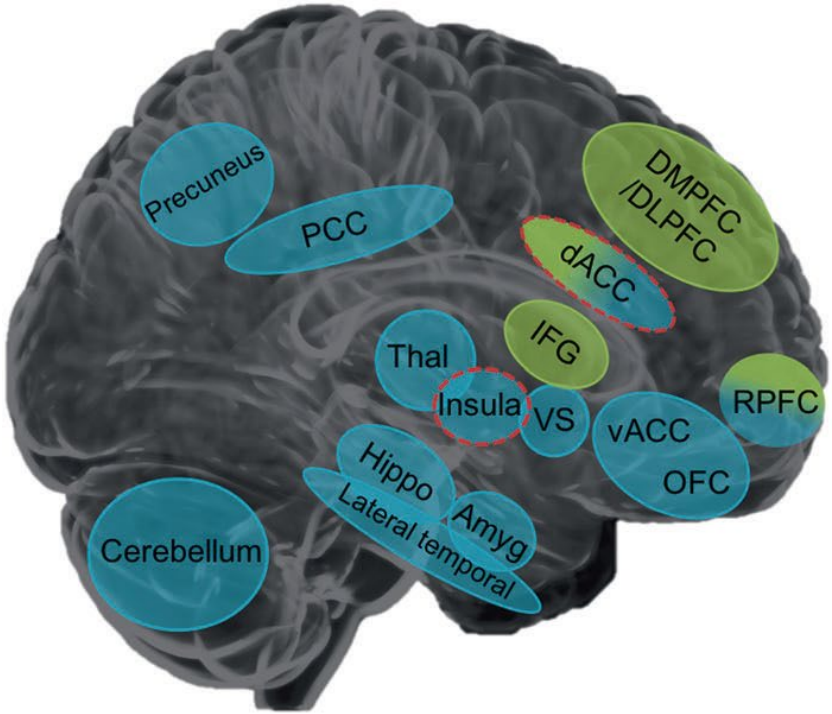
Balcioglu and Kose, 2018, Gosnell et al., 2018, Schmaal et al., 2020; Sudol and Mann, 2017

Suicidality: A Comprehensive Term



Bani-Fatemi et al., 2018; Suicide Prevention Resource Center, 2020

Regions involved in suicidal *thoughts* versus *behavior*



Diminished cognitive control of emotion and behavior, cognitive inflexibility, impaired valuation of different decision options

Mediating dynamic interactions between the extended VPFC and DPFC/IFG systems

Enhanced negative and blunted positive internal states, negative self-referencing, impairments in future thinking, rumination

Figure model derived from Schmaal et al., 2020

Veteran Studies

01

Yurgelun-Todd et al., 2011

Mild to severe TBI
FA in genu and cingulum
suicidal ideation

02

Lopez-Larson et al., 2013

Mild TBI
FA in thalamic radiations
suicide behaviors

Cognitive Dysfunction

- Important risk factor for suicidal thoughts and behaviors
- Altered white matter associated with poorer cognitive functioning in Veterans
- Thus, white matter alterations may contribute to cognitive dysfunction and suicidality

Bredemeier and Miller, 2015; Hayes et al., 2016; Keilp et al., 2014; Levin et al., 2010, Miller et al., 2017, Richard-Devantoy et al., 2014

Suicidality & Cognitive Dysfunction

Poorer cognitive functioning associated
ı suicidality in civilians

Limited Veteran studies of
ıropsychological functioning and
suicidality

Studies primarily focus on executive
g

Bredemeier and Miller, 2015, Brenner et al., 2015, Crocker et al., 2019, Homaifar et al., 2012, Jollant et al., 2011, Richard-Devantoy et al., 2015

Objectives

Aim 1

Examine white matter alterations in Veterans with and without SI

Aim 2

Examine relationships between white matter integrity and neuropsychological functioning

Procedures

- 72 Veteran participants
- Recruited from VASDHS via clinician referral or study advertisements as part of a larger Chronic Effects of Neurotrauma Consortium (CENC) project
- Comprehensive assessment
  - Diagnostic interviews
  - Neuropsychological testing
  - Self-report questionnaires
  - MRI scan

CENC

Cifu et al., 2018, Jurick et al., 2018

Eligibility Criteria

Inclusion Criteria

1) Iraq or Afghanistan Veteran
2) 18 – 50 years old
3) History of combat exposure (DRRI-2)

Exclusion Criteria

1) History of moderate or severe TBI
2) Diagnoses of bipolar disorder, dementia, or current psychotic disorder
3) Current substance dependence
4) Suicide attempt or intent in the last month
5) Contraindications to MRI

Vogt et al., 2013

Diagnostic Interviews

MINI

PTSD, MDD, substance use disorders, and suicidality

VCU

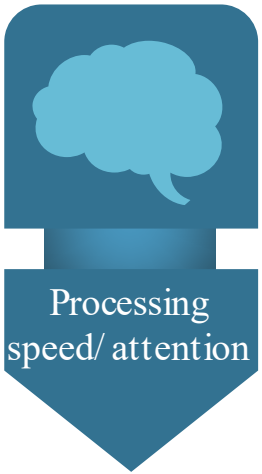
(rCDI-B and rCDI-G) TBI history and severity

Sheehan, 2014; Walker et al., 2015

MINI Suicidality Module

B2	Think (even momentarily) that you would be better off dead or wish you were dead or needed to be dead?	NO	YES
B3	Think (even momentarily) about or have mental images of harming or of hurting or of injuring yourself, - with at least some intent or awareness that you might die as a result?	NO	YES
B4	Think about suicide (killing yourself)?	NO	YES

Neuropsychological Tests



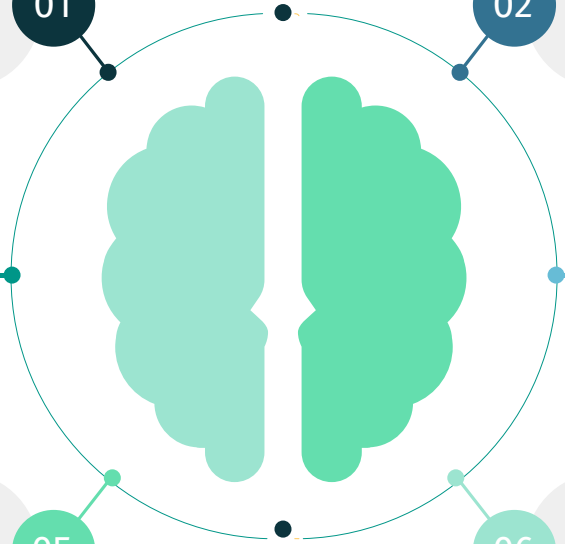
- D-KEFS Trail Making visual scanning, letter sequencing, & number sequencing
- D-KEFS CWIT color naming and word reading
- WAIS-IV digit span, coding, and symbol search

- BVMT total recall and delayed recall
- CVLT-II list A trials 1-5 total, short-delay and long-delay free recall

- WCST-64 perseverative and total errors
- D-KEFS Trail Making number-letter switching
- D-KEFS CWIT inhibition and inhibition-switching
- PASAT 2, 2.4, and 3 second correct

See Reference list

Regions of Interest (ROIs)



01 Internal capsule

02 Corona radiata

03 Cingulum

04 Superior longitudinal fasciculus

05 Corpus callosum

06 Uncinate fasciculus

Statistical Analyses

Aim 1

ANOVAs or ANCOVAs

- Determined whether FA differed between in each ROI
- Included significant demographic and clinical variables (e.g., TBI hx, PTSD) as covariates

Aim 2

Partial Correlations

- Examined associations between cognitive composites and FA in ROIs that differed by SI group in Aim 1
- Controlled for relevant demographic variables

04 Results

Table 1. *Descriptive and Group Differences on Demographic, Diagnoses, TBI Characteristics, and Cognitive Measures*

	Total Sample (N = 72)	**SI- group (n = 51)**	**SI+ group (n = 21)**		
	Mean (SD) or %	Mean (SD) or %	Mean (SD) or %	*t or* χ^2	*p*
Demographics					
Age	33.99 (6.43)	34.51 (7.01)	32.71 (4.63)	-1.28	.208
Years of education	15.04 (1.67)	15.27 (1.37)	14.48 (1.37)	-1.88	.064
% Male	90.3%	90.2%	90.9%	0.00	.971
% Caucasian/Middle Eastern	56.9%	62.7%	42.9%	0.02	.121
% Hispanic	36.1%	33.3%	40.9%	0.59	.444
% African American/Black	8.3%	5.9%	14.3%	1.38	.241
% Asian	9.7%	5.9%	19.0%	2.94	.087
% American Indian/Alaskan Native	9.7%	9.8%	9.5%	0.00	.971
% Native Hawaiian/Pacific Islander	2.8%	3.9%	0.0%	0.85	.357
% Other/Not Reported	20.8%	21.6%	19.0%	0.06	.811
Diagnoses					
% PTSD diagnosis	45.8%	41.2%	57.1%	1.53	.217
% MDD diagnosis	72.2%	68.6%	81.0%	1.13	.289
% History of mTBI	58.3%	54.9%	66.7%	0.85	.357
TBI Characteristics[a]					
% with LOC presence	66.7%	75.0%	66.7%	2.63	.105
% with PTA presence	76.2%	75.0%	50.0%	0.07	.798
% with blast history	45.2%	50.0%	78.6%	0.77	.381
Lifetime TBIs	3.55 (3.37)	4.07 (3.62)	2.50 (2.62)	0.98	.334
Time since injury (years)	7.38 (6.11)	6.73 (5.32)	8.68 (7.52)	-1.44	.157
Cognitive Measures					
Attention/processing speed composite	0.00	.08 (.60)	-.19 (.72)	-1.61	.112
Memory composite	0.00	.01 (.80)	.03 (.70)	0.23	.816
Executive functioning composite	0.00	.11 (.61)	-.27 (.72)	-2.34	**.022***

Notes: *$p < .05$; composites are in z-score metric.
Abbreviations: PTSD = posttraumatic stress disorder; MDD = major depressive disorder; mTBI = mild traumatic brain injury; LOC = loss of consciousness; PTA = post-traumatic amnesia.
[a] TBI variables represent percentages of those with history of mild TBI

Aim 1: SI Group Differences in FA

- Veterans who endorsed SI had *lower* FA in the superior and posterior corona radiata and superior longitudinal fasciculus

Table 2. *Results of ANOVA/ANCOVA Comparing Fractional Anisotropy Values Between Suicidal Ideation Groups*

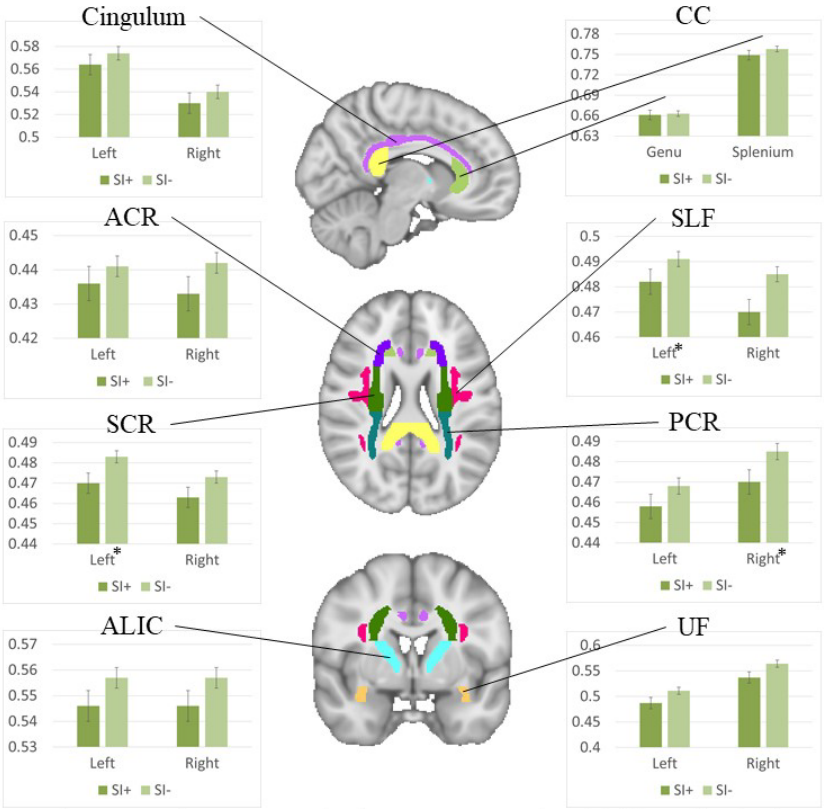
	ACR			PCR			SCR			Anterior Limb IC		
	F	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2
Left	0.56	.455	.01	2.27	.136	.03	5.59	**.021**	.08	2.90	.093	.04
Right	2.14	.148	.03	5.15	**.026**	.07	2.70	.105	.04	2.42	.124	.03

	Posterior Limb IC			Cingulum			SLF			UF		
	F	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2	*F*	*p*	η^2
Left	.011	.917	.00	.814	.370	.01	6.81	**.011**	.09	3.36	.071	.05
Right	1.46	.231	.02	.754	.388	.01	1.92	.170	.03	3.57	.063	.05

	Genu CC			Splenium CC		
	F	*p*	η^2	*F*	*p*	η^2
Total	.098	.755	.00	2.05	.156	.03

Notes: Left SCR included PTSD diagnosis and presence of LOC as covariates; Right SCR included PTSD and MDD diagnoses as covariates; SLF left included PTSD diagnosis as a covariate; Eta-squared (η^2) effect size interpretation = small (0.01), medium (0.06), large (0.14).
Abbreviations: ACR = Anterior Corona Radiata; PCR = Posterior Corona Radiata; SCR = Superior Corona Radiata; IC=Internal Capsule; SLF = Superior Longitudinal Fasciculus; UF = Uncinate Fasciculus; CC=Corpus Callosum

Figure 1. *Fractional Anisotropy Values by Suicidal Ideation Group in A Priori Regions of Interest*



Notes: *p<.05; ANOVA/ANCOVAs were performed to compare SI groups; Left SCR included PTSD diagnosis and history of mild TBI with LOC as covariates; Right SCR included PTSD and MDD diagnoses as covariates; SLF left included PTSD diagnosis as a covariate

Abbreviations: ACR = Anterior Corona Radiata; PCR = Posterior Corona Radiata; SCR = Superior Corona Radiata; ALIC = Anterior Limb of the Internal Capsule; SLF = Superior Longitudinal Fasciculus; UF = Uncinate Fasciculus; CC = Corpus Callosum

Aim 2: FA and Cognitive Composites

- Processing speed/attention associated with superior longitudinal fasciculus
- Executive functioning associated with superior corona radiata and superior longitudinal fasciculus
- Memory not associated with FA

Table 3. *Partial Correlations Among Fractional Anisotropy and Cognitive Composites (N = 72)*

Region of Interest	Processing Speed/ Attention		Memory		Executive Functioning	
	r	*df*	*r*	*df*	*r*	*df*
Right Posterior Corona Radiata	0.003	69	0.08	69	0.168	69
Left Superior Corona Radiata	0.153	69	0.07	69	**0.244***	69
Left Superior Longitudinal Fasciculus	**0.248***	69	0.22	69	**0.402****	69

Notes: *$p<.05$, **$p<.01$; Processing speed/attention composite correlations controlled for years of education; memory composite correlations controlled for age; executive functioning composite correlations controlled for years of education

Discussion

05

- Supports research showing white matter alterations among individuals endorsing suicidal ideation
- Current study demonstrated associations between these alterations and *objective* measures of cognitive functioning in Veterans

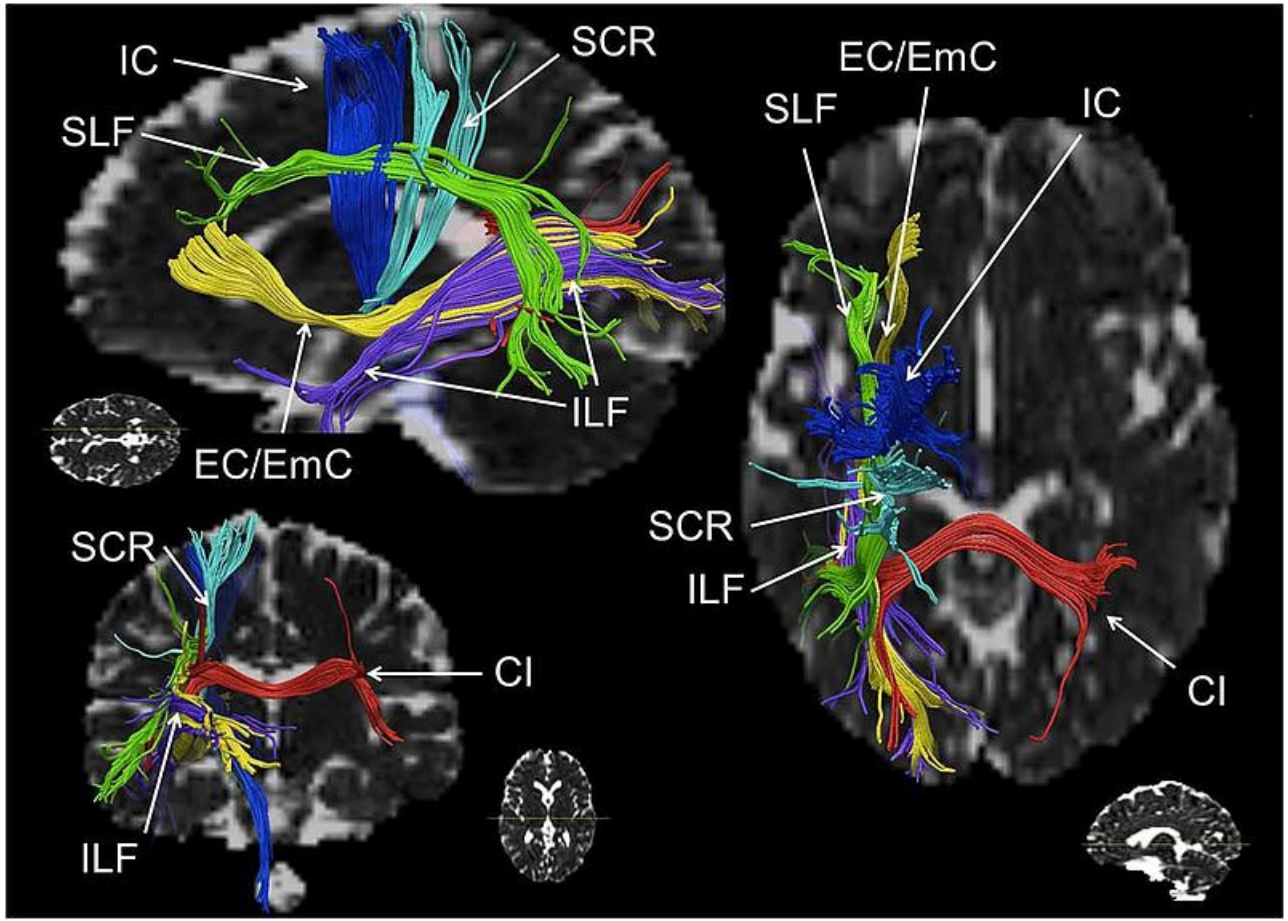


Figure model derived from Moeller et al., 2015

Corona Radiata

- White matter tract connecting brainstem to areas of cortex
- Associated with suicidality across diagnoses
- Lower FA in corona radiata associated with executive functioning

Jiang et al., 2019, Kim et al., 2015, Kraus et al., 2007, Lee et al., 2016, Leunissen et al., 2014; Taylor et al., 2015, Wallace et al., 2018

Default Mode Network (DMN)

- Studies suggest corona radiata plays an integral role in the DMN
- DMN is a set of regions engaged in self-referential processing and internally-focused tasks
- DMN activity correlated with suicidality

Buckner et al., 2008, Ellis and Rutherford, 2008, Fernandez-Espejo et al., 2012, Jollant et al., 2011, Luo et al., 2012, Malhi et al., 2020, O'Connor and Nook, 2014

Superior Longitudinal Fasciculus

Major association fiber track connecting poroparietal junction area and parietal lobe with frontal lobe

Implicated in suicidality across multiple psychiatric diagnoses

Integrity of this region associated with processing speed/attention and executive functioning

Kim et al., 2015, Lee et al, 2016, Owens et al., 2018, Smolker et al., 2015, Spitz et al., 2013, Urger et al., 2014, Veeramuthu et al., 2015, Wallace et al., 2018, Wang et al., 2016

Brooding

- A repetitive focus on one's distress
- Superior longitudinal fasciculus may play a role in brooding
- Brooding associated with suicidal ideation and attempts

Rogers and Joiner, 2017, Pisner et al., 2019

Executive Functioning

Umbrella term that encompasses several higher-order cognitive processes

Dysfunction may make it more challenging to:

1) Inhibit negative thoughts about self-harm
2) Adapt to stressful situations
3) Manage emotions

Bloemen et al., 2018, Bredemeier and Miller, 2015, Nigg et al., 2017, Snyder et al., 2015

Processing Speed/Attention

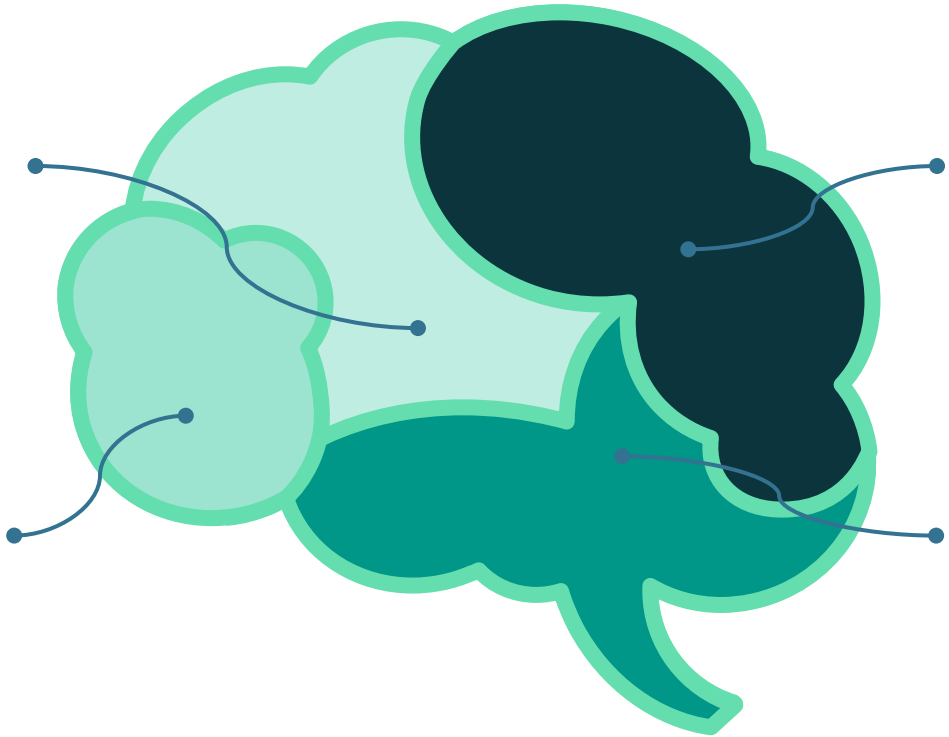
- Impaired selective attention may contribute to cognitive rigidity
- Lower-level processes such as processing speed may also contribute to executive function difficulties

Keilp et al., 2014

TBI

TBI characteristics not associated with SI group

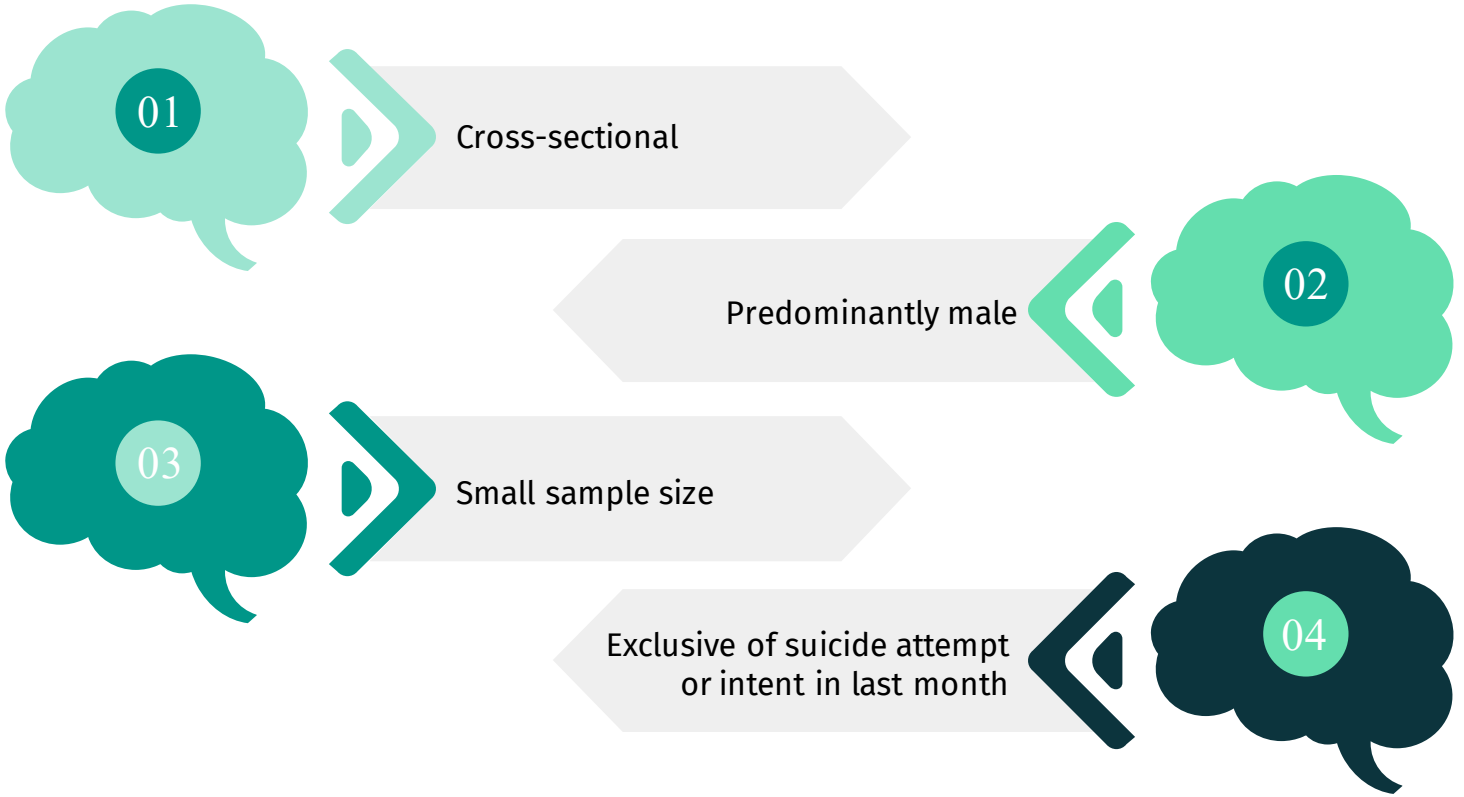
TBI characteristics not associated with FA in most ROIs



However, TBI is known to confer increased risk for suicide

Increased risk may be driven by comorbid psychiatric diagnoses

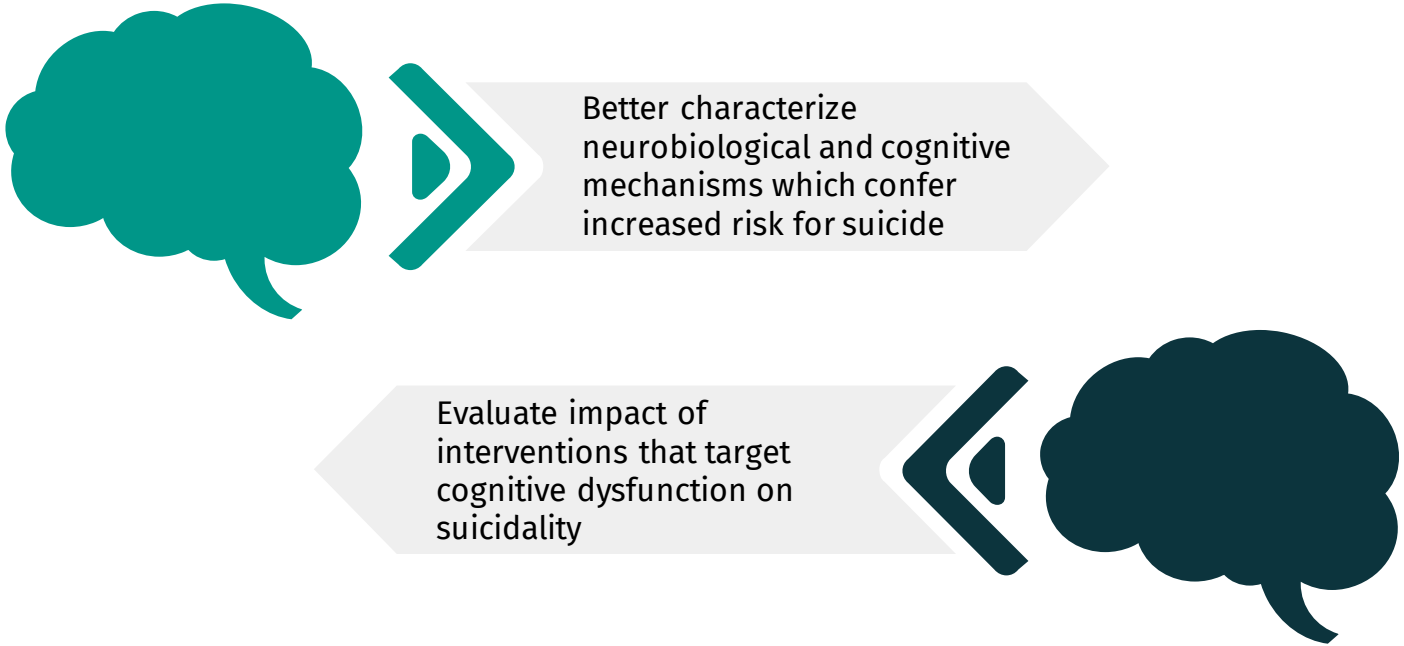
Limitations



Clinical Implications

- Potential implications for treatment geared towards effectively attenuating suicidal thoughts and behaviors
  - ➢ Cognitive functioning in suicide risk assessment
  - ➢ Interventions that target cognitive functioning (e.g., cognitive rehabilitation, computerized cognitive training)

Future Directions



Questions?

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