Biological correlates of suicide attempt during adolescence and young adulthood: integration of findings across multi-modal measures.

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Abstract

The biological correlates of suicide attempt are poorly understood in young people. Here we undertook a narrative review of the literature across biological units of analysis (brain structure and function, serum biomarkers, molecular biology) to summarize the markers associated with suicide attempt in samples of average age under 24. We suggest overall patterns in emotion, cognitive control, and social support, which emerge from alterations at each level.

Introduction

Suicide, the act of dying by one's own action with intention of death, is a leading cause of death worldwide, especially for young people. For those aged 10 to 34 suicide is the second leading cause of death, and comprises more total deaths per year than violent homicide (CDC, 2018; Morgan et al., 2018). Despite the evident severity of this suicide pandemic, much is left to be understood about the mechanisms underlying suicide risk. While the past few decades have involved significant advances in theoretical understandings of the biological, psychological, and sociocultural correlates of suicidal thoughts and behaviours, these findings have failed to slow a worldwide increase in suicide attempts and deaths (Hedegaard et al., 2018).

Currently, clinical practioners evaluate suicide risk primarily on the basis of the patient's self report of psychological symptoms and history (e.g. past suicide attempt, which has consistently shown to increase risk for subsequent attempt). Self report involves several challenges, including the potential for recollection bias, patient inability to express complex thoughts and emotions, and volitional deception by the patient to prevent interference with planned suicide attempt (Klimes-Dougan, 1998; Large et al., 2016; Ryan & Oquendo, 2020). It is evident that new risk probes that are more sensitive, specific, and reliable than those currently employed are urgently needed to improve the ability for practitioners to intervene in cases where suicide attempt will likely follow. As explicated by Glenn et al. (2017), a multiple levels of analysis approach is ideal for the prediction of suicide attempt by combining the best-known risk factors across levels of functioning and exploring their additive effect on risk prediction. As mentioned above much recent and past research has been conducted examining psychological constructs, generally by self report, as predictors of suicide attempt.

The “brain revolution,” spurred by novel advances in imaging, molecular genetics, and psychophysiology, has offered opportunity to more closely examine the underlying neural mechanisms of suicide risk, supported by the generally accepted premise that mind arises from complex interactions that are represented by neural activity; it follows that all psychopathology, including suicidal behavior, can be identified at the biological level in some capacity.

Here we choose to focus specifically on adolescence in our review on the biological correlates of suicide attempt due to both the tendency for suicidal thoughts and behaviors to onset during adolescence and also the significant yearly number of deaths by suicide in young people. From a developmental psychopathological approach it is likely that with the changes in brain structure, function, and integration that accompany development, the neurobiology of suicide could differ with age (Oquendo & Mann, 2008). Few studies at time of writing have explicitly examined within-sample age variation as a moderator of the relationship between certain risk factors and attempt.. As a particularly high risk group for suicide attempt and also as a group that are presumably more highly amenable to intervention given the neuroplasticity characteristic of youth, adolescents serve here as a useful focus to synthesize findings across micro-levels of biology.

While comprehensive and highly informative reviews of suicide biology do exist (see Lengvenyte et al., 2019; Pandey, 2014; Turecki, 2014), we have found none that specifically focus on youth in the multi-modal framework that we undertook here. This review is intended to be considered in conjunction with those more general undertakings to emphasize the nature of the developmental process and the likelihood that suicide is characteristically different with age. In this review we sought to explore correlates of suicide attempt in youth. While the original goal was to focus exclusively on homogeneously adolescent samples (i.e., age range 12-19), some

samples included wider age ranges, although the average age was below 24 years for all samples. We examined the biology of suicide attempt, which included neuroimaging structure and function, serum metabolite levels, DNA sequence variation, epigenetic modifications, and molecular stress markers. It is important to note that the majority of included studies involved living adolescents rather than post mortem analysis, such that most studies did not involve direct molecular-level access to neural tissue.

While evidence has suggested that fatal and non-fatal suicide attempt are distinct entities with potential differences in predictors (DeJong et al., 2010; Joo et al., 2016), these differences are likely to be small and an understanding of non-fatal suicide attempt is vital due to its association with subsequent death by suicide. In vivo studies also offer the opportunity to study interacting systems, which is sometimes not possible in post mortem samples (e.g., functional connectivity between brain regions evoked by task-related activations). In recognition of the specificity afforded by post mortem analysis (i.e., direct access to neural tissue and examination of molecular biology within context) we did include studies of adolescent post-mortem suicide brain, which are reviewed in the section on molecular biology (DNA, RNA, and protein).

Furthermore, only studies evaluating suicide attempt, fatal or non-fatal, as an outcome were included. Studies only evaluating suicidal thoughts or ideations were excluded, consistent with recent findings that suicidal ideations and behaviors are clinically distinct and preceded by differing risk factors (May & Klonsky, 2016). While correlates of suicidal thoughts are beyond the scope of this review, there is important work to be done in the future in synthesizing across thoughts and behaviors and noting the mechanistic differences at the biological level.

Brain structure and function: findings from imaging studies.

Magnetic resonance imaging has offered the opportunity to directly and non-invasively examine the structure and function of the brain in adolescents. Here we present the findings of studies involving regional volumes, activations, and interconnectivities in the context of suicide attempt.

Gray and white matter.

Of particular interest in the aetiology of suicide is the distribution of gray and white matter in brain. Gray matter refers to neural cell bodies and dendrites, while the white matter includes myelinated axons. Myelination improves the efficiency of signal transduction in brain and involves the cooperation of glial cells, which fine-tune neural connections and are recently being shown, in contrast to past presumption, to both directly and indirectly participate in the process of signal transduction, albeit not electrically. Over the typical course of childhood and adolescence the volume of gray matter in brain contracts, concomitant with an expansion in white matter tracts (Groeschel et al., 2010). The developmental reduction in gray matter volume is thought to be associated with the process of synaptic pruning, wherein less relevant or adaptive neural connections are eschewed in the interest of greater efficiency of signal transmission (Giedd et al., 1999). In studies conducted on the brain of adults who have died by suicide, it has been found that there exist white matter alterations in depressed suicide, specifically the presence in the white matter of hypertrophic astrocytes (Torres-Platas et al., 2011).

While imaging methodologies are not precise enough to detect molecular structural changes within white matter as accomplished in this post mortem study, structural and diffusion tensor studies have charted the relationship between white matter and gray matter in adolescents with suicide attempt. Johnston et al. (2017) studied gray and white matter volumes in brain of youth with bipolar disorder (38% past suicide attempt). They found that suicide attempters showed decreased gray matter volumes in right orbitofrontal cortex, right hippocampus, and bilateral cerebellum. They also observed decreased fractional anisotropy, a measure of white matter structural integrity, in the left uncinate fasciculus (a frontolimbic long-range white matter tract; Von Der Heide et al., 2013) and the right cerebellum. Fan and colleagues (2019) recruited a sample comprised of youth with both bipolar disorder and major depression and identified common gray and white matter disturbance in cases of past suicide attempt (48% of the sample) without interaction between suicide attempt status and diagnosis, suggesting a distinct pathophysiology to suicide over and above the neurobiology of diagnosed mood disorder. Specifically, they found that in left ventral prefrontal cortex Brodmann area 11, gray matter volume was decreased in suicide attempters. Fronto-limbic fractional anisotropy in the region including the uncinate fasciculus was lower in attempters than non-attempters, consistent with the study by Johnston et al. The uncinate fasciculus may be especially important in suicide attempt due to its involvement in emotional processing (Von Der Heide et al., 2013).

Another focus of study has been the white matter hyperintensity. The hyperintensity is a point of dense signal on the image within white matter and has been conceptualized as a lesion in the white matter (although possible in gray matter as well) related to impaired vascular function (Wardlaw et al., 2015). Of note, studies in adults and also animal models have related deficits in neurovascular integrity to mood alteration, and the blood brain barrier has been shown to be

disrupted in cases of depression and completed suicide, supporting a neuroinflammatory contribution to their respective pathophysiologies (Dudek et al., 2020; Pandey et al., 2013). In a 2004 study of child and adolescent psychiatric inpatients (28% lifetime suicide attempt), Ehrlich and colleagues found that white matter hyperintensities associated with increased likelihood of past suicide attempt only in patients with unipolar depression. It is interesting to note, as the authors found in this study, that hyperintensities increased with age (in line with a cerebrovascular conceptualization); in two follow up studies this team found that the relationship between white matter hyperintensity and suicide attempt was consistent in young adults and older patients, suggesting that these vascular alterations may hold promise as a biomarker of suicide attempt (although these samples were retrospective; Ehrlich et al., 2005; Pompili et al., 2007).

Regional volumes and cortical thickness.

In studies of regional volumes alterations Pan et al. (2015) found lower right superior temporal gyrus cortical volume in depressed adolescents with suicide attempt compared to healthy controls and no corresponding relationship for depressed adolescents without suicide attempt. In a later study McLellan et al. (2018) corroborated these results, finding that adolescents with treatment-resistant depression and suicide attempt history had smaller right superior temporal gyrus volumes than healthy controls, and similarly to the 2015 study, this relationship did not exist between adolescents with treatment-resistant depression but no suicide attempt history and healthy controls.

An interesting study by Fradkin et al. (2017) examined the relationship between cortical thickness and trait impulsivity in suicide attempters with MDD compared to healthy controls. While this study did not include a MDD/no attempt group, rendering it difficult to tease apart the distinct contributions of major depression and suicidality, the results are noteworthy and warrant further study: for some regions such as the middle frontal gyrus the relationship between cortical thickness and trait impulsivity differed in directionality based on group type. This notion of a fundamentally different interplay across levels of analysis between groups captures the complexity of interacting systems and should be followed up with further questions about the coordination (or lack of) between levels of body as a probe of suicide attempt.

Regional activations.

It is likely that if suicide attempt reflects differential response patterning to environmental stimulus (e.g. more severe interpretation of threat) then there exist certain regional activation tendencies which may indicate attempt risk. Suicide attempters may demonstrate higher or lower activity in certain brain regions which in turn correspond to suicidal behaviours and cognitions Neural activity in the context of experimental measurement may be either task dependent (evoked) or task independent (resting). Both approaches provide information on how brain responds to environment, and common neurobiological pathways likely exist across the two when considering suicide attempt risk.

In a 2016 study Cao et al. examined the amplitude of low-frequency fluctuation (z-scored as zALFF for analyses), a measure of spontaneous neural activity, in depressed youth with and without suicide attempt. They found that compared to non-attempters, suicide attempters showed

higher spontaneous activity in the right superior temporal gyrus, left middle temporal gyrus, and left middle occipital gyrus; and decreased activity in the left superior frontal gyrus and the left middle frontal gyrus. Of special note here is that the right superior temporal gyrus (rSTG) was identified in the prior section in two studies as structurally distinct between suicide attempters and non-attempters. The rSTG is implicated in language processing and also social perceptions. While it is tantalizing to speculate that this social role might be importantly altered in cases of suicide attempt based on psychological studies identifying social factors (Batty et al., 2018) as important risk and protective processes, there is clearly more research needed here to explore the potential for the rSTG's involvement in suicide.

In an emotional face task, Pan et al. (2013) found that compared to non-attempters, suicide attempters shown 50% angry faces exhibited greater activity in dorsal anterior cingulate gyrus, bilateral primary sensory cortices, left dorsolateral prefrontal cortex, and the right middle temporal gyrus.

The findings from these two studies are interesting yet present many individual regions of interest. Connectivities studies offer an opportunity to study the interactions between multiple regions as an insight to attempt risk.

Connectivities.

Connectivities provide insight to the coordination of neural activity across brain. While individual activations are important to understanding the elements of brain response and have been shown to predict behavior across various domains of psychology, connectonomics has

emerged as a promising frontier for better understanding (dis)integration across brain as a marker of psychopathology.

In a 2020 study Cao et al. employed independent components analysis to study resting functional network connectivities in depressed, young suicide attempters and non-attempters. They found that suicide attempters showed decreased internetwork functional connectivity between the default mode network (implicated in rest and self-knowledge) and the salience network (associated with emotion and detection and orientation to stimulus), and increased connectivity between the salience network and the right frontoparietal network, which is involved in executive control (Mark & Dosenbach, 2018; Seeley; 2019).

Johnson et al. (2017) found impaired amygdala prefrontal cortex connectivity in suicide attempters compared to non attempters in a bipolar sample, suggesting deficits in the interplay between higher-order cognitive processes and emotional salience (i.e., emotion dysregulation). Pan et al. (2013) observed that in attempters connectivity between the anterior cingulate and the insula was reduced, supporting the consensus that suicide attempt may uniquely involve difficulties in regulating emotion.

Stange et al. (2020) compared mood disordered lifetime suicide attempters, mood disordered lifetime suicide ideators with no lifetime attempt, mood disordered non ideators and non attempters, and also healthy controls on resting state functional connectivities. They observed attempt specific alterations within the cognitive control network and between the cognitive control network and the salience network, as well as between the cognitive control network and the default mode network. It is tempting to speculate that differences in cognitive control (which includes the dorsal attention and fronto-parietal networks) interconnections may

be associated with impulsivity or cognitive constriction, although these hypotheses must be tested in future research.

Alarcon et al. (2019) employed a paradigm of self face processing to evaluate whether self evaluation is important in suicide attempt. During the task they found that suicide attempters as well as high ideators showed greater amygdala functional connectivity with dorsolateral prefrontal cortex, dorsomedial prefrontal cortex, and precuneus compared to low ideators, who showed higher connectivity than healthy controls, suggesting a stepwise mechanism from suicidal thoughts to behaviours (but see May & Klonsky, 2016 for a critique of the epidemiological usefulness of combining thoughts and behaviors). Suicide attempters also uniquely showed higher connecitivity between left amygdala and rostral anterior cingulate cortex; given that independently rostral anterior cingulate activation was blunted in attempters, the authors suggest that this increase in connectivity is compensatory for a deficit in emotion regulatory capability.

Blood biomarkers.

Serum chemical levels may be important biomarkers of attempt risk. While non-invasive and direct access to brain chemical levels *in vivo* is generally limited at this time, substances in the blood may affect neural activity by travel across the blood brain barrier or alternatively, reflect genetic and epigenetic effects that are conserved across cells. Few studies have been conducted on serum chemical levels in youth with suicide attempt.

Studies which have not focused exclusively on youth have generally found that lower serum cholesterol is associated with increased risk of suicide attempt. However, as cholesterol is

known to vary with age (Kit et al., 2012), it remains unclear whether this effect holds within youth. Cholesterol participates in the signal transmission process in brain and has shown to interact with neurochemicals (Bjorkhem & Meaney, 2004).

Only one study was found which directly evaluated cholesterol levels in youth (mean age 22). Zhao et al. (2020) found that suicide attempters with MDD compared to non attempters with MDD exhibited higher total cholesterol and low density lipoprotein cholesterol, and lower high density lipoprotein cholesterol. The team also found that attempters had higher blood pressure and fasting blood glucose. The former could be related to various competing factors including stress, and the latter may suggest that neuronal glucose metabolism is impaired in suicide attempt. Of course, results from one study are insufficient to draw any strong conclusions. The relationship between cholesterol and suicide attempt, while well characterized in adult samples, merits further research in the context of development.

Another serum chemical of interest is oxytocin, which is involved in social interaction (Jones et al., 2017). Oxytocin has potential as a transdiagnostic marker of psychopathology, as it is found to be altered across phenotype clusters including autism and anxiety. (Leppanen et al., 2017; Yamasue & Domes, 2018). In fact, oxytocin may be an ideal target biomarker for suicide based on parallel psychological findings on the importance of social supports in suicide risk (see Van Orden et al., 2010 for an interpersonal theory on suicide). Research on oxytocin and suicide irregardless of age is limited, although studies on adults (Lee et al., 2009; Joken et al., 2012; Jahangard et al., 2020) suggest that suicidal behavior associates with lower serum and CSF oxytocin. The nature of social interaction changes with age, and adolescents and young adults are generally more sensitive to social nuance including peer rejection (Steinberg & Morris, 2001). In fact, recent studies have indicated that oxytocin circulation is age-specific (Elabd et al., 2014).

We found no studies comparing absolute levels of oxytocin between youth attempters and non-attempters. However, in a study on oxytocin change to social exclusion using the Cyberball paradigm, Chu et al. (2020) found that unextracted oxytocin levels decreased in depressed young adults with a suicide attempt history, but not for depressed patients or healthy controls. It appears in this case that suicide attempters may be more physiologically sensitive to social rejection. Interestingly, attempters' self-reported desire for emotional support did not change with the exclusion, while that of healthy controls did, suggesting a possible discoordination between levels of the social system. However, these results have not yet been replicated and further studies on the role of oxytocin in suicide are warranted.

Molecular biological risk probes.

Genes certainly play a role in explaining variability in behavior, in conjunction with lived experience. The interactions between gene and environment are well captured by epigenetics, the study of non-sequence level changes to the activity of the genome. Here we describe novel advances in understanding the genetics of suicide attempt in youth. While DNA sequence is generally stable with age and may stably confer risk, gene expression is known to vary as a function of age and experience. Included within this section are studies which encapsulate the central dogma of molecular biology, i.e. any unit of analysis from gene (DNA) to RNA (mRNA), and protein where measured; as such this section includes post-mortem studies on adolescent suicides, which provide greater access to molecular targets in brain.

It is of note that to our knowledge the literature is sparse on the molecular genetics of suicide attempt in young people (and also in adults). The reader will note that aside from there

being few studies available, findings are not particularly convergent. Clearly this is an area of critical importance for further research, and new genetic techniques such as GWAS may clarify the relationship between genetics and suicidal behaviour.

Variation in the organization of nucleotides at the level of the DNA leads to variation of protein environment within body, which acts on neurobiological targets to influence behavior. The risk conferred by 'suicide genes' is distal in nature and of small effect size given that life experience fine-tunes the protein landscape by epigenomic modification (Andriessen & Videtic-Paska, 2015). Despite this relatively small effect, an understanding of the genes which predispose youth to suicide attempt is vital as it could help identify those best served by a preventive approach as well inform the development of novel treatments.

Genes may confer risk for a particular age group but not others (Cadoni & De Luca, 2019), supporting a developmental approach. Behaviour genetics studies have found that familial relation does appear to increase suicide attempt risk independently of major psychiatric disorder (Brent et al., 1996). These studies provide the foundation for molecular genetic forays into understanding the specific differences that might be implicated in suicide attempt.

In the broader psychiatric genetic literature studies have typically employed candidate gene approaches, whole-genome analyses, and complex gene by environment (GxE) interactions assessments. In our search we mainly identified studies which evaluated polymorphisms in *a priori* candidate genes. There is a lack of GxE studies which are especially informative with respect to the developmental process. There is also limited research on the epigenome in youth suicide attempters, such as dynamic change in DNA methylation and microRNA levels.

While broadening of the search window to encapsulate all ages would certainly return a larger quantity of more methodologically diverse genetic studies (although the field of

psychiatric genetics is certainly young), we find it important here, in line with the objective of this review, to only focus on those studies conducted in young people, in line with our approach to suicide as a phenomenon especially sensitive to the developmental context. Candidate gene findings have shown to be especially difficult to replicate (Bosker et al., 2010; Marigorna et al., 2018), indicating that the context (e.g., developmental timing) may be important in understanding the interplay between genes and environment.

Serotonin.

Perhaps no set of genes has been more closely studied in the context of suicide than those involved in the regulation of 5-hydroxytryptamine (serotonin), a neurotransmitter involved in many neurobiological processes but most notably here in mood. Serotonergic neural projections are widespread in brain which relates to its diverse functions (Charnay & Leger, 2010). Genes involved in serotonergic signaling include receptor genes (the 5-HTn families), transporter genes (e.g., polymorphic region 5-HTTLPR), and synthesis-related genes (e.g., tryptophan hydroxylase). Serotonin modulating drugs such as the selective serotonin reuptake inhibitors, which prolong the availability of serotonin at the synapse, improve symptoms of depression and anxiety, suggesting that disturbances in serotonin levels might anticipate depressive or suicidal episodes, although it is difficult to tease apart depression and suicide as outcomes (Locher et al., 2017).

In studies not focused on youth, it has been found that some serotonergic genes do vary with suicidal behaviour (Antypa et al., 2013; Fanelli et al., 2019). However, distribution and density of various components of the serotonergic symptom do appear to normatively vary with

age (Morgan, 1987) as the molecular geography of brain regions continues to develop across the lifespan, thus it is critical to focus on youth rather than extrapolating developmentally sensitive information from samples of broader age ranges.

Few studies have explicitly focused on serotonergic function in suicide attempting youth. One case-control study (hospitalized suicide attempters vs. healthy controls) of twelve candidate single nucleotide polymorphisms (SNPs; selected based on prior literature findings) in French adolescents found that none of the differences survived corrections (Mirkovic et al., 2017), although there was a trend at p=0.09 for difference in variant rs7305115 of the tryptophan hydroxylase 2 (TPH2) gene, which had previously been validated in adult samples (Zhang et al., 2010). A family based association study of Ashkenazi Jewish adolescent suicide attempters found no evidence for a relation between 5-HT2a polymorphism T102C and suicidal behavior (Zalsman et al., 2005). Another more recent family association study of 5-HT2a by a separate team explored both the main effects of 5-HT2a polymorphisms on suicide attempt and also complex GxE interactions (Ben-Efraim et al., 2013). They found that variants rs6310 and rs 6305 were associated with suicide attempt in the total sample, and also that there was an interaction between rs6313 and lifetime stress.

In a post mortem study on teenage suicide victims Pandey et al. (2002) identified higher levels of 5-HT(2A) receptor, protein, and mRNA expression in the prefrontal cortex and hippocampus of suicide decedents compared to controls. As this study involved post mortem tissue it is unclear what the mechanism driving the increased 5-HT(2a) receptor number for suicide victims consists of. It does appear that there is some signal with respect to 5-HT2a and these results should be validated with GWAS in youth samples.

Stress response.

Life stress and physiological stress response have been implicated in youth suicide attempt (Steingberg & Mann, 2020). At the organismal level the hypothalamic-pituitary-adrenal (HPA) axis has been studied as a transdiagnostic marker for psychopathology. The HPA axis mobilizes body in response to external threat by triggering a complex mechanism which culminates in the release of hormone cortisol, which enters cells and evokes a variety of adaptive responses including increased glucose metabolism (Smith & Vale, 2006). While activation of the HPA axis may be adaptive in stress response chronic stress which overactivates this system can result in allostatic load which involves neurotoxic outcomes in brain and subsequent dysregulation of the physiological stress response (McEwen, 2005).

Melhem et al. (2016) found that young adult suicide attempters who experienced an experimental stressor (Trier Social Stress Test; Kirschbaum et al., 1993) showed lower total cortisol output during the task and lower cortisol at baseline compared to suicidal and non-suicidal non-attempters as well as healthy controls. Eisenlohr Mouhl et al. (2018) found that blunted cortisol response *prospectively* predicted future suicidal behavior (attempt or interrupted attempt) after 18 months in adolescent females even after controlling for ideation, depressive symptoms, and past suicidal behavior history. Interestingly, they also found that increased peer stress elevated suicide attempt risk only for those subjects who at the first measurement showed blunted cortisol responses.

Thus it appears that HPA axis blunting may serve as a predictive biomarker for suicide attempt risk, and that it specifically may act as a diathesis which lowers the threshold for suicide attempt, such that environmental stressors are more damaging.

Post-mortem studies have corroborated that youth suicide involves alterations in stress response. Pandey et al. (2019) found region specific alterations in corticotropin releasing factor (CRF) mRNA and receptors in teenage suicide brain. In another study Pandey et al. (2013) studied glucorticoid receptor GR-α and found decreased protein and gene expression in prefrontal cortex and amygdala of teenagers who died by suicide. Interestingly in both post mortem studies no differences were observed for hippocampus.

Integrations across units of analysis.

Here we briefly summarize common themes observed across biological units of analysis when considering youth suicide attempt.

Emotion.

Neuroimaging studies have revealed that important structural and functional alterations observed in young suicide attempters compared to non attempters occur in brain regions and networks associated with emotional processing including the uncinate fasciculus, anterior cingulate, salience network, amygdala, and insula.

It is likely that the observed disturbances in serotonergic function may contribute to some of these organizational differences downstream. It would be interesting to further study the biology of suicide attempt with respect to emotion in analyses which assess both molecular biology (e.g. serotonin) and higher order neural organization concurrently to better understand the nature of these relationships.

Cognitive control.

Several brain networks involved in cognitive control and impulsivity were observed to be altered in cases of suicide attempt. Interestingly, serotonin has been associated with impulsivity (Dalley & Roiser, 2012), and it is possible that dysregulation of the stress response system may also be associated with cognitive constriction.

Social support.

Right superior temporal gyrus emerged in multiple studies as a marker of suicide attempt. The rSTG, as described above, has been implicated in social perception. It is well understood that suicide attempt risk is associated with degree of social support. The described findings on oxytocin, a neuropeptide involved in social function, support the idea that at the biological level impaired social function may act as a risk factor for suicide attempt. In the context of stress response it was found that social stressors (peer distress) interacted with cortisol blunting to predict suicide attempt.

The small number of studies which assessed social support and impairment while including biological measures renders it difficult to derive any meaningful conclusions, however it is clear that further studies on the social brain and oxytocin could yield fruitful results for understanding at the biological level the well characterized role of lack of social support as a risk factor for suicide attempt.

Conclusions.

In this review we summarized the literature on biological markers of suicide attempt in young people. It is evident that the available research on this topic is limited, although common themes of emotion, cognitive control, and social function, do emerge across units of analysis. Consideration of development is critical to advancing the understanding of suicide biology.

References.

Alarcón, G., Sauder, M., Teoh, J. Y., Forbes, E. E., & Quevedo, K. (2019). Amygdala Functional Connectivity During Self-Face Processing in Depressed Adolescents With Recent Suicide Attempt. *Journal of the American Academy of Child and Adolescent Psychiatry*, *58*(2), 221–231. https://doi.org/10.1016/j.jaac.2018.06.036

Andriessen, K., & Videtic-Paska, A. (2015). Genetic vulnerability as a distal risk factor for suicidal behaviour: Historical perspective and current knowledge. *Zdravstveno Varstvo*, *54*(3), 238–251. https://doi.org/10.1515/sjph-2015-0026

Antypa, N., Serretti, A., & Rujescu, D. (2013). Serotonergic genes and suicide: A systematic review. *European Neuropsychopharmacology*, *23*(10), 1125–1142. https://doi.org/10.1016/j.euroneuro.2013.03.013

Batty, G. D., Kivimäki, M., Bell, S., Gale, C. R., Shipley, M., Whitley, E., & Gunnell, D. (2018). Psychosocial characteristics as potential predictors of suicide in adults: An overview of the evidence with new results from prospective cohort studies /692/699 /631/477/2811 review-article. *Translational Psychiatry*, *8*(1), 22–22. https://doi.org/10.1038/s41398-017-0072-8

Ben-Efraim, Y. J., Wasserman, D., Wasserman, J., & Sokolowski, M. (2013). Family-based study of HTR2A in suicide attempts: Observed gene, gene × environment and parent-of-origin associations. *Molecular Psychiatry*, *18*(7), 758–766. https://doi.org/10.1038/mp.2012.86

Björkhem, I., Meaney, S., & Fogelman, A. M. (2004). Brain Cholesterol: Long Secret Life behind a Barrier. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *24*(5), 806–815. https://doi.org/10.1161/01.ATV.0000120374.59826.1b

Bosker, F. J., Hartman, C. A., Nolte, I. M., Prins, B. P., Terpstra, P., Posthuma, D., Van Veen, T., Willemsen, G., Derijk, R. H., De Geus, E. J., Hoogendijk, W. J., Sullivan, P. F., Penninx, B. W., Boomsma, D. I., Snieder, H., & Nolen, W. A. (2011). Poor replication of candidate genes for major depressive disorder using genome-wide association data. *Molecular Psychiatry*, *16*(5), 516–532. https://doi.org/10.1038/mp.2010.38

Brent, D. A., Bridge, J., Johnson, B. A., & Connolly, J. (1996). Suicidal behavior runs in families: A controlled family study of adolescent suicide victims. *Archives of General Psychiatry*, *53*(12), 1145–1152. https://doi.org/10.1001/archpsyc.1996.01830120085015

Cadoni, C., & De Luca, M. A. (2019). Editorial: Deconstructing the influence of genetic and age vulnerability to psychiatric disorders. *Frontiers in Psychiatry*, *10*(JAN). https://doi.org/10.3389/fpsyt.2019.00013

Cao, J., Ai, M., Chen, X., Chen, J., Wang, W., & Kuang, L. (2020). Altered resting-state functional network connectivity is associated with suicide attempt in young depressed patients. *Psychiatry Research*, *285*. https://doi.org/10.1016/j.psychres.2019.112713

Cao, J., Chen, X., Chen, J., Ai, M., Gan, Y., Wang, W., Lv, Z., Zhang, S., Zhang, S., Wang, S., Kuang, L., & Fang, W. (2016). Resting-state functional MRI of abnormal baseline brain activity in young depressed patients with and without suicidal behavior. *Journal of Affective Disorders*, *205*, 252–263. https://doi.org/10.1016/j.jad.2016.07.002

Carroll, M. D., Lacher, D. A., Sorlie, P. D., Cleeman, J. I., Gordon, D. J., Wolz, M., Grundy, S. M., & Johnson, C. L. (2005). Trends in serum lipids and lipoproteins of adults, 1960-2002. *Journal of the American Medical Association*, *294*(14), 1773–1781. https://doi.org/10.1001/jama.294.14.1773

Charnay, Y., & Leger, L. (2010). Brain serotonergic circuitries. *Dialogues in Clinical Neuroscience*, *12*(4), 471–487. https://doi.org/10.31887/dcns.2010.12.4/ycharnay

Chu, C., Hammock, E. A. D., & Joiner, T. E. (2020). Unextracted plasma oxytocin levels decrease following in-laboratory social exclusion in young adults with a suicide attempt history. *Journal of Psychiatric Research*, *121*, 173–181. https://doi.org/10.1016/j.jpsychires.2019.11.015

Dalley, J. W., & Roiser, J. P. (2012). Dopamine, serotonin and impulsivity. *Neuroscience*, *215*, 42–58. https://doi.org/10.1016/j.neuroscience.2012.03.065

DeJong, T. M., Overholser, J. C., & Stockmeier, C. A. (2010). Apples to oranges?: A direct comparison between suicide attempters and suicide completers. *Journal of Affective Disorders*, *124*(1–2), 90–97. https://doi.org/10.1016/j.jad.2009.10.020

Dudek, K. A., Dion-Albert, L., Lebel, M., LeClair, K., Labrecque, S., Tuck, E., Perez, C. F., Golden, S. A., Tamminga, C., Turecki, G., Mechawar, N., Russo, S. J., & Menard, C. (2020). Molecular adaptations of the blood–brain barrier promote stress resilience vs. Depression. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(6), 3326–3336. https://doi.org/10.1073/pnas.1914655117

Ehrlich, S., Breeze, J. L., Hesdorffer, D. C., Noam, G. G., Hong, X., Alban, R. L., Davis, S. E., & Renshaw, P. F. (2005). White matter hyperintensities and their association with

suicidality in depressed young adults. *Journal of Affective Disorders*, *86*(2–3), 281–287. https://doi.org/10.1016/j.jad.2005.01.007

Ehrlich, S., Noam, G. G., Lyoo, I. K., Kwon, B. J., Clark, M. A., & Renshaw, P. F. (2004). White matter hyperintensities and their associations with suicidality in psychiatrically hospitalized children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*(6), 770–776. https://doi.org/10.1097/01.chi.0000120020.48166.93

Eisenlohr-Moul, T. A., Miller, A. B., Giletta, M., Hastings, P. D., Rudolph, K. D., Nock, M. K., & Prinstein, M. J. (2018). HPA axis response and psychosocial stress as interactive predictors of suicidal ideation and behavior in adolescent females: A multilevel diathesis-stress framework. *Neuropsychopharmacology*, *43*(13), 2564–2571. https://doi.org/10.1038/s41386-018-0206-6

Elabd, C., Cousin, W., Upadhyayula, P., Chen, R. Y., Chooljian, M. S., Li, J., Kung, S., Jiang, K. P., & Conboy, I. M. (2014). Oxytocin is an age-specific circulating hormone that is necessary for muscle maintenance and regeneration. *Nature Communications*, *5*(1), 1–11. https://doi.org/10.1038/ncomms5082

Fan, S., Lippard, E. T. C., Sankar, A., Wallace, A., Johnston, J. A. Y., Wang, F., Pittman, B., Spencer, L., Oquendo, M. A., & Blumberg, H. P. (2019). Gray and white matter differences in adolescents and young adults with prior suicide attempts across bipolar and major depressive disorders. *Journal of Affective Disorders*, *245*, 1089–1097. https://doi.org/10.1016/j.jad.2018.11.095

Fan, T., Wu, X., Yao, L., & Dong, J. (2013). Abnormal baseline brain activity in suicidal and non-suicidal patients with major depressive disorder. *Neuroscience Letters*, *534*(1), 35–40. https://doi.org/10.1016/j.neulet.2012.11.032

Fanelli, G., & Serretti, A. (2019). The influence of the serotonin transporter gene 5-HTTLPR polymorphism on suicidal behaviors: A meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *88*, 375–387. https://doi.org/10.1016/j.pnpbp.2018.08.007

Fradkin, Y., Khadka, S., Bessette, K. L., & Stevens, M. C. (2017). The relationship of impulsivity and cortical thickness in depressed and non-depressed adolescents. *Brain Imaging and Behavior*, *11*(5), 1515–1525. https://doi.org/10.1007/s11682-016-9612-8

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Liu, H., Zijdenbos, A., Paus, T., Evans, A. C., & Rapoport, J. L. (1999). Brain development during childhood and adolescence: A longitudinal MRI study [2]. *Nature Neuroscience*, *2*(10), 861–863. https://doi.org/10.1038/13158

Glenn, C. R., Kleiman, E. M., Cha, C. B., Deming, C. A., Franklin, J. C., & Nock, M. K. (2018). Understanding suicide risk within the Research Domain Criteria (RDoC) framework: A meta-analytic review. *Depression and Anxiety*, *35*(1), 65–88. https://doi.org/10.1002/da.22686

Groeschel, S., Vollmer, B., King, M. D., & Connelly, A. (2010). Developmental changes in cerebral grey and white matter volume from infancy to adulthood. *International Journal of Developmental Neuroscience*, *28*(6), 481–489. https://doi.org/10.1016/j.ijdevneu.2010.06.004

Hedegaard, H., Curtin, S. C., & Warner, M. (2018). Suicide Mortality in the United States, 1999-2017. *NCHS Data Brief*, *330*, 1–8.

Jahangard, L., Shayganfard, M., Ghiasi, F., Salehi, I., Haghighi, M., Ahmadpanah, M., Sadeghi Bahmani, D., & Brand, S. (2020). Serum oxytocin concentrations in current and recent suicide survivors are lower than in healthy controls. *Journal of Psychiatric Research*, *128*, 75–82. https://doi.org/10.1016/j.jpsychires.2020.05.014

Johnston, J. A. Y., Wang, F., Liu, J., Blond, B. N., Wallace, A., Liu, J., Spencer, L., Lippard, E. T. C., Purves, K. L., Landeros-Weisenberger, A., Hermes, E., Pittman, B., Zhang, S., King, R., Martin, A., Oquendo, M. A., & Blumberg, H. P. (2017). Multimodal neuroimaging of frontolimbic structure and function associated with suicide attempts in adolescents and young adults with bipolar disorder. *American Journal of Psychiatry*, *174*(7), 667–675. https://doi.org/10.1176/appi.ajp.2016.15050652

Jokinen, J., Chatzittofis, A., Hellström, C., Nordström, P., Uvnäs-Moberg, K., & Åsberg, M. (2012). Low CSF oxytocin reflects high intent in suicide attempters. *Psychoneuroendocrinology*, *37*(4), 482–490. https://doi.org/10.1016/j.psyneuen.2011.07.016

Joo, S. H., Wang, S. M., Kim, T. W., Seo, H. J., Jeong, J. H., Han, J. H., & Hong, S. C. (2016). Factors associated with suicide completion: A comparison between suicide attempters and completers. *Asia-Pacific Psychiatry*, *8*(1), 80–86. https://doi.org/10.1111/appy.12216

Kirschbaum, C., Pirke, K. M., & Hellhammer, D. H. (1993). *The 'Trier social stress test'—A tool for investigating psychobiological stress responses in a laboratory setting*. *28*(1–2), 76–81. https://doi.org/10.1159/000119004

Kit, B. K., Carroll, M. D., Lacher, D. A., Sorlie, P. D., DeJesus, J. M., & Ogden, C. L. (2012). Trends in serum lipids among US youths aged 6 to 19 years, 1988-2010. *JAMA - Journal of the American Medical Association*, *308*(6), 591–600. https://doi.org/10.1001/jama.2012.9136

Klimes-Dougan, B. (1998). Screening for suicidal ideation in children and adolescents: Methodological considerations. *Journal of Adolescence*, *21*(4), 435–444. https://doi.org/10.1006/jado.1998.0166

Large, M., Kaneson, M., Myles, N., Myles, H., Gunaratne, P., & Ryan, C. (2016). Meta-Analysis of Longitudinal Cohort Studies of Suicide Risk Assessment among Psychiatric Patients: Heterogeneity in Results and Lack of Improvement over Time. *PLOS ONE*, *11*(6), e0156322–e0156322. https://doi.org/10.1371/journal.pone.0156322

Lengvenyte, A., Conejero, I., Courtet, P., & Olié, E. (2021). Biological bases of suicidal behaviours: A narrative review. *European Journal of Neuroscience*, *53*(1), 330–351. https://doi.org/10.1111/ejn.14635

Leppanen, J., Ng, K. W., Kim, Y. R., Tchanturia, K., & Treasure, J. (2018). Meta-analytic review of the effects of a single dose of intranasal oxytocin on threat processing in humans. *Journal of Affective Disorders*, *225*, 167–179. https://doi.org/10.1016/j.jad.2017.08.041

Lester, D., & Beck, A. T. (1974). AGE DIFFERENCES IN PATTERNS OF ATTEMPTED SUICIDE'. *OMEGA*, *5*(4). https://doi.org/10.2190/9LL1-CN7Q-Q4XP-L628

Locher, C., Koechlin, H., Zion, S. R., Werner, C., Pine, D. S., Kirsch, I., Kessler, R. C., & Kossowsky, J. (2017). Efficacy and safety of selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and placebo for common psychiatric

disorders among children and adolescents: A systematic review and meta-analysis. *JAMA Psychiatry*, *74*(10), 1011–1020. https://doi.org/10.1001/jamapsychiatry.2017.2432

Marigorta, U. M., Rodríguez, J. A., Gibson, G., & Navarro, A. (2018). Replicability and Prediction: Lessons and Challenges from GWAS. *Trends in Genetics*, *34*(7), 504–517. https://doi.org/10.1016/j.tig.2018.03.005

May, A. M., & Klonsky, E. D. (2016). What Distinguishes Suicide Attempters From Suicide Ideators? A Meta-Analysis of Potential Factors. *Clinical Psychology: Science and Practice*, *23*(1), 5–20. https://doi.org/10.1111/cpsp.12136

McEwen, B. S. (2005). *Stressed or stressed out: What is the difference? 30*(5), 315–318. /pmc/articles/PMC1197275/

McLellan, Q., Wilkes, T. C., Swansburg, R., Jaworska, N., Langevin, L. M., & MacMaster, F. P. (2018). History of suicide attempt and right superior temporal gyrus volume in youth with treatment-resistant major depressive disorder. *Journal of Affective Disorders*, *239*, 291–294. https://doi.org/10.1016/j.jad.2018.07.030

Melhem, N. M., Keilp, J. G., Porta, G., Oquendo, M. A., Burke, A., Stanley, B., Cooper, T. B., Mann, J. J., & Brent, D. A. (2016). Blunted HPA Axis Activity in Suicide Attempters Compared to those at High Risk for Suicidal Behavior. *Neuropsychopharmacology*, *41*(6), 1447–1456. https://doi.org/10.1038/npp.2015.309

Mirkovic, B., Cohen, D., Laurent, C., Lasfar, M., Marguet, C., & Gerardin, P. (2020). A case-control association study of 12 candidate genes and attempted suicide in French adolescents. *International Journal of Adolescent Medicine and Health*, *32*(1). https://doi.org/10.1515/ijamh-2017-0089

Morgan, D. G., May, P. C., & Finch, C. E. (1987). Dopamine and Serotonin Systems in Human and Rodent Brain: Effects of Age and Neurodegenerative Disease. *Journal of the American Geriatrics Society*, *35*(4), 334–345. https://doi.org/10.1111/j.1532-5415.1987.tb04641.x

Morgan, E. R., Rowhani-Rahbar, A., Azrael, D., & Miller, M. (2018). Public Perceptions of Firearm- and Non–Firearm-Related Violent Death in the United States: A National Study. *Annals of Internal Medicine*, *169*(10), 734–734. https://doi.org/10.7326/M18-1533

Oquendo, M. A., & Mann, J. J. (2008). Suicidal Behavior: A Developmental Perspective. *Psychiatric Clinics of North America*, *31*(2), xiii–xiii. https://doi.org/10.1016/j.psc.2008.03.001

Pan, L. A., Hassel, S., Segreti, A. M., Nau, S. A., Brent, D. A., & Phillips, M. L. (2013). Differential patterns of activity and functional connectivity in emotion processing neural circuitry to angry and happy faces in adolescents with and without suicide attempt. *Psychological Medicine*, *43*(10), 2129–2142. https://doi.org/10.1017/S0033291712002966

Pan, Lisa A., Ramos, L., Segreti, A. M., Brent, D. A., & Phillips, M. L. (2015). Right superior temporal gyrus volume in adolescents with a history of suicide attempt. *British Journal of Psychiatry*, *206*(4), 339–340. https://doi.org/10.1192/bjp.bp.114.151316

Pandey, G. N. (2013). Biological basis of suicide and suicidal behavior. *Bipolar Disorders*, *15*(5), 524–541. https://doi.org/10.1111/bdi.12089

Pandey, G. N., Dwivedi, Y., Rizavi, H. S., Ren, X., Pandey, S. C., Pesold, C., Roberts, R. C., Conley, R. R., & Tamminga, C. A. (2002). Higher expression of serotonin 5-HT2A

receptors in the postmortem brains of teenage suicide victims. *American Journal of Psychiatry*, *159*(3), 419–429. https://doi.org/10.1176/appi.ajp.159.3.419

Pandey, G. N., Rizavi, H. S., Bhaumik, R., & Ren, X. (2019). Increased protein and mRNA expression of corticotropin-releasing factor (CRF), decreased CRF receptors and CRF binding protein in specific postmortem brain areas of teenage suicide subjects. *Psychoneuroendocrinology*, *106*, 233–243. https://doi.org/10.1016/j.psyneuen.2019.04.015

Pandey, G. N., Rizavi, H. S., Ren, X., Fareed, J., Hoppensteadt, D. A., Roberts, R. C., Conley, R. R., & Dwivedi, Y. (2012). Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *Journal of Psychiatric Research*, *46*(1), 57–63. https://doi.org/10.1016/j.jpsychires.2011.08.006

Pompili, M., Ehrlich, S., De Pisa, E., Mann, J. J., Innamorati, M., Cittadini, A., Montagna, B., Iliceto, P., Romano, A., Amore, M., Tatarelli, R., & Girardi, P. (2007). White matter hyperintensities and their associations with suicidality in patients with major affective disorders. *European Archives of Psychiatry and Clinical Neuroscience*, *257*(8), 494–499. https://doi.org/10.1007/s00406-007-0755-x

Ryan, E. P., & Oquendo, M. A. (2020). Suicide Risk Assessment and Prevention: Challenges and Opportunities. *FOCUS*, *18*(2), 88–99. https://doi.org/10.1176/appi.focus.20200011

Seeley, W. W. (2019). The Salience Network: A Neural System for Perceiving and Responding to Homeostatic Demands. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *39*(50), 9878–9882. https://doi.org/10.1523/JNEUROSCI.1138-17.2019

Smith, S. M., & Vale, W. W. (2006). The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues in Clinical Neuroscience*, *8*(4), 383–395. https://doi.org/10.31887/dcns.2006.8.4/ssmith

Stange, J. P., Jenkins, L. M., Pocius, S., Kreutzer, K., Bessette, K. L., Deldonno, S. R., Kling, L. R., Bhaumik, R., Welsh, R. C., Keilp, J. G., Phan, K. L., & Langenecker, S. A. (2020). Using resting-state intrinsic network connectivity to identify suicide risk in mood disorders. *Psychological Medicine*, *50*(14), 2324–2334. https://doi.org/10.1017/S0033291719002356

Steinberg, L. J., & Mann, J. J. (2020). Abnormal stress responsiveness and suicidal behavior: A risk phenotype. *Biomarkers in Neuropsychiatry*, *2*, 100011–100011. https://doi.org/10.1016/j.bionps.2020.100011

Steinberg, L., & Morris, A. S. (2001). Adolescent Development. *Annual Review of Psychology*, *52*(1), 83–110. https://doi.org/10.1146/annurev.psych.52.1.83

Torres-Platas, S. G., Hercher, C., Davoli, M. A., Maussion, G., Labonté, B., Turecki, G., & Mechawar, N. (2011). Astrocytic hypertrophy in anterior cingulate white matter of depressed suicides. *Neuropsychopharmacology*, *36*(13), 2650–2658. https://doi.org/10.1038/npp.2011.154

Turecki, G. (2014). The molecular bases of the suicidal brain. *Nature Reviews Neuroscience*, *15*(12), 802–816. https://doi.org/10.1038/nrn3839

Van Orden, K. A., Witte, T. K., Cukrowicz, K. C., Braithwaite, S. R., Selby, E. A., & Joiner, T. E. (2010). The Interpersonal Theory of Suicide. *Psychological Review*, *117*(2), 575–600. https://doi.org/10.1037/a0018697

Von Der Heide, R. J., Skipper, L. M., Klobusicky, E., & Olson, I. R. (2013). Dissecting the uncinate fasciculus: Disorders, controversies and a hypothesis. *Brain*, *136*(6), 1692–1707. https://doi.org/10.1093/brain/awt094

Wardlaw, J. M., Valdés Hernández, M. C., & Muñoz-Maniega, S. (2015a). What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *Journal of the American Heart Association*, *4*(6), 001140–001140. https://doi.org/10.1161/JAHA.114.001140

Wardlaw, J. M., Valdés Hernández, M. C., & Muñoz-Maniega, S. (2015b). What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. *Journal of the American Heart Association*, *4*(6), 001140–001140. https://doi.org/10.1161/JAHA.114.001140

Zalsman, G., Frisch, A., Baruch-Movshovits, R., Sher, L., Michaelovsky, E., King, R. A., Fischel, T., Hermesh, H., Goldberg, P., Gorlyn, M., Misgav, S., Apter, A., Tyano, S., & Weizman, A. (2005). Family-based association study of 5-HT2A receptor T102C polymorphism and suicidal behavior in Ashkenazi inpatient adolescents. *International Journal of Adolescent Medicine and Health*, *17*(3), 231–238. https://doi.org/10.1515/IJAMH.2005.17.3.231

Zhang, Y., Zhang, C., Yuan, G., Yao, J., Cheng, Z., Liu, C., Liu, Q., Wan, G., Shi, G., Cheng, Y., Ling, Y., & Li, K. (2010). Effect of Tryptophan Hydroxylase-2 rs7305115 SNP on suicide attempts risk in major depression. *Behavioral and Brain Functions*, *6*(1), 49–49. https://doi.org/10.1186/1744-9081-6-49

Zhao, K., Zhou, S., Shi, X., Chen, J., Zhang, Y., Fan, K., Zhang, X., Wang, W., & Tang, W. (2020). Potential metabolic monitoring indicators of suicide attempts in first episode

and drug naive young patients with major depressive disorder: A cross-sectional study. *BMC Psychiatry*, *20*(1), 387–387. https://doi.org/10.1186/s12888-020-02791-x