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A postmortem study

Zhang, L.

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CHAPTER 10

GENERAL DISCUSSION

Suicide is conceptualized as having three stages with increasing graveness: suicidal ideations, suicide attempts, and completed suicide. On a range from moderate to severe, the former two can be further divided into a temporary ideation/single attempt and intense ideations/repeated attempts (Klonsky et al., 2016). Suicide and its catalysts, i.e., neuropsychiatric disorders, have a series of symptoms that affect people socially, occupationally, educationally and interpersonally. Recently, pharmacological and physiological studies found that the anti-suicidal effects of ketamine on patients with treatment-resistant depression were associated with acute reductions in the functional connectivity of their prefrontal cortex-related circuits, involving the ACC, DLPFC and superior parietal regions (Chen et al., 2019). Therefore, one of the main goals of neurobiological research in this field is to understand the molecular, cellular, and neurocircuitry alterations that underlie and distinguish the transitions from occasional to relapsing and intense suicidal ideations, and from single to control-losing suicidal behaviors. For many, treatment with medications for opioid use disorder is associated with a substantial reduction in suicide mortality (Watts et al., 2022). The increasing stages of suicidal severity, together with these opioid-based, anti-suicidal effects have prompted the hypothesis that the molecular background of suicide may at least to some extent, overlap with addictive disorders (Williams et al., 2019).

Studies to clarify the neurobiology of suicide have progressed through the research of the human brain, both by antemortem neuroimaging and postmortem neuropathological studies. More specifically, neuroimaging is highly valuable to identify brain regions responsive to stress stimuli, and allow subsequent neurobiological investigations including genetic, epigenetic, transcriptional, translational approaches, and neural networking reconstructions. Understanding the neurobiological mechanisms underlying the two stages of suicidality, suicidal ideations and suicide attempts, can respectively reveal the specific neurocircuits involved in either suicidal thoughts or suicide acts, and can, in turn, provide novel ideas for suicide prevention. Therefore, we first summarize here the neuroimaging data in relation to suicidal ideations and attempts separately, which lays the basis for the rest of our General Discussion.

Neurocircuitry of suicidal ideations

The range of suicidal ideations varies from temporary thoughts to detailed planning. The major risk factors for suicidal ideations consist of several elements, such as psychiatric disorders, adverse life events and family history (Barry, 2019). We focus here on the findings in the human brains specifically associated with suicidal thoughts, irrespective of these underlying factors.

Volumetric measurement is the first step to study the association between the onset of suicide tendencies and vulnerable brain domains. There is a large amount of evidence showing that the cortical circuits are critically involved in suicidal ideations. Compared to non-psychiatric controls, patients with suicidal thoughts display decreased gray matter volumes in the orbital-frontal-precentral-parietal circuits and the insula (Drachman et al., 2022; Segreti et al., 2019; Taylor et al., 2015). Correspondingly, functional constructs implicated in these brain regions,

such as executive control, stress regulation, and emotional processing were also affected. Studies have subsequently shown that the white matter integrity in cortical regions and their connections with subcortical limbic structures, such as the basal ganglia and thalamus, was also decreased in relation to the intensity of suicidal ideations (Davey et al., 2021; Fan et al., 2019; Myung et al., 2016; Taylor et al., 2015), suggesting that the cognitive control over incentive salience and habits might have been compromised (Upadhyay et al., 2022). These findings were specific to the presence of suicidal thoughts, independent of the psychiatric status of the subjects.

In the second place, resting-state functional connectivity (rsFC), in individuals with suicidal ideations, shows decreases in global connectivity across the cortico-striato-thalamic loops (Du et al., 2017; Kim et al., 2017). Of note, although volumetric and structural alterations associated with suicidal ideations have not been reported in the habenula, its connectivity to emotion- and reward-processing circuits (e.g., habenula-precuneus and -inferior frontal gyrus) were found to decrease in patients with suicidal ideations, compared to those without suicidal thoughts (Qiao et al., 2020), with notably, the reduction being positively correlated with the frequency of suicidal thoughts (Wills et al., 2020). However, a significant increase in resting-state involving the connection between the precuneus and amygdala, was found only in females with first-episode MDD and suicidal ideation, suggesting that the gender-biased neural correlates of self-centered mental dominance and aggression might be enhanced in the early stage of suicidality (Cavanna and Trimble, 2006; Wei et al., 2018).

Alterations in task-based functional connectivity of suicide ideators are task-dependent. Under conflict- and self-monitoring conditions, a higher activation occurred in the anterior cingulate cortex (ACC) and related circuitry in individuals at risk for suicidal thoughts, which was strongly associated with their suicidal intensity (Matthews et al., 2012; Minzenberg et al., 2015a; Minzenberg et al., 2016; Minzenberg et al., 2015c). On the other hand, past suicidal ideations were associated with a lower activation in the prefrontal cortex-based circuit under goal-representation demands (Minzenberg et al., 2014).

Neurocircuitry of suicide attempts

Compared to suicidal ideations, volumetric reductions have been found in subcortical regions in individuals with suicidal behaviors. For example, in addition to cortical areas, decreased gray matter thickness has been shown in their functionally connected subcortical areas, such as the amygdala, hippocampus, basal ganglia, and thalamus in people with previous suicide attempts (Giakoumatos et al., 2013; Kang et al., 2020; Wang et al., 2020). Among suicide attempters, a history of high lethality behaviors was associated with extensively diminished gray matter in the major components of the temporal lobe, such as the temporal gyrus, parahippocampal gyrus, and fusiform gyrus, together with adjacent regions, e.g., the inferior frontal orbital gyrus, insula, caudate, lingual gyrus and cuneus (Giakoumatos et al., 2013; Huber et al., 2019; Soloff et al., 2012; Yang et al., 2020).

In patients with suicide attempts, increases in functional connectivity, as determined by resting-state fMRI, involves the activation of a multi-centered orbitofrontal cortex-precuneus-paracingulate reward circuit (Dimick et al., 2022). This psychobiological framework is of special relevance for the suicide-addiction comorbid nature. In non-drug addictions, such as pathological gambling, the activation of the orbitofrontal cortex was involved in craving-induced dopamine release and its D2 receptor-associated reductions in glucose metabolism (Koob and Volkow, 2016), and similar increases hold for the precuneus and paracingulate gyrus (Liu, 2010; Tarumov et al., 2019). Among these three hubs, the orbitofrontal cortex of suicide attempters had a higher connectivity with the dorsomedial prefrontal cortex and middle frontal gyrus compared to non-suicidal individuals (Chen et al., 2021). The connections between the precuneus and the supraorbital middle frontal gyrus and inferior parietal lobe were higher in suicide attempters than non-attempters among non-psychiatric youths (Cao et al., 2015). Moreover, its functional connectivity to the amygdala was higher in mood disorder patients with suicidal behaviors than in those with suicidal thoughts only (Zhang et al., 2021b). In patients with post-traumatic stress disorder, functional connectivity of the paracingulate gyrus to the pars orbitalis positively correlated with suicidality (Barredo et al., 2019). Of note, the neural connectivity of the habenula-parahippocampus circuit in individuals with suicidal behaviors was elevated compared to the healthy controls (Ambrosi et al., 2019). Additionally, the strength of the network between the abovementioned sensory cortex and striatum has been suggested to predict suicide-related behaviors (Marchand et al., 2012).

On the other hand, a prefrontal cortex-centered reduction in connectivity, suggestive of a loss of cognitive control, occurs in emotion-encoding circuits in suicide. For example, MDD patients with a history of suicidal behaviors had diminished functional connectivity between the ventral and medial prefrontal cortex and amygdala, compared to the controls and patients without attempts (Wang et al., 2020). Young suicide attempters showed decreased connectivity of the middle frontal gyrus with the superior parietal gyrus and anterior cingulate cortex compared to non-suicide attempters (Jun et al., 2021).

Task-based functional connectivity studies have demonstrated increases in decision-making and executive functions but decreases in reward-processing and cognitive control in association with suicide acts. During the Iowa Gambling Task that assesses decision-making, adolescents with suicide attempts and depression had a better performance than non-attempters with depression and the controls, involving a neural activation of the hippocampus, frontal and temporal cortical, striatal and thalamic regions (Pan et al., 2013). During Stroop task performance, higher activity was found in the frontal motor cortex to be associated with past suicidal behaviors (Minzenberg et al., 2015b). The activity of the motor cortex with its connection to the striatum is regarded a trait marker of suicide-related behaviors (Marchand et al., 2012).

On the other hand, suicide-attempting adolescents could be distinguished from their non-attempting counterparts by a blunted reward circuitry responsivity in the bilateral caudate

nucleus during negatively valenced self-processing (Quevedo et al., 2022). In contrast, in cognitive control task performance, a history of suicidal behavior was related to lower activity in midline parietal regions, including the precuneus and cuneus (Minzenberg et al., 2015c). During conflict-monitoring tasks, past suicidal behavior was associated with lower conflict-related anterior cingulate cortex, and in connectivity with multiple lateral and medial prefrontal, parietal and temporal cortical regions (Minzenberg et al., 2015a). However, in the ventrolateral and rostrolateral prefrontal cortex, frontal operculum, and insula, past suicidal behavior was associated with higher control-related activation (Minzenberg et al., 2015c). In individuals with long-term suicide risk who performed a goal-representation task, reported suicidal behavior was associated with lower control-related activation in the premotor cortex ipsilateral to the active primary motor cortex (Minzenberg et al., 2014).

Based on the above findings, structural and functional profiles of suicidal ideations and suicide attempts show considerable variance, suggesting that molecular fingerprints of these two processes may also differ. As a result, we carefully grouped the data for analysis in this thesis, with each category having a distinct relevance.

The originality of legal euthanasia brain samples in suicide research

As reviewed above, it is necessary to study suicide through every stage of the entire process. Therefore, a novelty of our current research is the introduction of brain samples from donors who died by legal euthanasia. There are three points of innovation: First, the applicants were driven by intense and persistent suicidal thoughts derived from incurable physical or/and psychiatric diseases. Second, studying the neuroimaging abnormalities involved in the neurocircuits associated with these strong and intense suicidal thoughts can discover hub brain regions with considerable relevance for the vulnerability, maintenance, and relapse associated with fatal suicidality. Therefore, in contrast to non-psychiatric or non-suicidal controls, we propose to investigate the neuroimaging profiles that map the neurocircuits in people with or without a psychiatric disease, who ultimately died by legal euthanasia. With these neural networks, one can observe the hubs and their functional connectivities in relation to strong and intense suicidal tendencies. Third, neuropathological alterations underlying legal euthanasia can imitate completed suicide but provide a short and precise postmortem interval against the postmortem decay of key molecules. In previous chapters, we demonstrated unique molecular features that were related to fatal suicidality by studying hypothalamic and hippocampal samples of individuals who died by legal euthanasia.

Neurobiological mechanisms of suicide

Neuroimaging studies have displayed differences in the pattern of dysfunctional features over the course of suicide processes. The divergent manifestations in structural and functional connectivity were shown in particular brain regions, especially the DLPFC, ACC and hippocampus. Although

these results reflect the differences between suicidal thoughts and suicidal acts, these studies did not provide information concerning the follow-up or prognosis in their analysis. On the other hand, neuropathological studies have so far mostly reported molecular or cellular findings from postmortem tissue of completed suicide cases. These changes can (partly) be independent of the underlying psychiatric disorders and take place in various anatomical structures, as illustrated in this thesis.

First of all, we found that completed suicide went together with distinct transcriptional alterations in the PFC relative to psychiatric disorders. Previous studies in our group have proposed two patterns of suicide-associated alterations in MDD (Zhao et al., 2015; Zhao et al., 2018; Zhao et al., 2016). One showed that suicide-associated alterations were presented while MDD-related changes were absent, compared to non-psychiatric controls. This was for example the case with an increased expression of glutamate- and gamma-aminobutyric acid (GABA)-related genes in the ACC. The other pattern was that alterations of the same genes in association with MDD and suicide, were both present, but they changed in opposite ways, especially in the dorsolateral prefrontal cortex (DLPFC). Interestingly, our former data did not report stress-related genes that showed elevations in suicide in addition to an increase in MDD. This supported the view that the molecular fingerprints of suicide might be distinct from MDD in the prefrontal areas.

In this thesis, and in addition to MDD, bipolar disorder (BD) and schizophrenia (SCZ) were added as conditions to our research cohorts (Zhang et al., 2020a, b; Zhang et al., 2021a). We addressed the expression of glial genes in the PFC and found that the majority of detected genes were not activated in suicide, except for the genes that reflected microglial phagocytosis (*CD68*) and neuronal monitoring (*P2RY12*). In addition, the altered microglia expression of different phenotypes has demonstrated that psychiatric disorders share specific pathogenic mechanisms in the prefrontal cortex, such as dopaminergic activation (*ALDH1L1*) and metabolic dysregulation of glutamate (*GS*) in MDD and SCZ, and synaptic pruning deficiency (*TREM2*) in BD and SCZ.

Second, the human brain samples from the NBB (hypothalami and hippocampi) have allowed us to further analyze the concept of “fatal suicidality” in non-psychiatric controls and MD patients. We, surprisingly, found that the infundibular nucleus (INF) was a hypothalamic nucleus sensitive to suicide and MD in terms of different molecular patterns. Another important finding in these materials was that we confirmed the participation of the endogenous opioid system in suicide. This was shown by the dramatic increase of POMC neurons in the INF of MD patients who had completed suicide. Large sample epidemiological studies have emphasized that repeated suicide attempts, underlying psychiatric disorders and substance use disorders are the highest risk factors for attempting suicide (Fazel and Runeson, 2020). Repeated attempts are critically connected to suicidal fatality. Among the first-time suicide attempters, approximately 30% repeat suicidal behaviors. The proportion of completed suicides in individuals with repeated attempts is 500 to 1000 times higher than in the general public (Harvard, 2021). This repeatability

of suicidal behaviors is the basis for the hypothesis, that a similar mechanism may be involved as present in addictive disorders. Also, medications for opioid use disorder were found associated with a substantial reduction in suicide mortality (Watts et al., 2022). The relationship between fatal suicidality and an activation of the opioid system activation in MD has additionally been confirmed by the increase of a subgroup of POMC-neurons that co-expressed progesterone receptors in the legal euthanasia subset. Epidemiological studies have further shown that the influence of progesterone on neural systems is related to the risk for suicide (Ho et al., 2022). Our data indicate that the POMC neurons may be involved in this mechanism.

Third, with increased sample sizes and detailed psychiatric records, more observations can be performed on the molecular differences between suicidal ideations and suicide attempts, and on suicidal severity (single/repeated attempts). By discussing the hippocampal results in this thesis, we conclude that from non-psychiatric controls to MD and then suicide, there may be a process of cellular homeostasis (in non-psychiatric controls) that changes into an activation (in MD) and subsequently into an overactivation-apoptosis (in suicide). In the actual practice of human postmortem studies in literature, however, results were often derived only from brain samples from donors with MD who died by suicide versus non-psychiatric controls, and the conclusions often seemingly based on the interest of the investigator as being related either to suicide or MD (Zhao et al., 2019). Therefore, our grouping aims to include only one suicide-related variable in every comparison.

In the second review of this thesis, we propose that suicide can be regarded as a cognitive disorder, and suicide-associated cognitive impairments have indeed been reported to be persistent across ages (Zhang et al., 2022). It has been found that the volumetric alteration of the entorhinal cortex was linked to the development of mild cognitive impairment (López et al., 2014). Our current study showed that in the entorhinal cortex of individuals with non-fatal suicidality, a strongly positive correlation was present between age and CD68 expression, indicative of a microglia subset that typically function to clear cellular debris and promote microglial phagocytosis. We, therefore, consider the possibility that compared to individuals without suicidal thoughts, those who had pre-existing suicidality, even though it was not fatal, might present with specific cellular changes in certain brain regions that maintain throughout the lifetime.

In recent years, investigations associated with molecular pathology in suicide mostly focused on the prefrontal cortex, including the DLPFC and ACC, which no doubt are partly because of their involvement in executive functions, especially decision-making and impulse control (Bush et al., 2002; Liu et al., 2012; Philiastides et al., 2011). However, studies aimed to discover the brain areas that respond to the onset and development of suicidal thoughts, especially the thoughts that led to fatal outcomes, have not yet been published. The completion of suicide has a certain degree of randomness, which does not accurately reflect the severity of suicidality when the completers were still alive. Therefore, studies that address biomarkers

in key brain regions of suicidal ideations may identify therapeutic targets for future treatment strategies for suicide individuals before they attempt.

FUTURE RESEARCH

On the basis of the results obtained in this thesis, three projects are formulated for future research.

Endogenous opioid system and suicide

A previous history of suicide attempts, underlying psychiatric disorders, and substance use disorders represent the highest risk factors for subsequent suicide attempts (Fazel and Runeson, 2020). Repeated suicidal behaviors are critically connected to suicidal fatality. The repetition of suicidal behaviors is the basis for the hypothesis, that a similar mechanism may be involved as in relapses of addictive disorders. In addition, treatment with medications for opioid use disorder has been found associated with a substantial reduction in suicide mortality (Watts et al., 2022). Thus, addressing the molecular features of neural networks that specifically respond to suicidality, mental disorders and addiction is imperative for an early prevention of suicide acts. Our next step of work is to profile the expression of key molecules in the endogenous opioid system in suicide-related brain areas and to observe whether the opioid activity is associated with MD, suicide tendencies and accomplished suicide.

The neurobiological independence of suicide

Neurobiological alterations in key brain areas are decisive features that distinguish suicide from comorbid psychiatric disorders. Comparing the molecular fingerprints of suicide with or without underlying psychiatric disorder may therefore provide specific or/and shared treatments for these two psychiatric aspects. Our current findings have identified brain regions that are sensitive to fatal suicidality in both depression patients and non-psychiatric controls, as well as regions that are only sensitive in psychiatric patients. Therefore, the next stage of our research will be to find differences or similarities in suicide-specific changes in these brain regions between patients with psychiatric disorder and controls. We hope that by understanding the neurobiological independence of suicide, we may be able to provide new generation treatments for the suicidal populations with or without psychiatric disorders, and for the suicidal populations with or without psychiatric diagnosis.

Sex differences in bipolar disorder

Gender differences penetrate every aspect of BD, from epidemiology, onset and development, clinical symptoms and cognitive flexibility to neuroimaging and biological data, comorbidity,

treatments, and prognosis. It is a clinical consensus that sex is a major factor in influencing treatment outcomes for BD (Altshuler et al., 2010). However, it is poorly understood which key brain areas show neurobiological evidence of sex differences. To the best of our knowledge, the gender differences we reported in glial expression in the DLPFC disclosed the first human brain region that had clear sexual dimorphisms in BD (Zhang et al., 2020b). In the first review of this thesis, the complex interactions are summarized between gender and clinical manifestations in BD, in as much as they are implicated in the prefrontal regions, as well as in cognitive functions integrated in emotion- and reward-related regulations. In addition, there is substantial overlap in gender-biased alterations of the primary and secondary symptoms of BD, which may share neurobiological portraits and even magnify the differences. As a next step, we will focus on the biological hallmarks that display sex-specific changes in the DLPFC of BD and try to discover new therapeutic targets for BD treatments.

REFERENCES

- Altshuler, L.L., Kupka, R.W., Helleman, G., Frye, M.A., Sugar, C.A., McElroy, S.L., Nolen, W.A., Grunze, H., Leverich, G.S., Keck, P.E., 2010. Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the Stanley Foundation bipolar treatment outcome network. *American Journal of Psychiatry* 167, 708-715.
- Ambrosi, E., Arciniegas, D.B., Curtis, K.N., Patriquin, M.A., Spalletta, G., Sani, G., Frueh, B.C., Fowler, J.C., Madan, A., Salas, R., 2019. Resting-state functional connectivity of the habenula in mood disorder patients with and without suicide-related behaviors. *The Journal of neuropsychiatry and clinical neurosciences* 31, 49-56.
- Barredo, J., Aiken, E., van't Wout-Frank, M., Greenberg, B.D., Carpenter, L.L., Philip, N.S., 2019. Neuroimaging correlates of suicidality in decision-making circuits in posttraumatic stress disorder. *Frontiers in psychiatry* 10, 44.
- Barry, L.C., 2019. Passive suicidal ideation in older adults: Implications for suicide prevention. *The American Journal of Geriatric Psychiatry* 27, 1411-1413.
- Bush, G., Vogt, B.A., Holmes, J., Dale, A.M., Greve, D., Jenike, M.A., Rosen, B.R., 2002. Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proceedings of the National Academy of Sciences* 99, 523-528.
- Cao, J., Chen, J.-m., Kuang, L., Ai, M., Fang, W.-d., Gan, Y., Wang, W., Chen, X.-r., Xu, X.-m., Wang, H.-g., 2015. Abnormal regional homogeneity in young adult suicide attempters with no diagnosable psychiatric disorder: a resting state functional magnetic imaging study. *Psychiatry Research: Neuroimaging* 231, 95-102.
- Cavanna, A.E., Trimble, M.R., 2006. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129, 564-583.
- Chen, M.-H., Lin, W.-C., Tu, P.-C., Li, C.-T., Bai, Y.-M., Tsai, S.-J., Su, T.-P., 2019. Antidepressant and antisuicidal effects of ketamine on the functional connectivity of prefrontal cortex-related circuits in treatment-resistant depression: a double-blind, placebo-controlled, randomized, longitudinal resting fMRI study. *Journal of affective disorders* 259, 15-20.
- Chen, Z., Xia, M., Zhao, Y., Kuang, W., Jia, Z., Gong, Q., 2021. Characteristics of intrinsic brain functional connectivity alterations in major depressive disorder patients with suicide behavior. *Journal of Magnetic Resonance Imaging* 54, 1867-1875.
- Davey, D.K., Jurick, S.M., Crocker, L.D., Hoffman, S.N., Sanderson-Cimino, M., Tate, D.F., Velez, C.S., Delano-Wood, L., Jak, A.J., 2021. White matter integrity, suicidal ideation, and cognitive dysfunction in combat-exposed Iraq and Afghanistan Veterans. *Psychiatry Research: Neuroimaging* 317, 111389.
- Dimick, M.K., Hird, M.A., Sultan, A.A., Mitchell, R.H., Sinyor, M., MacIntosh, B.J., Goldstein, B.I., 2022. Resting-state functional connectivity indicators of risk and resilience for self-harm in adolescent bipolar disorder. *Psychological medicine*, 1-10.
- Drachman, R., Colic, L., Sankar, A., Spencer, L., Goldman, D.A., Villa, L.M., Kim, J.A., Oquendo, M.A., Pittman, B., Blumberg, H.P., 2022. Rethinking "Aggression" and Impulsivity in Bipolar Disorder: Risk, Clinical and Brain Circuitry Features. *Journal of affective disorders*.

- Du, L., Zeng, J., Liu, H., Tang, D., Meng, H., Li, Y., Fu, Y., 2017. Fronto-limbic disconnection in depressed patients with suicidal ideation: a resting-state functional connectivity study. *Journal of affective disorders* 215, 213-217.
- Fan, S., Lippard, E.T., Sankar, A., Wallace, A., Johnston, J.A., 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.
- Fazel, S., Runeson, B., 2020. Suicide. *N Engl J Med* 382, 266-274.
- Giakoumatos, C.I., Tandon, N., Shah, J., Mathew, I.T., Brady, R.O., Clementz, B.A., Pearlson, G.D., Thaker, G.K., Tamminga, C.A., Sweeney, J.A., 2013. Are structural brain abnormalities associated with suicidal behavior in patients with psychotic disorders? *Journal of psychiatric research* 47, 1389-1395.
- Harvard, 2021. Attempters' Longterm Survival.
- Ho, T.C., Gifuni, A.J., Gotlib, I.H., 2022. Psychobiological risk factors for suicidal thoughts and behaviors in adolescence: a consideration of the role of puberty. *Molecular psychiatry* 27, 606-623.
- Huber, R.S., Subramaniam, P., Kondo, D.G., Shi, X., Renshaw, P.F., Yurgelun-Todd, D.A., 2019. Reduced lateral orbitofrontal cortex volume and suicide behavior in youth with bipolar disorder. *Bipolar Disorders* 21, 321-329.
- Jun, C., Xiaorong, C., Jianmei, C., Ming, A., Yao, G., Jinglan, H., Li, K., 2021. The association between resting state functional connectivity and the trait of impulsivity and suicidal ideation in young depressed patients with suicide attempts. *Frontiers in psychiatry*, 1292.
- Kang, W., Shin, J.H., Han, K.M., Kim, A., Kang, Y., Kang, J., Tae, W.S., Paik, J.W., Lee, H.W., Seong, J.K., 2020. Local shape volume alterations in subcortical structures of suicide attempters with major depressive disorder. *Human brain mapping* 41, 4925-4934.
- Kim, K., Kim, S.-W., Myung, W., Han, C.E., Fava, M., Mischoulon, D., Papakostas, G.I., Seo, S.W., Cho, H., Seong, J.-K., 2017. Reduced orbitofrontal-thalamic functional connectivity related to suicidal ideation in patients with major depressive disorder. *Scientific reports* 7, 1-11.
- Klonsky, E.D., May, A.M., Saffer, B.Y., 2016. Suicide, suicide attempts, and suicidal ideation. *Annual review of clinical psychology* 12, 307-330.
- Koob, G.F., Volkow, N.D., 2016. Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry* 3, 760-773.
- Liu, J., 2010. Increased regional homogeneity in internet addiction disorder: a resting state functional magnetic resonance imaging study. *Chinese medical journal* 123, 1904-1908.
- Liu, J., Zubieta, J.-K., Heitzeg, M., 2012. Sex differences in anterior cingulate cortex activation during impulse inhibition and behavioral correlates. *Psychiatry Research: Neuroimaging* 201, 54-62.
- López, M.E., Bruna, R., Aurtenetxe, S., Pineda-Pardo, J.Á., Marcos, A., Arrazola, J., Reinoso, A.I., Montejo, P., Bajo, R., Maestú, F., 2014. Alpha-band hypersynchronization in progressive mild cognitive impairment: a magnetoencephalography study. *Journal of Neuroscience* 34, 14551-14559.
- Marchand, W.R., Lee, J.N., Johnson, S., Thatcher, J., Gale, P., Wood, N., Jeong, E.-K., 2012. Striatal and cortical midline circuits in major depression: implications for suicide and symptom expression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 36, 290-299.

- Matthews, S.C., Spadoni, A.D., Lohr, J.B., Strigo, I.A., Simmons, A.N., 2012. Combat-exposed war veterans at risk for suicide show hyperactivation of prefrontal cortex and anterior cingulate during error processing. *Psychosomatic medicine* 74, 471.
- Minzenberg, M.J., Lesh, T., Niendam, T., Yoon, J.H., Cheng, Y., Rhoades, R., Carter, C.S., 2015a. Conflict-related anterior cingulate functional connectivity is associated with past suicidal ideation and behavior in recent-onset schizophrenia. *Journal of Psychiatric Research* 65, 95-101.
- Minzenberg, M.J., Lesh, T., Niendam, T., Yoon, J.H., Cheng, Y., Rhoades, R.N., Carter, C.S., 2015b. Frontal motor cortex activity during reactive control is associated with past suicidal behavior in recent-onset schizophrenia. *Crisis*.
- Minzenberg, M.J., Lesh, T.A., Niendam, T.A., Cheng, Y., Carter, C.S., 2016. Conflict-related anterior cingulate functional connectivity is associated with past suicidal ideation and behavior in recent-onset psychotic major mood disorders. *The Journal of neuropsychiatry and clinical neurosciences* 28, 299-305.
- Minzenberg, M.J., Lesh, T.A., Niendam, T.A., Yoon, J.H., Cheng, Y., Rhoades, R.N., Carter, C.S., 2015c. Control-related frontal-striatal function is associated with past suicidal ideation and behavior in patients with recent-onset psychotic major mood disorders. *Journal of affective disorders* 188, 202-209.
- Minzenberg, M.J., Lesh, T.A., Niendam, T.A., Yoon, J.H., Rhoades, R.N., Carter, C.S., 2014. Frontal cortex control dysfunction related to long-term suicide risk in recent-onset schizophrenia. *Schizophrenia research* 157, 19-25.
- Myung, W., Han, C., Fava, M., Mischoulon, D., Papakostas, G., Heo, J., Kim, K., Kim, S., Kim, D., Kim, D., 2016. Reduced frontal-subcortical white matter connectivity in association with suicidal ideation in major depressive disorder. *Translational psychiatry* 6, e835-e835.
- Pan, L., Segreti, A., Almeida, J., Jollant, F., Lawrence, N., Brent, D., Phillips, M., 2013. Preserved hippocampal function during learning in the context of risk in adolescent suicide attempt. *Psychiatry Research: Neuroimaging* 211, 112-118.
- Philiastides, M.G., Auzsztulewicz, R., Heekeren, H.R., Blankenburg, F., 2011. Causal role of dorsolateral prefrontal cortex in human perceptual decision making. *Current biology* 21, 980-983.
- Qiao, D., Zhang, A., Sun, N., Yang, C., Li, J., Zhao, T., Wang, Y., Xu, Y., Wen, Y., Zhang, K., 2020. Altered static and dynamic functional connectivity of habenula associated with suicidal ideation in first-episode, drug-naïve patients with major depressive disorder. *Frontiers in psychiatry*, 1439.
- Quevedo, K., Teoh, J.Y., Liu, G., Santana-Gonzalez, C., Forbes, E.E., Engstrom, M., 2022. Neural substrates of rewarding and punishing self representations in depressed suicide-attempting adolescents. *Journal of Psychiatric Research*.
- Segreti, A.M., Chase, H.W., Just, M., Brent, D., Pan, L., 2019. Cortical thickness and volume reductions in young adults with current suicidal ideation. *Journal of affective disorders* 245, 126-129.
- Soloff, P.H., Pruitt, P., Sharma, M., Radwan, J., White, R., Diwadkar, V.A., 2012. Structural brain abnormalities and suicidal behavior in borderline personality disorder. *Journal of psychiatric research* 46, 516-525.
- Tarumov, D., Trufanov, A., Chakchir, O., Abdulaev, S., Partsernyak, A., Efimtsev, A., Bystrova, D., Kurasov, E., Shamrey, V., Zhelezniak, I., 2019. Possibilities of Resting State Functional Magnetic Resonance Imaging in the Assessment of the Functional State of the Brain in Patients with Opioid Addiction. *Journal of Psychiatry and Psychiatric Disorders* 3, 168-178.

- Taylor, W.D., Boyd, B., McQuoid, D.R., Kudra, K., Saleh, A., MacFall, J.R., 2015. Widespread white matter but focal gray matter alterations in depressed individuals with thoughts of death. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 62, 22-28.
- Upadhyay, J., Verrico, C.D., Cay, M., Kodele, S., Yammine, L., Koob, G.F., Schreiber, R., 2022. Neurocircuitry basis of the opioid use disorder–post-traumatic stress disorder comorbid state: conceptual analyses using a dimensional framework. *The Lancet Psychiatry* 9, 84-96.
- Wang, L., Zhao, Y., Edmiston, E.K., Womer, F.Y., Zhang, R., Zhao, P., Jiang, X., Wu, F., Kong, L., Zhou, Y., 2020. Structural and functional abnormalities of amygdala and prefrontal cortex in major depressive disorder with suicide attempts. *Frontiers in psychiatry*, 923.
- Watts, B.V., Gottlieb, D.J., Riblet, N.B., Gui, J., Shiner, B., 2022. Association of medication treatment for opioid use disorder with suicide mortality. *American journal of psychiatry* 179, 298-304.
- Wei, S., Chang, M., Zhang, R., Jiang, X., Wang, F., Tang, Y., 2018. Amygdala functional connectivity in female patients with major depressive disorder with and without suicidal ideation. *Annals of General Psychiatry* 17, 1-7.
- Williams, N.R., Heifets, B.D., Bentzley, B.S., Blasey, C., Sudheimer, K.D., Hawkins, J., Lyons, D.M., Schatzberg, A.F., 2019. Attenuation of antidepressant and antisuicidal effects of ketamine by opioid receptor antagonism. *Molecular psychiatry* 24, 1779-1786.
- Wills, K.E., Gosnell, S.N., Curtis, K.N., Velasquez, K., Fowler, J.C., Salas, R., 2020. Altered habenula to locus coeruleus functional connectivity in past anorexia nervosa suggests correlation with suicidality: a pilot study. *Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity* 25, 1475-1480.
- Yang, Y., Chattun, M.R., Yan, R., Zhao, K., Chen, Y., Zhu, R., Shi, J., Wang, X., Lu, Q., Yao, Z., 2020. Atrophy of right inferior frontal orbital gyrus and frontoparietal functional connectivity abnormality in depressed suicide attempters. *Brain Imaging Behav.* 14, 2542-2552.
- Zhang, L., Lucassen, P.J., Salta, E., Verhaert, P.D., Swaab, D., 2022. Hippocampal neuropathology in suicide: Gaps in our knowledge and opportunities for a breakthrough. *Neurosci. Biobehav. Rev.* 132, 542-552.
- Zhang, L., Verwer, R.W., Lucassen, P.J., Huitinga, I., Swaab, D.F., 2020a. Prefrontal cortex alterations in glia gene expression in schizophrenia with and without suicide. *J. Psychiatr. Res.* 121, 31-38.
- Zhang, L., Verwer, R.W., Lucassen, P.J., Huitinga, I., Swaab, D.F., 2020b. Sex difference in glia gene expression in the dorsolateral prefrontal cortex in bipolar disorder: Relation to psychotic features. *J. Psychiatr. Res.* 125, 66-74.
- Zhang, L., Verwer, R.W., Zhao, J., Huitinga, I., Lucassen, P.J., Swaab, D.F., 2021a. Changes in glial gene expression in the prefrontal cortex in relation to major depressive disorder, suicide and psychotic features. *J. Affect. Disord.* 295, 893-903.
- Zhang, R., Zhang, L., Wei, S., Wang, P., Jiang, X., Tang, Y., Wang, F., 2021b. Increased amygdala-paracentral lobule/precuneus functional connectivity associated with patients with mood disorder and suicidal behavior. *Frontiers in human neuroscience*, 589.
- Zhao, J., Lucassen, P.J., Swaab, D.F., 2019. Suicide is a confounder in postmortem studies on depression. *Biol. Psychiatry* 86, e37-e40.
- Zhao, J., Qi, X.-R., Gao, S.-F., Lu, J., van Wamelen, D., Kamphuis, W., Bao, A.-M., Swaab, D., 2015. Different stress-related gene expression in depression and suicide. *Journal of psychiatric research* 68, 176-185.

Zhao, J., Verwer, R., Gao, S.-F., Qi, X.-R., Lucassen, P.J., Kessels, H., Swaab, D., 2018. Prefrontal alterations in GABAergic and glutamatergic gene expression in relation to depression and suicide. *J. Psychiatr. Res.* 102, 261-274.

Zhao, J., Verwer, R., Van Wamelen, D., Qi, X.-R., Gao, S.-F., Lucassen, P.J., Swaab, D., 2016. Prefrontal changes in the glutamate-glutamine cycle and neuronal/glial glutamate transporters in depression with and without suicide. *Journal of psychiatric research* 82, 8-15.