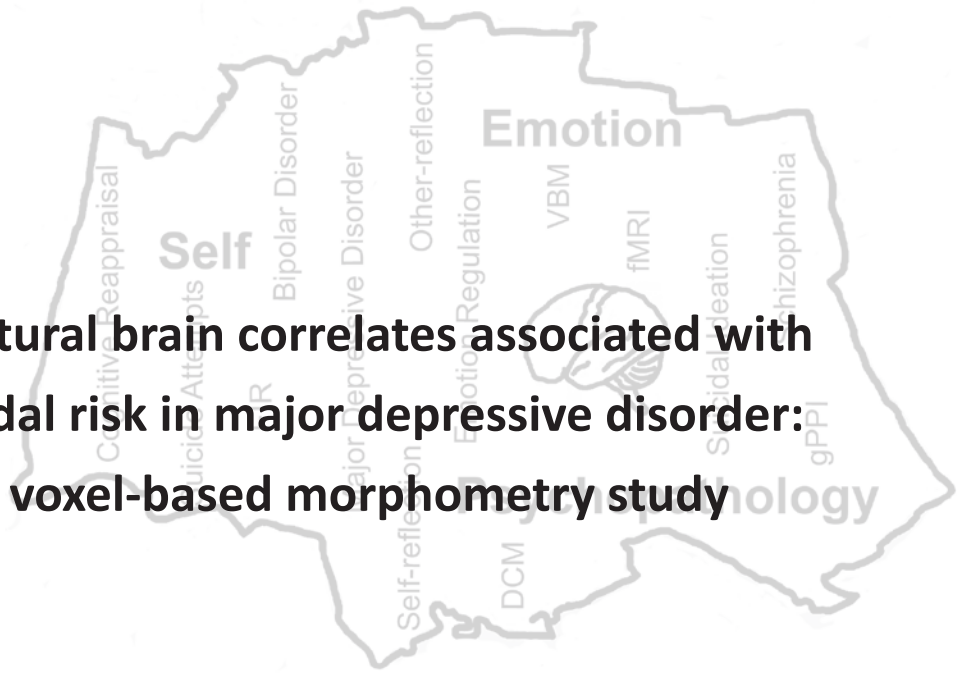
Emotion, self and psychopathology

Zhang, Liwen

CHAPTER 4



Structural brain correlates associated with suicidal risk in major depressive disorder: A voxel-based morphometry study

Liwen Zhang, Esther M. Opmeer, Henricus G. Ruhé, Nic J.A. van der Wee, Dick J. Veltman, Marie-José van Tol, André Aleman

Manuscript in preparation

Abstract

Background: Suicidal ideation (SI) and previous suicide attempts (SA) are important predictors of future suicidal risk. Investigating their structural brain correlates may enhance our understanding of the biological basis of suicidal risk and might help in finding biomarkers to aid suicide prevention.

Methods: Structural alterations were investigated using voxel-based morphometry (VBM) analysis in patients with major depressive disorder with current ideation and/or past attempts (suicidal risk patient [SRP]; n=68) or no ideation and attempts (patient controls [PC]; n=125), and matched healthy controls (HC; n=64). Effects of SI and SA (present/absent, separate dummies) on grey matter (GM) and white matter (WM) volumes were investigated using multiple regression analysis in patients only. Additionally, we compared SRP to PC and HC on GM/WM volumes (one-way ANOVA).

Results: Regression analysis demonstrated a negative association between suicidal risk (SI and SA combined) and GM volumes in the dorsolateral prefrontal cortex extending to the ventrolateral prefrontal cortex (p_{FWE}=.039), which could not be attributed to SI or SA alone. Compared to PC, SRP showed marginally smaller GM volumes in this area (p_{FWE}=.066). Effects were unaffected by severity of depression, current diagnosis of anxiety disorders, or medication use. No WM-alterations were observed.

Conclusions: Reduced lateral prefrontal volumes in SRP may represent a trait-like vulnerability. This suggests that investigating a composite effect of current SI and past SA may be more informative for future suicidal risk. Future studies might link this prefrontal structural alterations to its functioning, for instance the association with disturbed cognitive control of emotions.

Key words: Suicidal ideation; Suicide attempts; Voxel-based morphometry; Major depressive disorder

Introduction

Each year, almost one million people commit suicide (Krug et al., 2002), and the suicide rate has increased by approximately 24 percent from 1999 to 2014 (Curtin et al., 2016). Therefore, suicide prevention is important, yet challenging. It has been shown that around 90 percent of suicidal behavior occurs in people with psychiatric disorders (Harris and Barraclough, 1997), especially major depressive disorder (MDD) (Angst et al., 1999). Both suicide attempts (SA) and suicidal ideation (SI) have been found to be important risk factors for future suicide (Fawcett et al., 1990; Hawton and van Heeringen, 2009; Kessler et al., 1999), although not consistently for SI (Large et al., 2011). On the other hand, SA and SI have been found to be differential processes, for instance, the high association between psychiatric disorders and suicidal behavior is mainly driven by an association with SI instead of SA (Nock et al., 2009), and suicidal ideators with SA and those without SA show differences in experienced stressful events (McFeeters et al., 2015). Furthermore, in line with the fact that not all patients with SI would finally commit SA (Curtin et al., 2016), the transition from SI to SA seems important for suicidality (Klonsky et al., 2016). This implies that investigating risks for suicidal behavior in relation to both SI and SA may provide important but different information. To this end, the present study focused on structural mechanisms underlying suicidal processes, by investigating MDD patients with SI and/or SA and those patients without SI and SA but still having a comparable psychiatric illness.

Voxel-based morphometry (VBM) is a widely used method to investigate structural alterations (Ashburner and Friston, 2000). Previous studies of structural alterations related to suicidal behavior have focused on patients with SA. Although with few studies (n=6) and small samples (mostly fewer than 20) included, a meta-analysis of studies comparing subjects with SA versus patient controls found support for lower grey matter (GM) volumes in the rectal gyrus of the orbitofrontal cortex (OFC), temporal gyrus and caudate nucleus in suicide attempters (van Heeringen et al., 2014). Moreover, a more recent study (Ding et al., 2015) reported reduced GM volumes in the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC) and OFC in patients with mood disorders (MDD and bipolar disorder) who had a history of SA compared to healthy individuals. Most of these areas have been involved in emotion regulation (ER) (Buhle et al., 2014; Ochsner and Gross, 2005; Ochsner et al., 2012), which links these findings to the suggestion that dysfunctional ER plays an important role in suicidal behavior (Aleman and Denys, 2014; Jollant et al., 2011). However, it is unclear whether

these observed structural alterations in patients with past SA are also associated with SI, since SA would imply occurrence of earlier SI (Klonsky et al., 2016). To our best knowledge, no VBM studies have been conducted on pure effects of SI in adult patients, although effects of SI have been studied in pediatric individuals (Caplan et al., 2010).

Therefore, we aimed to investigate structural alterations specifically related to suicidal risk in MDD patients by using VBM, while controlling explicitly for psychiatric disease related effects by including a patient control group. Moreover, we explored whether there were differential structural abnormalities in relation to SI and SA. Given altered brain volumes observed in SA patients in previous studies and the importance of regions involved in ER for suicidal behavior, we expected to find lower GM volumes in those regions important for ER (e.g., prefrontal cortex) in relation to suicidal risk.

Methods

Participants

Participants were selected from the neuroimaging baseline measurement of the Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008; van Tol et al., 2010). Inclusion criteria for patients for the current analyses were: i) a life-time MDD diagnosis based on the Composite International Diagnostic Interview (CIDI, life-time version 2.1) (World Health Organization, 1997); ii) no comorbid disorders other than anxiety disorder; iii) no current use of antidepressant (AD) (in the month before inclusion) other than selective serotonin reuptake inhibitor (SSRI), venlafaxine (a serotonine noradrenaline reuptake inhibitor [SNRI]) or infrequent use of benzodiazepine (not within 48 hours prior to scanning). One hundred and ninety three MDD patients fulfilling criteria for a life-time diagnosis of MDD were included. Moreover, 64 healthy controls (HC) were included, who were required to have no current or past psychiatric disorders (confirmed by the CIDI). All participants were magnetic resonance imaging (MRI)-compatible (e.g., not pregnant or no metal implants).

Current SI was measured with the first five items of the semi-structured Scale for Suicide Ideation (SSI; (Beck et al., 1979) concerning attitudes towards living and dying. A positive score on at least one of the five SSI-items indicated presence of current SI. A history of SA was assessed with an explicit question (SA-question): “Have you ever made a serious attempt to end your life, for instance by harming or poisoning yourself or by getting into an accident?”. According to the SSI-score and

answer to the SA-question, MDD patients were categorized into two groups: i) suicidal risk patients (SRP; 'SSI>0' and/or 'QSA=yes'; n=68); ii) patient controls (PC; 'SSI=0 and QSA=no'; n=125). In the HC sample the SSI and SA-question were also administered to exclude HC with current SI or past SA.

The present study was approved by the medical ethical committees of the University Medical Center Groningen (UMCG), VU University Medical Center Amsterdam (VUMC), and Leiden University Medical Center (LUMC). All participants provided written informed consent.

Clinical assessment and measures

For patients, SSI, SA-question and current and past diagnoses of MDD and/or anxiety using the CIDI (World Health Organization, 1997) were assessed during a baseline interview that was held approximately two months before MRI-scanning. On the day of scanning, the Beck Anxiety Inventory (BAI, Beck et al., 1988) and the Montgomery-Asberg Depression Scale (MADRS, Montgomery and Asberg, 1979) were assessed to measure current severity of anxiety and depression, respectively. Of note, for comparing the groups on current severity of depression, a subtotal MADRS-score was calculated for each participant by excluding the suicide item (MADRS-total score minus score on the suicide item 10), because our patients were categorized in terms of suicidality. Assessment on current psychotherapy use (in the past six-months from baseline interview) was based on sub-items of the Trimbos/iMTA questionnaire for costs associated with psychiatric illness (TIC-P) (Hakkaart-van Roijen et al., 2002), which assesses contacts with psychologists, psychiatrists, psychotherapists or relevant institute in relation to mental problems.

Image acquisition

Structural MRI data were acquired using Philips 3T MR-scanners (Best, the Netherlands) at three locations, including Groningen, Leiden (both SENSE-8 channel head coil), and Amsterdam (SENSE-6 channel head coil). Anatomical scanning was conducted with a sagittal 3D gradient-echo T1-weighted sequence (TR=9 ms, TE=3.5 ms, matrix 256 × 256, isotropic voxel of 1 mm, slice gap=0 mm, 170 slices).

Data analysis

Demographic data

All groups were compared on age, level of education, subtotal MADRS-score, BAI-score, sex, and scanning site using one-way analyses of variance (ANOVAs) and chi-square tests where appropriate. In addition, we compared SRP to PC on these variables, as well as on current (i.e., half-year) diagnosis of MDD and/or anxiety disorder, use of psychotherapy, and medication use. For SRP, the SI severity was calculated as sum of the first five items of the SSI (range from 1 to 10), in which each item scores from 0 to 2. Higher SSI-score indicates higher SI severity.

Voxel-based morphometry

Voxel-based morphometry (VBM) analysis was performed by using statistical parametric mapping (SPM12, version 6685, www.fil.ion.ucl.ac.uk/spm) running under Matlab (R2013a; the Math Works Inc., Natick, MA). First, the origin of the structural image was manually reoriented to the anterior commissure (AC). Pre-processing for VBM analysis consisted of tissue segmentation into GM, WM, and CSF (using six prior probability maps), applying the DARTEL tools for creating a data-specific DARTEL template (based on GM, WM and CSF segments) to which all segments were subsequently normalized (for GM, WM and CSF, modulation by the Jacobian determinants was applied so that the volume of each voxel was identical before and after normalization), normalisation to Montreal Neurological Institute (MNI) space, and smoothing with a full width at half maximum (FWHM) Gaussian kernel of 8 mm. Moreover, a GM and WM mask was created to exclude non-GM/WM voxels from subsequent analyses. These optimal threshold GM and WM masks were created based on all participants using the Masking toolbox (http://www.fil.ion.ucl.ac.uk/spm/ext/#Masking).

Pre-processed data were analyzed within the framework of the general linear model (GLM). For our main purpose of investigating structural variations in relation to vulnerability to suicidal behaviour, we set up multiple regression models in patients only, with presence of SI (present/absent) and presence of SA (present/absent) as two separate dummy variables. We tested for both the pure and combined effects of SI and SA, in order to explore the unique and shared contribution of SI and SA to potential GM/WM volumes alterations in SRP. Scanning site was added as covariate (two dummies), and we corrected for brain size variations between participants by

entering brain volume (i.e., sum of GM and WM) as a global measure using proportional scaling. Whole-brain analyses were performed for both GM and WM, applying the optimal threshold GM/WM mask. We repeated these regression analyses after adding amended MADRS-score (i.e., total score minus score on suicidality item) and presence of anxiety (dummy variable) as covariates. In a subsequent step, sex (dummy variable) and medication use (SSRI and/or venlafaxine as one dummy variable) were added as covariates, to control for their potential effects on the results.

Furthermore, in order to explore the comparison with control groups, we built a one-way ANOVA model for GM and WM respectively, with group (3: SRP, PC and HC) as the independent variable. For GM, because of our a priori hypothesis that SRP have reduced regional volumes, we performed planned comparisons between SRP and PC, and between SRP and HC. Scanning site was added as covariate of no interest, and brain size variations were corrected for by modelling them as proportionally scaled globals. Whole-brain analyses were performed for both GM and WM, in which the GM and WM mask was used, respectively. We repeated these analyses by adding sex (dummy variable) and amended MADRS-score as covariates in a step-wise manner, to control for their potential confounding effects.

For all analyses, the statistical threshold was set to $p<.05$ family wise error (FWE) whole-brain corrected for multiple comparisons at the cluster-level (after correction for non-stationary of smoothness, http://fmri.wfubmc.edu/cms/software#NS), with an initial voxel-wise height threshold of $p<.001$ uncorrected. In addition, effects occurring in GM regions previously associated with SA in the meta-analysis of van Heeringen et al. (2014) (i.e., the left rectal gyrus, left superior temporal gyrus and left caudate nucleus), were reported at the same threshold ($p<.05$ FWE corrected at the cluster level), with correction for the spatial extent within these regions of interest. For this purpose, we created a binary mask based on the corresponding Automated Anatomical Labeling (AAL) labels, implemented in the WFU Pick Atlas toolbox (Tzourio-Mazoyer et al., 2002).

Results

Sample description

Two HC were excluded due to presence of SI or SA. In order to match demographics between groups and clinical variables between patient groups, 17 PC

and 12 HC were excluded. In total, there were 226 participants included in the analyses (HC, n=50; PC, n=108; SRP=68). In the SRP group, 44 patients had current SI and 34 patients had a history of SA (10 patients reported both current SI and past SA).

Groups (HC, PC and SRP) did not differ statistically on age, level of education, sex ratio, and scanning site. Patient groups had higher level of current depression and anxiety than HC. In addition, PC and SRP were comparable on all demographic and clinical variables, except for their level of depression (15.70 [PC] versus 18.72 [SRP]; p=.03). Detailed demographical and clinical information is listed in Table 1 (Table S1 also describes demographics in two sub-groups of SRP: suicidal ideators [i.e., patients with presence of SI] and suicide attempters [i.e., patients with presence of SA]).

VBM results

For the GM analysis, in the regression model in the patients with or without SI and/or SA, there was a negative association between suicidal risk (presence of SI and/or SA) and GM volumes in the right DLPFC extending to the VLPFC (Figure 1; p_{FWE}=.039, k=494, z=4.35, t=4.48, *x, y, z*=39, 45, 2), as well as in the left DLPFC extending to the VLPFC, although without reaching statistical significance (p_{FWE}=.14, k=292, z=3.65, t=3.73, *x, y, z*=-48, 38, 27). However, this relation was not uniquely driven by SI or SA alone as the presence of either SI or SA alone did not result in significant associations with GM volumes. Also, there were no associations between WM alteration and presence of SI and/or SA. Factors including depression severity, presence of anxiety, sex, and medication use had no influence on these results.

Furthermore, for the GM, the model including SRP, PC and HC showed no significant main effect for group. However, our planned comparison of SRP compared to PC showed a trend-wise GM reduction in the right DLPFC extending to the VLPFC (Figure 1S; p_{FWE}=.066, k=476, z=4.02, t=4.10, MNI-coordinate *x, y, z*=38, 45, 0), and a comparable DLPFC/VLPFC cluster in the left hemisphere without reaching statistical significance (p_{FWE}=.18, k=247, z=3.81, t=3.88, MNI-coordinate *x, y, z*=-48, 38, 27). Comparing SRP to HC did not reveal GM volume differences. There were no increased GM volumes in SRP compared to PC and HC. Adding sex, and depression severity as covariates gave similar results. Regarding WM, there was

no significant main effect of group or effects resulting from the planned comparisons. No effects were observed in our hypothesized GM areas.

Table 1 Demographics and clinical information for HC, PC and SRP

Variables		HC	PC	SRP	All groups		PC vs SRP	
					F/χ^2	*p*	t/χ^2	*p*
Age	*M(SD)*	40.08 (9.89)	36.63 (10.33)	37.66 (9.76)	2.01	.14	.66	.51
Education level (years)	*M(SD)*	13.22 (2.36)	12.25 (2.95)	11.94 (3.15)	3.00	.052	.66	.51
Male/Female	*N*	19/31	32/76	27/41	2.22	.33	1.90	.17
Scanning site[a] (AMC/LUMC/UMCG)	*N*	19/22/9	36/35/37	16/31/21	7.55	.11	3.44	.18
MADRS_subtotal[b]	*M(SD)*	.76 (1.53)	15.70 (7.11)	18.72 (9.73)	98.53	<.001*	2.17	.03*
MADRS_suicide item[b]	*M(SD)*	.02 (.02)	.39 (.07)	.98 (.16)	17.96	<.001*	3.36	.001*
BAI[c]	*M(SD)*	2.16 (2.68)	14.76 (9.33)	16.01 (9.65)	46.25	<.001*	.85	.40
SI severity[d]	*M(SD)*			1.45 (1.61)				
Number of SA				0.84 (1.18)				
Psychotherapy use (no/yes)	*N*		22/86	14/54			.001	.97
SSRI (no/yes)	*N*		75/33	47/21			.002	.96
Venlafaxine (SNRI, no/yes)	*N*		101/7	63/5			.05	.82
Current diagnosis (mdd/mdd$^+$/anxiety)	*N*		35/47/26	22/39/7			5.86	.053

Abbreviations: AMC=Academic Medical Center Amsterdam; BAI=Beck Anxiety Inventory; HC=healthy controls; LUMC=Leiden University Medical Center; MADRS=Montgomery-Asberg Depression Scale; MDD=major depressive disorder; MDD$^+$=major depressive disorder with a comorbidity of anxiety; PC=patient controls; SRP=suicidal risk patients; SNRI= Serotonine noradrenaline reuptake inhibitor; SSRI= Selective serotonin reuptake inhibitor; UMCG=University Medical Center Groningen. *p<.05. [a]The scanning part for VU University Medical Center Amsterdam was conducted at AMC. [b]Sub-total MADRS score and score on the MADRS suicide item are not available for three PC and three SRP who were not included in the analyses including covariate of depression severity. [c]One HC, four PC and one SRP do not have BAI scores. [d]In patients with presence of SI, one SRP patient does not have complete SSI information.

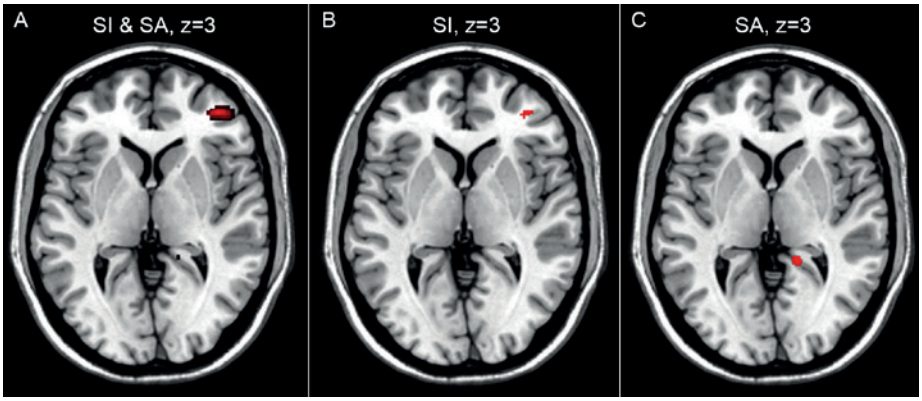


Figure 1 There was a negative association between suicidal risk (presence of SI and/or SA) and GM volumes in the right DLPFC extending to the VLPFC. Abbreviations: DLPFC=dorsolateral prefrontal cortex; GM=grey matter; SA=suicide attempts; SI=suicidal ideation; VLPFC=ventrolateral prefrontal cortex.

Discussion

In this study, we examined structural brain alterations in relation to presence of current suicidal ideation (SI) and past suicide attempts (SA) in patients with major depressive disorder (MDD). Most importantly, we found reduced grey matter (GM) volumes in the dorsolateral prefrontal cortex (DLPFC) extending to the ventrolateral prefrontal cortex (VLPFC) in association with general suicide risk (a composite of SI and SA), that could not be attributed to SI or SA alone. There were no associations of white matter (WM) volumes related to suicidal risk factors (SI, SA or combined effects). These results suggest that reduced GM volulmes in the lateral prefrontal cortex (PFC) might underlie the structural features of suicidal risk, in particular when considering the effects of SI and SA simultaneously.

Reduced GM volume in the lateral PFC was confirmed only in our regression analysis of main interest. Our marginally significant effects in the ANOVA might be due to a power drop compared to the regression analysis, where we explained differential and combined effects of SI and SA instead of suicidal risk only. The functional significance of the reduced DLPFC/VLPFC volumes associated with SI and SA needs to be clarified further though. The DLPFC and VLPFC are important prefrontal areas subserving cognitive control (Miller and Cohen, 2001). Deficiencies in cognitive control domains, for instance in decision making, verbal fluency,

problem-solving, attentional bias to negative events, have been closely associated with suicidal behavior, with the involvement of the DLPFC/VLPFC (Jollant et al., 2011; Richard-Devantoy et al., 2014). Furthermore, the cognitive control of the lateral PFC has also been involved in an emotional context, including response inhibition in an context of negative emotional processing (Goldstein et al., 2007) and implementing cognitive control to regulate emotion (Buhle et al., 2014; Diekhof et al., 2011; Kalisch, 2009). Indeed, it has been suggested that disturbed emotion regulation (ER) is essential in suicidal behavior (Aleman and Denys, 2014; Jollant et al., 2011), the structural alterations in the DLPFC/VLPFC may underlie dysfunction of this prefrontal area during cognitive control of emotion and behavior. It might be speculated that when confronted with negative events (e.g., stressful situations, pain), difficulties in cognitive control of emotion might be associated with enhanced emotional intensity, and may particularly in these individuals lead to suicidal thoughts, or even attempts. Therefore, we propose that the observed GM alterations in the DLPFC/VLPFC in relation to SI and SA may represent a trait-like feature of suicidal risk. If replicated, the identification of this structural abnormality might help to find structural markers for (imminent) suicidal behavior.

In our investigation of SI alone, no altered GM/WM volumes were statistically observable. This suggests that presence of SI is either not necessarily associated with biological abnormalities in brain volumes, or does not have sufficient power to detect brain volume alterations. Notably, the present SI patients mostly showed mild forms of SI (average SI severity was 2.26 out of 10, ranging from1 to 7). Severity of SI has been hypothesized to mediate the transition process from SI to SA (Klonsky et al., 2016), which implies that the suicide act would occur only when SI is severe enough. However, the narrow variations of SI severity in our sample prevents us from further exploring whether GM/WM volumes vary with SI severity, for which future studies would be of interest. In the mean while, our results suggest that even with only mild SI, when comsidering past SA simultaneously, the integrated effect of SI and SA could still be informative, which may aid the search for early suicide biomarkers.

Alternatively, not observing differences in GM/WM volumes in relation to SI may be due to structural alterations appearing at a later stage than SI, consistent with previous findings of a meta-analysis on GM volumes differences in relation to SA compared to PC (van Heeringen et al., 2014). However, we did not find strong

influences of SA on GM/WM volumes, as the effects were only significant when both SA and SI were considered simultaneously. The retained WM volumes observed in the present study replicate previous findings (Kim et al., 2015; Nery-Fernandes et al., 2012; van Heeringen et al., 2014), although not consistently (Rusch et al., 2008). Regarding GM volumes in relation to SA, in addition to the meta-analysis (van Heeringen et al., 2014), there have been mixed results in individual studies, including reduced but also increased GM volumes in different areas across studies, as well as preserved GM volumes (Ding et al., 2015; Kim et al., 2015; Monkul et al., 2007; Nery-Fernandes et al., 2012; Spoletini et al., 2011). These discrepancies might be explained by the fact that previous studies of SA did not consider the potential confounding effects from current SI. Perhaps the GM alterations in association with SA observed in previous studies stem from an integrated effect of both current SI and past SA, as demonstrated in the present study. However, information of SI was not available in previous studies, which prevents us from testing this hypothesis. Also, most of the conducted studies (including studies in the meta-analysis study) have a small sample size of patients with SA (lower than 20), which might contribute to the observed mixed results. Replication in bigger samples as we had is therefore needed.

Some limitations of the current study need to be mentioned. First, the present data were collected at three different locations. Although the same MRI scanning parameters were used across the three scanning sites, and scanning site was added as covariate of no interest to the analyses, this might still have influenced the results. Second, it remains unclear to what extent our results could generalize to populations with other psychiatric disorders. Future investigation of SI and SA in other psychiatric populations (e.g., schizophrenia) might be interesting. Third, the assessments of SI and SA were based on a basline interview (i.e., scale for suicide ideation [SSI]) conducted around two-month before scanning. Whether mild forms of SI and SA changes during this period, and if any changes will affect the present results are not clear. However, scores on the suicide item from the Montgomery-Asberg Depression Scale (MADRS), a measure conducted on day of scanning, also indicate mild suicidal severity. This might imply that the level of SI and SA remains stable in general during the two-month gap between the baseline interview and MRI-scanning. Fourth, review studies have suggested that patients with suicidal behavior are impaired in several aspects of neurocognitive functions, such as decision-making, emotional attention,

problem-solving and impulsivity (Jollant et al., 2011; O'Connor and Nock, 2014). It is unclear to what extent our observed structural alterations underlie the aberrant neurocognitive functions in relation to suicidal behavior, and whether structural alterations precede impaired neurocognitive functions, or are the consequence of such dysfunctions. Future studies may further examine the relationship between structural and functional changes in relation to suicidal behavior.

In conclusion, we showed decreased volumes in the DLPFC/VLPFC in relation to a combined effect of presence of current SI and presence of SA, while no separate effects of current SI and SA on brain volumes were observable. This prefrontal structural alteration might represent trait-like vulnerability for suicidal behavior, which might be associated with dysfunctional ER and deficient inhibition of suicidal acts.

Acknowledgements

Financial support of the NESDA study was obtained from the Geestkracht program of the Netherlands Organization for Healthy Research and Development (Zon-Mw, grant number 10.000.1002). We appreciate participation of VU University Medical Center Amsterdam, University Medical Center Groningen, Leiden University Medical Center, GGZ ingest, Arkin, GGZ Rivierduinen, Lentis, GGZ Friesland, GGZ Drenthe, Scientific Institute for Quality of Healthcare (IQ healthcare), Netherlands Institute for Health Services Research (NIVEL) and Netherlands institute of Mental Health and Addiction (Trimbos Institute). Dr. H.G. Ruhé was supported by a VENI grant (NWO/ZonMW grant number 016.126.059), and also Dr. M.J. van Tol was awarded a VENI grant (NWO grant number 016.156.077). L. Zhang was supported by the China Scholarship Council during her PhD study at University of Groningen.

Supplementary information

Table S1 Demographics and clinical information for HC, PC and SRP

Variables		suicidal ideators[a]	suicide attempters[a]
Age	*M(SD)*	36.89 (10.14)	39.32 (8.68)
Level of education (years)	*M(SD)*	12.20 (3.04)	11.68 (3.11)
Sex (male/female)	*N*	20/24	10/24
Scanning site (AMC/LUMC/UMCG)	*N*	11/19/14	9/14/11
MADRS_subtotal[b]	*M(SD)*	18.58 (10.08)	19.29 (8.42)
MADRS_suicide item[b]	*M(SD)*	1.09 (1.44)	.87 (1.06)
BAI[c]	*M(SD)*	15.57 (9.48)	18.03 (9.60)
SI severity[d]	*M(SD)*	2.26 (1.48)	.74 (1.40)
Number of SA	*M(SD)*	.50 (1.13)	1.68 (1.17)
Psychotherapy use (no/yes)	*N*	11/33	6/28
SSRI (no/yes)	*N*	28/16	24/10
Venlafaxine (SNRI, no/yes)	*N*	43/1	30/4
Current diagnosis (mdd/mdd^{+}/anxiety)	*N*	17/23/4	6/23/5

Abbreviations: AMC=Academic Medical Center Amsterdam; BAI=Beck Anxiety Inventory; HC=healthy controls; LUMC=Leiden University Medical Center; MADRS=Montgomery-Asberg Depression Scale; MDD=major depressive disorder; MDD^{+}=major depressive disorder with a comorbidity of anxiety; PC=patient controls; SRP=suicidal risk patients; SNRI= Serotonine noradrenaline reuptake inhibitor; SSRI= Selective serotonin reuptake inhibitor; UMCG=University Medical Center Groningen. [a]Suicidal ideators are defined as patients with presence of current suicidal ideation, and suicide attempters as patients with past suicide attempts. There are 10 patients with both suicidal ideation and suicide attempts. [b]Sub-total MADRS score and score on the MADRS suicide item are not available for one SI and two SA. [c]One suicide attempter does not have BAI scores. [d]SI severity was calculated as sum of the first five items from the Scale for Suicide Ideation (range from 1 to 10) . In suicidal ideators, one patient does not have complete SSI information.

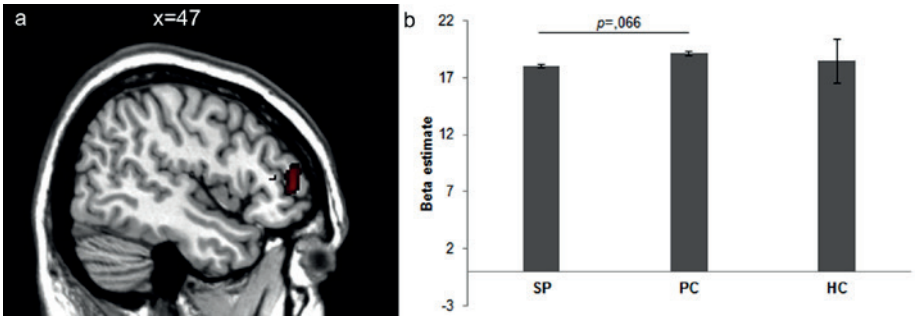


Figure S1 (a) Compared to PC, SRP showed a trend-wise reduction in GM volumes in the DLPFC extending into the VLPFC. (b) A visual illustration of this cluster in SRP, PC, and HC was shown, with HC showing intermediate GM volumes beween SRP and PC. The error bar is one SE in each direction. Abbreviations: DLPFC=dorsolateral prefrontal cortex; GM=grey matter; HC=healthy controls; PC=patient controls; SRP=suicidal risk patients; VLPFC=ventrolateral prefrontal cortex.

PART 2

Self-reflection