Differential relations of suicidality in depression to brain activation during emotional and executive processing

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ABSTRACT
Suicidal behavior is highly prevalent in major depressive disorder (MDD), though not present in all patients. It is unclear whether the tendency for suicidal behavior is associated with a unique functional neuroanatomical signature identifiable through neuroimaging. In this study, we investigated brain activation in suicidal and non-suicidal patients with MDD during facial emotion processing and executive control. Functional magnetic resonance imaging (fMRI) data from the NESDA-fMRI study (MDD patients N = 103, healthy controls N = 26, HC) were analyzed. Patients were divided in a group of suicide attempters (N = 18, SA), suicide ideators (N = 31, SI) and a patient-control group (N = 73, PC). A gender discrimination task with emotional faces and the Tower of London executive planning task were investigated. An ANOVA was performed to compare brain activation among suicidal patients (SA + SI), PC and HC first and then among SI, SA, PC and HC. Significance was determined as meeting p < .05 family wise error (FWE) corrected at the voxel-level. We observed that SA patients showed lower activation in the bilateral fusiform gyri during emotional faces processing compared to SI, PC and HC. No group differences were found during executive planning. Results were independent of childhood emotional maltreatment, depression severity, anxiety severity, use of psychotherapy and SSRI-use. Results suggest that a propensity for suicidal behavior in MDD is associated with abnormal emotional processing but not executive functioning, represented by altered face processing compared to non-suicidal patients and controls. While in need of replication, these results indicate that altered fusiform gyrus activation during emotion processing may serve as a marker for suicidality.

1. Introduction
Suicide is a global leading cause of mortality with an enormous personal and societal impact (Aleman and Denys, 2014; Hawton and van Heeringen, 2009; Nock et al., 2009; World Health Organization, 2012). It has been proposed that suicidal behavior encompasses a complex cascade from sensitivity to an environmental trigger, to suicide ideation and then to suicide attempts and suicidal acts (Jollant et al., 2011; World Health Organization, 2012). Identifying the risk factors in the development of suicidal behavior would increase the effectiveness of prevention (World Health Organization, 2012).

Suicide ideation and behavior is strongly associated with psychopathology, most notably depression (Bernal et al., 2007; Harris and Barraclough, 1997; Haukka et al., 2008; Nock et al., 2009; Pokorny, 1983). However, not all MDD patients show signs of suicide ideation and attempts, and it is difficult to predict whether patients with a diagnosis of MDD with suicide ideation will go on to make suicide plans or attempts based on clinical symptoms and signs only (Nock et al., 2009; World Health Organization, 2012). It has been proposed that suicidal behavior encompasses a complex cascade from sensitivity to an environmental trigger, to suicide ideation and then to suicide attempts and suicidal acts (Jollant et al., 2011; World Health Organization, 2012). Identifying the risk factors in the development of suicidal behavior would increase the effectiveness of prevention (World Health Organization, 2012).

Suicide ideation and behavior is strongly associated with psychopathology, most notably depression (Bernal et al., 2007; Harris and Barraclough, 1997; Haukka et al., 2008; Nock et al., 2009; Pokorny, 1983). However, not all MDD patients show signs of suicide ideation and attempts, and it is difficult to predict whether patients with a diagnosis of MDD with suicide ideation will go on to make suicide plans or attempts based on clinical symptoms and signs only (Nock et al., 2009; World Health Organization, 2012). It has been proposed that suicidal behavior encompasses a complex cascade from sensitivity to an environmental trigger, to suicide ideation and then to suicide attempts and suicidal acts (Jollant et al., 2011; World Health Organization, 2012). Identifying the risk factors in the development of suicidal behavior would increase the effectiveness of prevention (World Health Organization, 2012).
2009). Studying the neurobiological factors associated with degrees/stages of suicidality would not only help to identify biomarkers for the development of suicidal behavior, but would provide valuable information to better understand processes underlying suicidal behavior, which may ultimately guide assessment and treatment of depressed individuals with suicide ideation/attempts and may inform prevention strategies (Aleman and Denys, 2014).

It has been proposed that the vulnerability for suicidal behavior relates to abnormal value attribution of emotional material and altered regulatory emotional and behavioral control, associated with changes in the amygdala, orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), ventrolateral-, dorsolateral-(DLPFC) and medial prefrontal brain areas (Jollant et al., 2011). Previous studies have shown that patients with past suicide attempts tend to pay more attention to suicide-related stimuli (e.g., ‘cutting’, ‘bullet’ or ‘death’) and generally negative stimuli in attentional bias paradigms than depressed patients without past suicide attempts and healthy comparison subjects (Becker et al., 1999; Cha et al., 2010; Nock et al., 2010), and that executive dysfunctions are characteristics of MDD-patients with current ideation (Marzuk et al., 2005). This suggests that altered evaluation of emotional information, mediated by limbic structures including the amygdala (Phillips et al., 2003), may be altered in patients at risk for suicide. Moreover, altered regulatory emotional and behavioral control related to inadequate functioning of the DLPFC under conditions of high task demands may further contribute to the likelihood of suicide thoughts and acts. Simultaneous investigation of both primary emotional evaluation and executive control in MDD-patients with and without suicidal behavior could elucidate on the basic emotional and cognitive processes that facilitate suicidal acts in an extreme emotional and despairing context. However, to date no such study has been performed.

Therefore, the aim of our study was to examine neural correlates of emotion processing and executive functioning associated with suicidality in a sample of MDD patients. We hypothesized that compared to MDD patients without suicidal ideas and no history of suicide attempts (patient controls; PC) and healthy controls (HC), patients with suicidal characteristics (i.e., current suicide ideation and/or past suicide attempts; SP) would show abnormal amygdala activation in response to faces with negative emotional expressions. This may particularly be the case for angry expressions, as they may signal social disapproval, to which people with suicidal tendencies may be oversensitive (Van Heerening et al., 2011). We also hypothesized that SP might have altered activation in the DLPFC and ACC during positive faces condition. The DLPFC, ACC and amygdala were selected as main regions of interest according to the previous reported effect (Jollant et al., 2008, 2011) and the main effects of the faces task that we previously reported included these regions (Demenescu et al., 2011). During executive control processing, we expected that SP would show reduced DLPFC and dorsomedial prefrontal cortex (DMPFC) activation compared with PC and HC. We focused on these regions because of their proposed role in suicidal behavior and their relevance for the Tower of London task (van Tol et al., 2011). Furthermore, because not all suicide thoughts transit to suicide attempts, and steps of this continuum may have different substrates, we hypothesized that distinctive alterations of brain activation during emotional and executive control might differentiate SP with current suicide ideation (SI) from SP with suicide attempts (SA). Finally, as a well-recognized predictor of depression and suicidal behavior (Hoertel et al., 2015; Khan et al., 2015), childhood emotional maltreatment (CEM) has been reported to have an effect on facial processing in the NESDA sample (van Harmelen et al., 2013). Therefore, we controlled for CEM by including this variable as a covariate of no interest.

2. Methods and materials

2.1. Participants

Data were available from the neuroimaging sub-project of the ongoing large cohort longitudinal Netherlands Study of Depression and Anxiety (NESDA) (Penninx et al., 2008). One-hundred and twenty-nine participants with complete behavioral data and high-quality fMRI data for both tasks were included in these analyses. For the current analyses, we only included participants with a life-time diagnosis of MDD (n = 103) according to the Composite International Diagnostic Interview (CIDI-lifetime version 2.1). After matching the demographic characteristics, we included 26 healthy participants without a current or life-time DSM-IV diagnosis or suicidality. Presence of current suicide ideation and past attempt was assessed by the semi-structured Scale for Suicide Ideation (SSI) (Beck et al., 1979) and an explicit question on suicide attempts (QSA; yes/no), respectively, at the interview before the fMRI scanning (see the supplementary material for detailed question). We divided patients into suicide attempters (SA, QSA = yes; n = 18), suicide ideators (SI, SSI > 0 and QSA = no; n = 31) and non-suicidal patient controls (PC, SSI = 0 and QSA = no; n = 54). All SA reported a history of non-fatal attempts, of which 13 reported no current suicide ideation at the time of scanning. The NESDA-fMRI study was approved by the ethical review boards of each participating center, involving the University Medical Center Groningen (UMCG), VU Medical Center (VUMC) Amsterdam, and the Leiden University Medical Center (LUMC). All participants provided written informed consent after receiving a detailed study description.

2.2. Clinical variables and measurements

Severity of current suicide ideation was calculated by the sum of the scores of the first five items of SSI, which were used as a screening instrument of patients’ attitudes toward dying, living, and suicide desire. Other SSI-items related to the specifics of suicide plans were not administered in the context of the observational NESDA study. Depression and anxiety severity were assessed by the Inventory of Depressive Symptomatology (IDS) (Rush et al., 1996) and Beck Anxiety Inventory (BAI) (Beck et al., 1988), respectively. Because the IDS has one item on suicidal behavior, we calculated adjusted total scores by excluding the suicidal item (i.e., total IDS-score – score of item 16) in order to compare severity of depressive symptomatology other than suicidal behavior. Childhood emotional maltreatment (CEM) was measured with the NEMESIS trauma interview (De Graaf et al., 2004), which assesses occurrence and frequency of emotional neglect, emotional abuse, physical abuse or sexual abuse before the age of 16 years. We defined CEM as the incidence of multiple incidents (more than once) of emotional neglect and/or emotional abuse before the age of 16 years (van Harmelen et al., 2013) and used as a covariate in the analyses.

2.3. Task paradigms

2.3.1. Faces task

An event-related emotional faces task was conducted to investigate brain activation during emotion processing (Demenescu et al., 2011). During the presentation of angry, fear, happy, neutral, and sad facial expressions (from the Karolinska Directed Emotional Faces System) (Lundqvist et al., 1998), participants were instructed to indicate the gender of the actor on the photograph by pressing a button with their index finger (left = male; right = female). Twenty-four color pictures were presented for each emotional face condition (12 male, 12 female) and 80 for the scrambled faces. An arrow was presented with each scrambled face to indicate which button participants should press (left/right). Each face stimulus was shown for 2.5s following by an inter-stimulus interval varying from 0.5 to 1.5s. Each unique person/
expression combination was not shown more than four times. Reaction times (RT) were recorded.

2.3.2. Tower of London task
A pseudo-randomized, self-paced event-related parametric version of the Tower of London (ToL) task was employed to examine brain activation during executive planning (van Tol et al., 2011). A starting configuration and a target configuration were presented, each consisting of three colored beads on three pegs. Participants were instructed to evaluate the minimum number of moves needed to get from the starting to the target configuration (ranging from 1 to 5) by choosing one of two possible answers at the bottom of the screen. During baseline trials, participants were requested to count the number of yellow and blue colored beads. The task was paced by the participant, but duration of each trial was no longer than 60s. Accuracy of responses and RTs were recorded.

2.4. Image acquisition
Functional imaging data were acquired with a 3T Philips MR-scanner at each of the three participating centers. For radio-frequency transmission and reception, a SENSE-8 channel head coil was used in Groningen and Leiden and a SENSE-6 channel head coil in Amsterdam. 39 slices of every echo planar images (EPI) volume were acquired using a T2*-weighted gradient echo sequence (TR = 2300 ms, TE = 28 ms, matrix size: 64 × 64, in-plane resolution: 3 × 3 mm, slice thickness: 3 mm) in Groningen. 35 axial slices per EPI-volume were obtained using a T2*-weighted gradient echo sequence (TR = 2300 ms, TE = 30 ms, matrix size: 96 × 96, in-plane resolution: 2.29 × 2.29 mm, slice thickness: 3 mm) in Amsterdam and Leiden. EPIs were acquired parallel to the anterior commissure-posterior commissure plane in ascending interleaved order, with no gap. An anatomical MRI was acquired with a 3D gradient-echo T1-weighted sequence (TR = 9 ms, TE = 3.5 ms, matrix size: 256 × 256, voxel size: 1 × 1 × 1 mm, 170 slices).

2.5. Statistical analyses
2.5.1. Demographical and behavioral data
Demographic, psychometric assessment and behavioral data were analyzed with IBM SPSS software (SPSS v.22.0, IBM). Analyses of variance (ANOVA), Chi-square tests and t-tests were employed when appropriate with a significance level of p < .05.

Faces task A repeated measures ANOVA (RM-ANOVA) was built for differences in RTs, with group (3; SP, PC, HC) as between-subject factor and emotional expressions (5; angry, fearful, happy, sad, neutral) as within-subject factor, and age and years of education as covariates. In case a significant effect was detected, post hoc t-tests were conducted to identify its direction, with significance set at p < .05 (two-tailed) after Bonferroni correction for multiple comparisons.

To investigate whether a history of suicidal attempt was differentially related to neural abnormalities relative to suicidal ideation, the following RM-ANOVA analysis was performed on RTs with group (4; SA, SI, PC, HC) and emotion expression (5; angry, fearful, happy, sad, neutral) as independent factors, and age and years of education as covariates.

ToL task An RM-ANOVA was built to test for differences in accuracy and RTs for correct trials, with group (3; SP, PC, HC) as between-subject factor and step (5; step1, step2, step3, step4, step5) as within-subject factor, and age and year of education as covariates. The same threshold factor and step (5: step1, step2, step3, step4, step5) as within-subject factor, and age and years of education as covariates.

2.5.2. fMRI data
fMRI data were processed and analyzed using Statistical Parametric Mapping software (SPM8 v5236, Wellcome Trust Center for Neuroimaging, http://www.fil.ion.ucl.ac.uk/spm) implemented in Matlab 7.8 (The Math Works Inc., Natick, MA, USA). Before preprocessing, functional images were reoriented to the anterior commissure and in alignment with the anterior-posterior commissure plane. Preprocessing included slice time correction, spatial realignment, co-registration between the anatomical T1 image and mean EPI-image, spatial normalization to the standard Montreal Neurological Institute (MNI) space, reslicing to a 3 × 3 × 3 mm grid and spatial smoothing with an 8 mm full-width at half maximum (FWHM) Gaussian kernel.

Faces task After single-subject model estimation (Schmaal et al., 2015), five contrasts ([angry > scrambled], [happy > scrambled], [neutral > scrambled], [sad > scrambled], and [fearful > scrambled]) were calculated for each participant.

Firstly, to test for the main effect of suicidality, a flexible-factorial model was set up with group (SP, PC, HC) as between-subject factor and emotional expression (angry, happy, neutral, sad, and fearful) as within-subject factor. Scanning site (two dummy variables), age, and years of education were added as covariates. Additionally, due to the known sex differences during decision-making (Jollant et al., 2008), we controlled for the sex differences by covarying for gender.

Secondly, to test for effects of stage of suicidality, a full-factorial model was conducted with group (SA, SI, PC, HC) and emotion expression as factors and scanning site, age, and years of education as covariates. Gender was covaried as well in our model.

ToL task After single subject model estimation, we weighted the trial type 1 to 5 with [-1.5, -1, -.5, 1, 2] to create a parametric contrast representing increasing task load for correct trials for each participant (for details, see van Tol et al., 2011). A one-way ANOVA was set up at group level with group (SP, PC, HC) as between-subject factor and parametric load contrast images as dependent variable. Scanning site (two dummy variables), age, and years of education were added as covariates.

In addition, a second one-way full-factorial model was built with group (SA, SI, PC, HC) as independent variable and task load contrast maps as the dependent variable.

Because executive function has recently been found to be associated with depression but not specifically with suicidal behavior (Richard-Devantooy et al., 2014, 2016), and we previously observed group differences during Tower of London execution in the NESDA neuroimaging study (van Tol et al., 2011), we explicitly tested the differences between depressed patients and healthy controls (i.e., SP(SA + SI) + PC > HC) in both main and secondary analyses.

2.5.2.1. Sensitivity analyses
To test whether our results were affected by depression severity, anxiety severity, childhood emotional maltreatment (CEM) and treatment-use (psychotherapy and SSRI-use), we repeated our analyses by including depression severity (IDS-score excluding suicidal item, demeaned within group), demeaned BAI-scores, CEM (yes/no), psychotherapy-use (yes/no), and SSRI-use (yes/no) as covariates in the model and tested them one by one, respectively. In addition, we repeated our analyses by removing age and level of education as covariates.

2.5.2.2. Statistical thresholding
Statistical parametric maps in all analyses were thresholded at p < .001 uncorrected at the voxel-level and post hoc t-tests had to meet p < .05 family wise error (FWE) corrected at the voxel-level to be considered significant. For effects occurring in our regions of interest (ROI), small volume correction (SVC) for the spatial extent of the ROIs was applied, with a threshold of p < .05, FWE corrected at the voxel-level. Our ROIs were selected based on previous studies on suicidality and the main effect of task in previous reports using the same task. For SVC for the faces task, we created a composite anatomical mask encompassing the dilated
bilateral amygdala (dilation = 5 mm), ACC and DLPFC (including the bilateral superior frontal gyri and middle frontal gyri) using the Anatomical Automatic Labeling (AAL) atlas system implemented in the Wake Forest University Pick Atlas toolbox (WFU-pick atlas, Winston Salem, North Carolina). The dilation of the amygdala was based on the reported main effect of this task, which extended to the anterior hippocampus from the amygdala (Demenescu et al., 2011). For the ToL, the composite ROI for SVC included the DLPFC and the DMPFC (including the bilateral medial superior frontal gyri according to the AAL system) (Hermann et al., 2014). Effects occurring outside our ROIs had to meet $p < .05$ FWE whole brain corrected at the voxel-level.

3. Results

3.1. Clinical characteristics and behavioral results

Groups did not differ on age, years of education, sex and scanning site (Table 1). SA did not differ from SI and PC on the current severity of depression (IDS-scores minus suicidality item) and anxiety (BAS-scores), half-year CIDI diagnosis, childhood emotional maltreatment (CEM), medication use (including SSRI, other antidepressants and benzodiazepine) and psychotherapy use ($p > .05$; Table 1).

**Faces task** No main effect of emotional expression ($F_{4, 492} = 0.86$, $p > .05$) or interaction between them ($F_{8, 492} = 1.12$, $p > .05$) was found on response times. Although plotting the data indicated a tendency for slower reactions in suicidal patients to all emotional faces, compared with HC and patient controls (Supplementary Fig. S1a), no main effect of group ($F_{2, 123} = 1.66$, $p = .20$) was present.

In the follow-up analysis with SA, SI, PC and HC, no emotion expression ($F_{4,488} = 0.92$, $p > .05$), main effect of group ($F_{3,122} = 1.45$, $p = .23$), nor interaction ($F_{12,488} = 0.88$, $p > .05$) were observed. Although plotting showed a tendency of slower response to all emotional faces in suicide ideators compared to suicide attempters, patient controls and HC, no main effect of group was seen (Supplementary Fig. S1b).

**Tol. task** A main effect of task difficulty was found on RTs during Tol ($F_{4,496} = 10.48$, $p < .001$); the more difficult, the slower the response to the trial (i.e., step1 < step2 < step3 < step4 < step5; $p < .001$) (Supplementary Fig. S1b). No main effect of group ($F_{2,124} = 0.16$, $p > .05$) or interaction between group and task load ($F_{8,496} = 0.50$, $p > .05$) was found ($F_{3,125} = 1.76$, $p > .05$).

No effect of group ($F_{3, 123} = 0.13$, $p > .05$) or interaction of group and task difficulty ($F_{12, 492} = 0.40$, $p > .05$) on RTs was observed in the four-group model (SA, SI, PC, HC).

In both models, no main effect of group or interaction effect of group and task difficulty was found on accuracy.

3.2. fMRI results

**Faces task** No main effect of group or interaction between group and emotion expression was found in the analysis with three groups (SP, PC, HC).

In the analysis with four groups (SA, SI, PC, HC), a main effect of group was found in the bilateral fusiform gyrri (FFA) extending to lingual gyri. Post hoc t-tests showed that suicide attempters (SA) had lower activation than patient controls (PC) and healthy controls (HC) in the bilateral FFA during processing of all emotional faces. Moreover, SA showed lower activation in the bilateral FFA compared to both suicide ideators (SI) and depressed patients without suicidal attempts (combined group of SI and PC). HC showed no difference from SI or PC during all faces processing. Group effects in the other brain areas did not survive correction for multiple comparisons. No group × condition interaction was observed.

Moreover, FFA has been found correlated with amygdala activation during emotional faces processing (Fairhall and Ishai, 2007). To check this, we extracted amygdala signals and correlated these with FFA activation. A significant positive correlation between FFA and amygdala activation was observed ($r = 0.23$, $p < .001$).

Our results did not change when adding childhood emotional maltreatment, depressive severity, anxiety severity and treatments (use of SSRI or psychotherapy) as covariates. The FFA effect did not change after excluding suicide attempters with current ideation from the SA group (Table 2B; Fig. 1). Table 2A provides a full listing of results for the four group analysis on faces task. Adding gender or removing age and level of education as covariates showed similar results (Supplementary Table S1).

**Tol. task** A main effect of group was observed in the left premotor cortex, DLPFC and postcentral gyrus in the analysis including three groups at $p < .001$ uncorrected. Post-hoc test showed that all MDD patients had lower activation in the premotor cortex than HC (Table 3).

For the analysis including four groups, a main effect of group was found in the left insula, left DLPFC and left postcentral gyrus at our explorative threshold of $p < .001$, uncorrected, indicating greater activation with increasing task load in the insula and postcentral gyrus in SA than other groups and lower activation in the DLPFC in PC than other groups. However, higher activation in the left insula in SA or non-suicide patients than HC and higher activation in the premotor cortex in HC than all MDD patients were only observed subthreshold (insula:

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**Table 1**

Clinical characteristics ($n = 129$).

<table>
<thead>
<tr>
<th>Group</th>
<th>Suicide attempters</th>
<th>Suicide ideators</th>
<th>Patient controls</th>
<th>Healthy controls</th>
<th>F</th>
<th>t*</th>
<th>Chi-square</th>
<th>Likelihood ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size N</td>
<td>18</td>
<td>31</td>
<td>54</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age Mean(SD)</td>
<td>37.72(9.68)</td>
<td>36.19(10.85)</td>
<td>37.61(10.37)</td>
<td>38.96(7.94)</td>
<td>.37</td>
<td></td>
<td></td>
<td></td>
<td>.78</td>
</tr>
<tr>
<td>Years of education Mean(SD)</td>
<td>11.33(1.94)</td>
<td>12.35(3.31)</td>
<td>11.94(2.88)</td>
<td>13.12(1.88)</td>
<td>1.79</td>
<td></td>
<td></td>
<td></td>
<td>.15</td>
</tr>
<tr>
<td>Sex(male/female) N</td>
<td>4/14</td>
<td>15/16</td>
<td>20/34</td>
<td>13/13</td>
<td>4.71</td>
<td></td>
<td></td>
<td></td>
<td>.19</td>
</tr>
<tr>
<td>Scan site (AMC/LUMC/UMCG) N</td>
<td>2/6/10</td>
<td>5/16/10</td>
<td>12/22/20</td>
<td>8/14/4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>Childhood emotional maltreatment (yes/no) N</td>
<td>14/4</td>
<td>19/12</td>
<td>30/24</td>
<td>2.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.23</td>
</tr>
<tr>
<td>IDS’ Mean(SD)</td>
<td>28.44(10.46)</td>
<td>25.23(11.77)</td>
<td>24.83(10.21)</td>
<td>.79</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.46</td>
</tr>
<tr>
<td>BAI Mean(SD)</td>
<td>18.00(8.54)</td>
<td>13.32(8.60)</td>
<td>14.19(9.59)</td>
<td>1.62</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.20</td>
</tr>
<tr>
<td>Current diagnosis (MDD/MDD* /ANX) N</td>
<td>3/12/3</td>
<td>15/14/2</td>
<td>37/30/7</td>
<td>6.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.20</td>
</tr>
<tr>
<td>Psychotherapy use (yes/no) N</td>
<td>16/2</td>
<td>23/8</td>
<td>42/12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.43</td>
<td></td>
</tr>
<tr>
<td>SSRI-use (yes/no) N</td>
<td>10/8</td>
<td>9/22</td>
<td>17/37</td>
<td>4.13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.13</td>
</tr>
<tr>
<td>Use of other antidepressants (yes/no) N</td>
<td>2/16</td>
<td>2/29</td>
<td>2/52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.53</td>
<td></td>
</tr>
<tr>
<td>Use of benzodiazepine (yes/no) N</td>
<td>2/16</td>
<td>4/27</td>
<td>2/52</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.25</td>
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</table>

Abbreviations: AMC, Amsterdam Medical Center; LUMC, Leiden University Medical Center; UMCG, University Medical Center Groningen; IDS-, Inventory of depressive symptomatology (self-report, minus the suicide-related item (item 16); BAI: Beck’s Anxiety Inventory; MDD: patients with major depressive disorder; MDD + patients with major depressive disorder with a comorbid anxiety disorder (Social Anxiety Disorder, Panic Disorder, and/or Generalized Anxiety Disorder); ANX, patients with an anxiety disorder (Social Anxiety Disorder, Panic Disorder, and/or Generalized Anxiety Disorder).

* Unfrequent on average less than 50% of the time.
Together, these findings suggest that neural mechanisms of emotion processing might differ between suicide attempters and healthy people regarding performance and regional brain activation during emotion processing. However, suicide attempters did not differ compared to suicide ideators, patient controls and healthy people during non-emotional executive planning.

4. Discussion

We investigated the neural correlates of suicidality in MDD patients during emotion processing and non-emotional executive planning. Suicide attempters showed lower activation of the fusiform gyri compared to suicide ideators, patient controls and healthy people during emotion processing. However, suicide attempters did not differ from other suicide patients (i.e. suicide ideators and patient controls) and healthy people regarding performance and regional brain activation during the execution of a non-emotional visuo-spatial planning task. Of note, our results were not explained by childhood emotional maltreatment, treatment use, depression severity or anxiety severity. Together, these findings suggest that neural mechanisms of emotion processing might differentiate current suicidal thought from past suicidal behavior, while frontal involvement in planning ability under non-emotional conditions may be relatively intact in suicidal patients compared to non-suicidal patients. Further prognostic study is necessary to estimate prognostic value of our findings.

A distinct activation pattern was observed in suicide attempters during emotion processing of all faces in the fusiform gyri extending to lingual gyri. This brain region is regarded as fusiform facial area (FFA) and plays an important role in face identification (Grill-Spector et al., 2004; Kanwisher et al., 1997) and perception of emotions in facial stimuli (Radua et al., 2010). Furthermore, maladaptive FFA functioning has been repeatedly associated with suicidal behavior in neuroimaging studies using different modalities. For instance, functional MRI studies have shown lower FFA activation to neutral faces after presentation of angry cues in adolescent SA compared to HC (Pan et al., 2013) and more activation in self-versus other faces in patients with high levels of suicidality (Quevedo et al., 2016). On the other hand, lower regional homogeneity during resting state in suicide attempters without mental illness (Cao et al., 2015) and smaller grey matter volumes in high-lethality attempters with borderline personality disorder compared to HC (Soloff et al., 2014) have also been found. Our results add to these findings by suggesting that suicide attempters might have altered responses to social emotional stimuli. Because this FFA dysfunction was specific for suicide attempters, we further suggest this neural dysfunction may be selectively associated with a predisposition to active

Table 2A
Results of the group by emotional expression analysis for the faces task (n = 129).

<table>
<thead>
<tr>
<th>Main effect of group</th>
<th>K</th>
<th>Side</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>F</th>
<th>Z</th>
<th>P(FWE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusiform gyrus extending to lingual gyrus</td>
<td>50</td>
<td>R</td>
<td>19</td>
<td>30</td>
<td>−73</td>
<td>−8</td>
<td>11.40</td>
<td>4.74</td>
<td>.02*</td>
</tr>
<tr>
<td>Fusiform gyrus extending to lingual gyrus</td>
<td>36</td>
<td>L</td>
<td>19</td>
<td>−30</td>
<td>−79</td>
<td>−14</td>
<td>6.09</td>
<td>3.33</td>
<td>.05*</td>
</tr>
</tbody>
</table>

Table 2B
Results of the sensitivity analysis: group by emotional expression (n = 124).

<table>
<thead>
<tr>
<th>Main effect of group</th>
<th>K</th>
<th>Side</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t</th>
<th>Z</th>
<th>P(FWE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fusiform gyrus extending to lingual gyrus</td>
<td>55</td>
<td>R</td>
<td>19</td>
<td>30</td>
<td>−70</td>
<td>−8</td>
<td>12.05</td>
<td>5.17</td>
<td>.01*</td>
</tr>
<tr>
<td>Fusiform gyrus extending to lingual gyrus</td>
<td>9</td>
<td>L</td>
<td>19</td>
<td>−21</td>
<td>−82</td>
<td>−11</td>
<td>7.15</td>
<td>3.72</td>
<td>.05*</td>
</tr>
</tbody>
</table>

*significant at P(FWE) < .05.

SA, suicide attempters; SI, suicide ideators; HC, healthy controls.

\( P(FWE) = .09, Z = 4.39; \) premotor cortex: \( P(FWE) = .10, Z = 4.33; \) Table 4.

Adding depressive severity, CEM, anxiety severity or treatments to the model did not change the results. Results did not change after removing age and level of education as covariate (Supplementary Tables S2 and S3).

4. Discussion

We investigated the neural correlates of suicidality in MDD patients during emotion processing and non-emotional executive planning. Suicide attempters showed lower activation of the fusiform gyri compared to suicide ideators, patient controls and healthy people during emotion processing. However, suicide attempters did not differ from other suicide patients (i.e. suicide ideators and patient controls) and healthy people regarding performance and regional brain activation during the execution of a non-emotional visuo-spatial planning task. Of note, our results were not explained by childhood emotional maltreatment, treatment use, depression severity or anxiety severity. Together, these findings suggest that neural mechanisms of emotion processing might differentiate current suicidal thought from past suicidal behavior, while frontal involvement in planning ability under non-emotional conditions may be relatively intact in suicidal patients compared to non-suicidal patients. Further prognostic study is necessary to estimate prognostic value of our findings.

A distinct activation pattern was observed in suicide attempters during emotion processing of all faces in the fusiform gyri extending to lingual gyri. This brain region is regarded as fusiform facial area (FFA) and plays an important role in face identification (Grill-Spector et al., 2004; Kanwisher et al., 1997) and perception of emotions in facial stimuli (Radua et al., 2010). Furthermore, maladaptive FFA functioning has been repeatedly associated with suicidal behavior in neuroimaging studies using different modalities. For instance, functional MRI studies have shown lower FFA activation to neutral faces after presentation of angry cues in adolescent SA compared to HC (Pan et al., 2013) and more activation in self-versus other faces in patients with high levels of suicidality (Quevedo et al., 2016). On the other hand, lower regional homogeneity during resting state in suicide attempters without mental illness (Cao et al., 2015) and smaller grey matter volumes in high-lethality attempters with borderline personality disorder compared to HC (Soloff et al., 2014) have also been found. Our results add to these findings by suggesting that suicide attempters might have altered responses to social emotional stimuli. Because this FFA dysfunction was specific for suicide attempters, we further suggest this neural dysfunction may be selectively associated with a predisposition to active
behavior rather than reflecting correlates of current suicide thoughts or depression per se. This implies that neural underpinnings of emotional reactivity may not follow a linear scale reflecting suicidal staging. Additionally, it has been reported that the fusiform gyrus shows enhanced connectivity with the amygdala during processing emotional face but no other faces and may serve as a feedforward modulator to the amygdala (Fairhall and Ishai, 2007). The amygdala is also thought to affect the fusiform gyrus by modulating re-entrant scene features to FFA (Vuilleumier et al., 2004). Although we did not find altered amygdalar activation in suicide patients, the post-hoc exploration correlating the FFA activation and extracted amygdalar signals showed significant positive correlation between FFA and amygdalar activation. Together with this, reduced FFA involvement in suicide attempters suggests that impaired face identification might be associated with less appropriate signaling from emotional processing areas than in suicide ideators and depressed patients. Moreover, previous studies on facial processing pointed out that suicide attempters have significant impairments in perceiving negative facial signals such as angry and disgust compared to non-suicidal patients (Jollant et al., 2008; Richard-Devantoy et al., 2013). Indeed, our findings suggest that such abnormal activation may not be limited to negative facial expressions but may extend to positive and neutral expressions, in distinguishing suicide attempters from suicide ideators.

Notably, we did not observe any differences between depressed patients with or without suicidality, which might be due to the heterogeneity of suicidal groups (i.e., including patients with current ideation and past attempts). Previous functional studies in suicide patients found orbitofrontal and anterior cingulate cortex abnormalities during emotion processing (Jollant et al., 2008; Pan et al., 2013; Olié et al., 2015). However, in these studies, the authors only conducted analyses in small samples of males (n = 13) or adolescents (n = 14). Moreover, Jollant et al. (2008) and Olié et al. (2015) contrasted angry with neutral faces, which may cause the inconsistency. Nonetheless, no difference was shown in the OFC, ACC or DLPFC during emotional processing between the two suicidal groups. This may alternatively imply that the valuation-related processing in these regions might be equivalently associated with past suicide behavior and current ideation. More detailed interviews on suicide ideation and attempts are needed, because the semi-structured scales or one single question may lead to a lenient definition of suicidal behaviors and might not well distinguish patients with suicidal attempt and ideation.

On the other hand, only trend-wise differences in the insula and premotor cortex during visual-planning were found between suicide attempters and ideators/non-suicide patients. Previous studies on executive function have focused on suicide attempters and consistently found frontal abnormalities in these patients (Audenaert et al., 2002; Jollant et al., 2010; Willeumier et al., 2011). Neuropsychological studies have found executive deficits in both patients with suicide ideation (Marzuk et al., 2005) and suicide attempts (Gujral et al., 2014). Therefore, our study does not support a strong involvement of regions

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Table 3

Results of the main analysis on ToL task including three patient groups (SP, PC, HC).

<table>
<thead>
<tr>
<th>Regions</th>
<th>MNI coordinates</th>
<th>Main effect of group</th>
<th>Kᵃ</th>
<th>Kᵇ</th>
<th>Side</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>F</th>
<th>Z</th>
<th>P(uncorrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premotor cortex</td>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td>L</td>
<td>6</td>
<td>−21</td>
<td>−6</td>
<td>57</td>
<td>10.23</td>
<td>3.78</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dorsolateral prefrontal cortex</td>
<td></td>
<td></td>
<td>8</td>
<td></td>
<td>L</td>
<td>44</td>
<td>−33</td>
<td>12</td>
<td>36</td>
<td>9.69</td>
<td>3.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td></td>
<td></td>
<td>9</td>
<td></td>
<td>L</td>
<td>30</td>
<td>−15</td>
<td>−42</td>
<td>12</td>
<td>10.28</td>
<td>3.79</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Post hoc tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HC &gt; MDD_all</td>
<td></td>
<td></td>
<td>16</td>
<td>14</td>
<td>L</td>
<td>6</td>
<td>−21</td>
<td>−6</td>
<td>57</td>
<td>4.27</td>
<td>4.11</td>
<td>.05*</td>
</tr>
</tbody>
</table>

ᵃ. Cluster size in whole-brain analysis;ᵇ. Cluster size after small volume correction;ᶜ. with a primary threshold at p < .001 uncorrected. ToL, Tower of London; SP, suicide patients; PC, patient controls; HC, healthy controls; MDD, major depressive disorder (including SP and PC).

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Fig. 1. Effect of group (main analysis) and 90% confidence intervals centered at the bilateral fusiform gyri. SA, suicide attempter; SI, suicide ideator; PC, patient control; HC, healthy control.
Table 4
Results of the secondary analysis on ToL task including four patient groups (SA, SI, PC, HC).

<table>
<thead>
<tr>
<th>Regions</th>
<th>MNI coordinates</th>
<th>K4</th>
<th>K6</th>
<th>Side</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>F</th>
<th>Z</th>
<th>Puncorrected</th>
</tr>
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<tbody>
<tr>
<td><strong>Main effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premotor cortex</td>
<td>4 – L</td>
<td>6</td>
<td>-21</td>
<td>-6</td>
<td>57</td>
<td>6.89</td>
<td>3.48</td>
<td>&lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>10 – L</td>
<td>48</td>
<td>-39</td>
<td>-3</td>
<td>3</td>
<td>7.03</td>
<td>3.52</td>
<td>&lt; .001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>4 – L</td>
<td>30</td>
<td>-15</td>
<td>-42</td>
<td>12</td>
<td>6.97</td>
<td>3.50</td>
<td>&lt; .001</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th><strong>Post hoc tests</strong></th>
<th>K4</th>
<th>K6</th>
<th>Side</th>
<th>BA</th>
<th>x</th>
<th>y</th>
<th>t</th>
<th>Z</th>
<th>P(FWE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HC &gt; MDD_all</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Premotor cortex</td>
<td>14</td>
<td>13</td>
<td>L</td>
<td>6</td>
<td>-21</td>
<td>-6</td>
<td>57</td>
<td>4.05</td>
<td>3.91</td>
</tr>
<tr>
<td>SA &gt; NON-SA patients (SI + PC)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>64</td>
<td>- L</td>
<td>48</td>
<td>-42</td>
<td>-3</td>
<td>3</td>
<td>3.95</td>
<td>3.83</td>
<td>.05**/ .49^</td>
</tr>
<tr>
<td>SA &gt; NON-SA(SI + PC + HC)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula</td>
<td>68</td>
<td>- L</td>
<td>48</td>
<td>-42</td>
<td>-3</td>
<td>0</td>
<td>4.38</td>
<td>4.21</td>
<td>.04**/ .16^</td>
</tr>
<tr>
<td>SA &gt; HC</td>
<td>35</td>
<td>- L</td>
<td>48</td>
<td>-39</td>
<td>-3</td>
<td>-3</td>
<td>4.58</td>
<td>3.49</td>
<td>.09^</td>
</tr>
</tbody>
</table>

Tol, Tower of London; SA, suicide attempters; SI, suicide ideators; PC, patient controls; HC, healthy controls; MDD, major depressive disorder (including SA, SI and PC).
a. Cluster size in whole-brain analysis; b. Cluster size after small volume correction; c. with a primary threshold at p < .001 uncorrected; d. Significance at cluster-level; d. Significance at voxel-level.

Important for executive functioning in differentiating between suicide attempters and patients without attempts. Nevertheless, the trendwise difference may entail that compared to dysfunction of emotion processing, the neural functioning during executive processing in suicide patients might be disrupted albeit to a lesser extent. Furthermore, the insula has been implicated in primary interoceptive representations (Craig, 2009), response selection (Taylor et al., 2009) and novelty-seeking (Sugiura et al., 2000). In depressive patients, altered insular function has also found to be involved in the ineffective anticipation and processing of aversive experience (Giesecke et al., 2005; van Tol et al., 2011). Therefore, trendwise hyper insular activation in suicide attempters might indicate increased propensity for salience detection together with inability to select appropriate behavioral responses to cope with environmental demands.

To the best of our knowledge, our study is the first to study neural correlates during both emotion processing and executive control directly comparing suicide attempters, suicide ideators, MDD patient controls and healthy controls. However, our results should be understood within the context of the following limitations. First, our semi-structured scale for suicide ideation and one additional question on suicide attempts did not include assessments of frequency and detailed suicidal thoughts, and cannot fully assess clinical judgment on credibility and validity of their behavior. However, this approach allows investigating suicidal ideation without disrupting the rapport between interviewer and patient, which enhances data quality during the survey. Second, our sample selection resulted in a relatively small sample of subjects with previous attempts and included attempters with current suicidal ideations. Furthermore, we restricted our analyses to regions of interest that were strongly activated during the task, as previously reported (Demenescu et al., 2011; van Tol et al., 2011). We may therefore have been less sensitive to effects occurring in other brain regions associated with emotional processing and suicidality. Finally, by using a cross-sectional design, it was not possible for us to study the long-term development of suicidality or predict its course, for which longitudinal prospective studies are necessary.

In summary, our findings contribute to our understanding of the neural underpinnings of suicidality, suggesting that primary evaluation of emotional stimuli may be affected to a stronger extent than executive control. Altered facial processing to emotional information represent by FFA abnormality could differentiate suicidal attempts from suicidal ideations, and this may qualify for a candidate marker of suicidal risk after thorough replication. Distinctive brain mechanisms of emotion processing in different steps of suicidal behaviors suggest that the presence of suicidal ideation and suicidal attempts in depressed patients may be associated with differential neuropathology and therefore may have implications for treatment.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.jpsychires.2018.08.018.

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Conflicts of interest
Hui Ai, Jan-Bernard C. Marsman, Dick J. Veltman and Esther M. Opmeer declare no conflict of interest. Nic van der Wee received speaking fees from Eli Lilly and Wyeth; and served on advisory panels of Eli Lilly, Pfizer, Wyeth and Servier. Marie-José van Tol received speakers fees from Lundbeck n.v. Henricus G. Ruhé received speaking fees from Lundbeck n.v. Astra Zeneca and an Investigator Initiated Trial grant from Lundbeck n.v. André Alemán received an investigator-initiated unrestricted research grant from Bristol-Myers Squibb and speakers bureau honoraria from Lundbeck n.v. All of these activities are not directly related to the present study and, therefore, do not form a conflict of interest.