Reduced somatostatin in subgenual anterior cingulate cortex in major depression

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A B S T R A C T  

Converging evidence suggests a central role for dysfunction of the subgenual anterior cingulate cortex (sgACC) in the pathophysiology of major depressive disorder (MDD). Underlying mechanisms may include altered GABAergic function. Expression of somatostatin (SST), an inhibitory neuropeptide localized to a subset of GABA neurons, has been shown to be lower in the dorsolateral prefrontal cortex of male MDD subjects. Here, to investigate whether alterations in SST may contribute to sgACC dysfunction in MDD, and whether the alterations display sex-specificity, we measured sgACC SST at the mRNA and precursor peptide levels in a large cohort of subjects with MDD. SST mRNA levels were analyzed by quantitative PCR (qPCR) in the postmortem sgACC from male (n=26) and female (n=25) subjects with MDD and sex-matched subjects with no psychiatric diagnosis (n=51). Prepro-SST protein levels were assessed in a subset of subjects (n=42 pairs) by semi-quantitative Western blot. The mRNA expression of SST was significantly reduced by 38% in female subjects and by 27% in male subjects with MDD. The characteristic age-related decline in SST expression was observed in control (Pearson R=−0.357, p=0.005) but not MDD (R=−0.104, p=0.234) subjects, as low expression was detected across ages in MDD subjects. Protein expression was similarly reduced by 19% in both MDD groups, and findings were more robust in female (p=0.0056) than in males (p=0.0373) compared to respective controls. In conclusion, low SST represents a robust pathological finding in MDD. Specifically, alterations in SST signaling and/or SST-bearing GABA neurons may represent a critical pathophysiological entity that contributes to sgACC dysfunction and that matches to the high female vulnerability to develop MDD.

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Introduction  

An extended corticolimbic circuitry regulating mood has been implicated in the pathophysiology and treatment of MDD (Semino-wicz et al., 2004). One of the components of this circuitry, the sgACC has been shown to play a major role in both the induction of the depressive state and in treatment response to multiple modalities (Agid et al., 2007). For example, positive response from a baseline depressed state, regardless of treatment modality (electroconvulsive therapy, deep brain stimulation, and antidepressant or placebo) is associated with a decrease in sgACC activity (George et al., 1999; Mayberg et al., 1999; Nobler et al., 2001; Mayberg, 2002). Furthermore, with tryptophan depletion or recollection of a sad memory, transient increase in sgACC activity occurs in healthy non-depressed subjects (Mayberg et al., 1999; Talbot and Cooper, 2006).

Increasing evidence suggests an impaired excitation/inhibition balance in MDD potentially mediated by decreased GABA content, as observed by proton magnetic spectroscopy in occipital and frontal cortices (Sanacora et al., 1999, 2004), or by transcranial magnetic stimulation paradigms (Levinson et al., 2010), which is reversed after antidepressant treatments (Sanacora et al., 2002, 2003). As GABA synthesis and release is found largely in inhibitory neurons, these results suggest that altered GABA neuronal microcircuitry and associated inhibition may contribute to altered sgACC function in MDD (Valentine and Sanacora, 2009). Dysregulation of the neuronal-interneuronal microcircuitry within the sgACC has yet to be elucidated. Morphometric studies have reported reduced density and size of cortical neurons (Brodmann transitional area 10–47, 47) (Rajkowska et al., 1999), recently attributed to interneurons in some studies (Brodmann area 9, 17, and 47), but not all (Brodmann Area 24) (Rajkowska et al., 2007; Maciag et al., 2010). The nature of the affected cells in MDD is beginning to be characterized, using cellular markers expressed in distinct interneuronal populations. Accordingly, the density of calbindin-immunoreactive (CR) interneurons was significantly reduced in occipital and orbitofrontal cortices of MDD subjects (Rajkowska et al., 2007; Maciag et al., 2010), but unchanged in two other studies in cingulate and dorsolateral prefrontal cortex (Beasley et al., 2002; Cotter et al., 2002). In the context of a survey of markers for GABA neuron populations, we recently identified a
Table 1 Characteristics of male subjects.

<table>
<thead>
<tr>
<th>Case Mode of death</th>
<th>Cause of death</th>
<th>Race</th>
<th>Age</th>
<th>PMI</th>
<th>pH</th>
<th>RNA ratio</th>
<th>RIN</th>
<th>Case DSM-IV diagnoses</th>
<th>Mode of death</th>
<th>MDD subtype</th>
<th>Cause of death</th>
<th>Race</th>
<th>Age</th>
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<th>pH</th>
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<td>60</td>
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<td>6.79</td>
<td>1.5</td>
<td>9.0</td>
<td>505 MDD</td>
<td>Suicide</td>
<td>Recurrent and familial</td>
<td>Gunshot</td>
<td>W</td>
<td>57</td>
<td>12.8</td>
<td>7.14</td>
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<tr>
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<td>Asphyxiation due to hanging</td>
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<td>22</td>
<td>20.0</td>
<td>7.04</td>
<td>1.4</td>
<td>7.4</td>
<td>513 MDD</td>
<td>Suicide</td>
<td>Recurrent and familial</td>
<td>GSW of chest</td>
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<td>Ruptured abdominal aortic aneurysm</td>
<td>W</td>
<td>62</td>
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<td>6.39</td>
<td>1.4</td>
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<td>613 MDD</td>
<td>Suicide</td>
<td>Recurrent and familial</td>
<td>Hanging</td>
<td>W</td>
<td>59</td>
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<td>6.95</td>
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<td>W</td>
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<td>Familial</td>
<td>Asphyxiation due to hanging</td>
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<td>8.1</td>
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<td>1.4</td>
<td>7.9</td>
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<td>Familial</td>
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<td>1161 MDD</td>
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<td>Hanging</td>
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<td>7.2</td>
<td>1226 MDD</td>
<td>Natural</td>
<td>Recurrent</td>
<td>ASCVD</td>
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<td>8.4</td>
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<td>Recurrent</td>
<td>Electrocution</td>
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<td>1.5</td>
<td>8.2</td>
<td>943 MDD</td>
<td>Suicide</td>
<td>Familial</td>
<td>Combined drug overdose</td>
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<td>6.45</td>
<td>1.6</td>
</tr>
<tr>
<td>1372</td>
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<td>Asphyxiation due to compression of upper torso</td>
<td>W</td>
<td>37</td>
<td>20.5</td>
<td>6.56</td>
<td>1.6</td>
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<td>10010 MDD</td>
<td>Suicide</td>
<td>Recurrent</td>
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<td>6.56</td>
<td>1.6</td>
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<td>Recurrent</td>
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<td>20.0</td>
<td>6.55</td>
<td>2.0</td>
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Mean 51.0 17.2 6.7 1.6 8.1
SD 9.4 6.9 0.3 0.3 0.7

Mean 51.4 15.5 6.7 1.6 8.1
SD 10.3 5.8 0.3 0.2 0.7

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**a** No statistical differences in any cofactor variability (p < 0.05 by one way ANOVA)

**b** ASCVD indicates arteriosclerotic cardiovascular disease; ASHCVD indicates arteriosclerotic hypertensive cardiovascular disease.

**c** Indicates prescribed medications at time of death (B, Benzodiazepines; C, Anticonvulsants; D, Antidepressants; L, Lithium; N, No medications; O, Other medication(s); P, Antipsychotic; and U, Unknown).

**e** Alcohol dependence, current at time of death.

**f** Alcohol abuse, in remission at time of death.

**g** History of psychotic features

**h** Other substance dependence, current at time of death.

**i** Other substance abuse, in remission at time of death.

**j** In full remission at time of death.

**k** Alcohol abuse, current at time of death.

**l** History of psychotic features

**m** Other substance dependence, in remission at time of death.

**o** Other substance abuse, current at time of death.

**p** In partial remission at time of death.

**q** Other substance dependence, in remission at time of death.

**r** Alcohol dependence, in remission at time of death.

**s** Other substance abuse, current at time of death.

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significant decrease in SST expression in the dorsolateral prefrontal cortex of subjects with MDD (Sibille et al., 2011). SST’s original function was identified as inhibition of human growth hormone, but further studies have shown a generally inhibitory function across different organ systems, including the central nervous systems (CNS) (Viollet et al., 2008). SST acts presynaptically by inhibiting glutamate release, activating potassium leak current, or inhibiting voltage-dependent calcium currents, depending on the anatomical structure (Baraban and Tallent, 2004). Postsynaptically, SST inhibits neurons through dendritic hyperpolarization, by activation of either voltage dependent \( (I_h) \) or voltage-independent \( (I_{K(L)}) \) \( K^+ \) currents and inhibition of voltage-activated \( Ca^{2+} \) currents and consecutive \( Ca^{2+} \)-induced currents (Baraban and Tallent, 2004). Furthermore, SST is upregulated in the hippocampus of a rat model of electroconvulsive treatment (Newton et al., 2003). As a neuropeptide in the CNS, SST is co-localized and co-released in a GABA+ /CB+ interneuron subset (Viollet et al., 2008).

In this study, we first sought to determine SST expression in MDD subjects compared to subjects with no psychiatric diagnosis in the sgACC, hence extending our prior studies in the dorsolateral prefrontal cortex. Based on prior evidence suggesting sex differences in disease-related SST changes (Melloni et al., 2009), and in view of the robust sexual dimorphism in MDD prevalence (Kessler et al., 2003), we also determined whether MDD-related SST expression changes display sex-specific patterns, by comparing MDD-related SST changes between two large cohorts of male and female MDD subjects and subjects with no psychiatric diagnosis. Moreover, since age-associated decrease in SST mRNA can explain within-group variability in measures (Sibille et al., 2011), we further investigated the effect of age in the control and MDD subgroups. Finally, as the short half-life of the SST protein complicates its quantification in postmortem tissue (Hayes et al., 1991), using quantitative Western blot techniques, we measured SST preproto-peptide, as the closest protein match, to indirectly estimate SST protein levels in MDD.

Materials and methods

Human subjects

After consent was obtained from the next of kin, brain specimens in the Brain Tissue Donation Program at the University of Pittsburgh were obtained during autopsies conducted at the Allegheny County Medical Examiner’s Office (Pittsburgh, PA, USA). Two cohorts of MDD subjects were examined (male, \( n = 26 \); female, \( n = 25 \)). Each subject was matched for sex and as closely as possible for age with one control subject (Tables 1, 2). Subject groups did not differ in mean age, PMI, RNA integrity number \( (\text{RIN}) \), RNA ratio, or brain pH as determined by one way ANOVA \( (p > 0.05) \).

For all subjects, consensus DSM-IV diagnoses of MDD were made by an independent committee of experienced clinical research scientists at a case conference utilizing information obtained from clinical records, toxicology exam and a standardized psychological autopsy (Glantz et al., 2000). The latter incorporates a structured interview, conducted by a licensed clinical psychologist with family members of the index subject, to assess diagnosis, psychopathology, medical, social and family histories, as well as history of substance abuse using the structured clinical interview for DSM disorders \( (\text{SCID}) \) and other assessment tools (Spitzer et al., 1992). Using the information judged to be reliable at the diagnostic conference, a symptom score \( (1 = \text{unequivocal yes}; \ 0.5 = \text{unequivocal no}) \) was calculated based on the presence at time of death, or a prior history, of nine symptoms of depression: depressed mood, anhedonia, appetite disturbance, sleep disturbance, psychomotor change, anergia, self-rejection, impaired concentration of decision-making, and suicidality. All procedures were approved by the University of Pittsburgh’s Committee for the Oversight of Research Involving the Dead and Institutional Review Board for Biomedical Research.

Tissue preparation

As previously described (Volk et al., 2000), the right hemisphere of each brain was sectioned along the coronal plane, immediately frozen and stored at \(-80^\circ C\). Samples containing all six cortical layers, but excluding the adjacent white matter, were harvested from coronal cryostat sections \( (20 \mu m) \) at the anatomical level corresponding to sgACC (Brodman area 25) and collected into tubes containing Trizol reagent (Invitrogen, Carlsbad, CA, USA) for RNA isolation. The location of the sgACC was determined from Nissl-stained sections using cytoarchitectonic criteria as previously described (Volk et al., 2000). Total RNA was isolated from Trizol homogenates of sections, further purified by RNeasy columns (Qiagen, Valencia, CA, USA) and RNA integrity \( (\text{RIN}) \) was assessed by measuring using the Bioanalyzer 2100 (Agilent Technologies, Walbronn, Germany) (Imbeaud et al., 2005). To generate cDNA, 1 \( \mu g \) total RNA was mixed with oligo-dT primers and SuperScript II Reverse Transcriptase \( (\text{RT}) \) as per manufacturer’s protocol (Invitrogen, Carlsbad, CA).

Real-time quantitative polymerase chain reaction \( (\text{qPCR}) \)

qPCR analyses (Glorioso et al., 2006) were performed using SST-specific primers and three internal controls on sgACC cDNA samples as described previously (Sibille et al., 2009). In brief, small PCR products \( (80–120 \text{ base-pairs}) \) were amplified in quadruplets on an Opticon real-time PCR machine (BioRad Cie, Waltham, MA, USA), using universal PCR conditions \( (65^\circ C–59^\circ C \text{ touch-down}) \), followed by 35 cycles \( (15\ s \ at \ 95^\circ C; 10\ s \ at \ 59^\circ C; 10\ s \ at \ 72^\circ C) \). cDNA \( (150\ pg) \) was amplified in 20 \( \mu l \) reactions \( (0.3\times \text{Sybr-green}; 3\ mM \text{MgCl2}; 200\ \mu m\ dNTPs; 200\ \mu m\ primers) \). 0.5 unit Platinum Taq DNA polymerase \( (\text{Invitrogen, Carlsbad, CA, USA}) \). Primer dimers were assessed by amplifying primers without cDNA and retained if they produced no dimers or non-specific signal only after 35 cycles. Each qPCR run included two subjects per pair, 3 pairs with amplification of all 4 transcripts of interest in quadruplicate using a plate with 96 wells \( (6\ \text{subjects} \times 4\ \text{transcripts} \times 4\ \text{replications}) \). Three internal control transcripts encoding for beta-actin, cyclophilin A, and glyceraldehyde-3-phosphate dehydrogenase were amplified for each subject. The difference in cycle threshold for SST was calculated by subtracting the mean cycle threshold for the three internal controls from the cycle threshold of the SST transcript. This difference in cycle threshold \( (\text{dct}) \) represents the log2-transformed expression ratio of SST to the geometric mean of the three internal control transcripts \( (\text{Vandesompele et al., 2002}) \); and the relative expression level of SST was determined as \( 2^{−\text{ddCt}\times 10} \).

qPCR statistical analysis

Diagnosis-related expression differences in SST signal was determined by analysis of covariance \( (\text{ANCOVA}) \) using SPSS (SPSS, Inc., Chicago, IL). The qPCR data were averaged across the four replicates and transformed into relative expression levels \( (2^{−\text{ddCt}\times 10}) \) so that plots of data are intuitive (i.e., higher values represent greater relative expression). To determine relevant covariates, nominal factors were each tested as the main factor in single ANOVA, and scale covariates were tested by Pearson correlation. Multiple comparisons with covariates (see result section for specific covariates used in each ANCOVA) were controlled by adjusting for simultaneous inference of significance levels using the Bonferroni–Holm method (Volk et al., 2000) in which \( p \)-values are ordered from the smallest \( (i = 1) \) to the largest \( (i = N) \) among multiple comparisons; the significance level for each comparison is defined as \( \alpha = 0.05/(N+1−i) \). MDD/control pairing and covariate factors with significant effects were used in the
Table 2
Characteristics of female subjects.

<table>
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<th>Case Mode of death</th>
<th>Race</th>
<th>Age</th>
<th>PMI</th>
<th>pH</th>
<th>RNA ratio</th>
<th>RIN</th>
<th>Mode of death</th>
<th>DSM-IV diagnoses</th>
<th>Cause of death</th>
<th>Race</th>
<th>Age</th>
<th>PMI</th>
<th>pH</th>
<th>RNA ratio</th>
<th>RIN</th>
<th>Medications</th>
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<td>Natural ASCVD W 60 9.5 6.9 1.9 8.7</td>
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<td>Suicide</td>
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<td>556</td>
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<td>Suicide</td>
<td>Recurrent</td>
<td>Gunshot</td>
<td>W 62</td>
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<td>9.2</td>
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<tr>
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<td>Natural</td>
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<td>Recurrent</td>
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<td>Asphyxiation</td>
<td>W 47</td>
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<td>Pulmonary embolism</td>
<td>W 39</td>
<td>11.2</td>
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<td>1.8</td>
<td>8.0</td>
<td>B D O</td>
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<td>Recurrent</td>
<td>Pulmonary thrombosis</td>
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<td>D O</td>
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<td>Incised wounds</td>
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<td>Pulmonary thromboembolism W 50 23.5 6.7 1.3 7.7</td>
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<td>Recurrent</td>
<td>Intrapitoneal hemorrhage</td>
<td>W 60</td>
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<td>CO P D W 57 14.9 6.8 1.9 9.0</td>
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<td>Trauma</td>
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<td>B D O P</td>
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<tr>
<td>Subarachnoid hemorrhage W 74 24.9 6.6 1.9 7.0</td>
<td>10028</td>
<td>MDD</td>
<td>Suicide</td>
<td>Single episode</td>
<td>Gunshot</td>
<td>W 72</td>
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<td>1.4</td>
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<td>B D O</td>
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<tr>
<td>Subarachnoid hemorrhage W 74 24.9 6.6 1.9 7.0</td>
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<td>Suicide</td>
<td>Single episode</td>
<td>Gunshot</td>
<td>W 72</td>
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<td>1.4</td>
<td>7.0</td>
<td>B D O</td>
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</table>

| Mean 49.0 16.6 6.7 1.7 8.3 | SD 15.0 5.8 0.3 0.3 0.7 | Mean 47.8 17.1 6.6 1.7 8.2 | SD 14.4 4.9 0.3 0.3 0.7 |

Note: No statistical differences in any cofactor variability (p<0.05 by one way ANOVA).

a. ASCVD indicates arteriosclerotic cardiovascular disease; ASHCVD indicates arteriosclerotic hypertensive cardiovascular disease.
b. PMI indicates postmortem interval in hours.
c. Indicates prescribed medications at time of death (B, Benzodiazepines; C, Anticonvulsants; D, Antidepressants; L, Lithium; N, No medications; O, Other medication(s); P, Antipsychotic; and U, Unknown).

- History of psychotic features.
- Alcohol abuse, current at time of death.
- Other substance dependence, in remission at time of death.
- In partial remission at time of death.
- Alcohol dependence, suicide at time of death.
- Other substance dependence, current at time of death.
- Alcohol dependence, current at time of death.
- Alcohol abuse, in remission at time of death.
- Other substance abuse, in remission at time of death.
- Other substance abuse, current at time of death.
- Other substance abuse, current at time of death.
ANCOVA model with SST mRNA as the dependent variable and subject group as the main effect. Exploratory analysis including multiple covariate factors with trend-like effects ($p < 0.2$) in the ANCOVA model did not affect the results and are not reported. Variance homogeneity was tested by the Kruskal–Wallis test.

**Protein isolation**

Acetone precipitation of proteins was carried out following the RNA extraction from the TRIzol samples of brain tissues. The lower red phenol-chloroform phase was used for protein isolation, using

![Fig. 1. SST transcript expression is reduced in MDD subjects. SST expression (in relative expression of the control group mean) is displayed for each control (circles) and MDD subject (triangles) in the combined group (A) and in the male (B) and female (C) cohorts. The mean value is shown for each subject group (black hash marks). Standard deviation is shown in red. *: $p < 0.05$; **: $p < 0.01$ (ANCOVA analysis).](image1)

![Fig. 2. SST transcript inverse correlation with age is reduced in females and in MDD. mRNA signal and trend line are shown for control subjects (circles) in black, and in red for controls (triangles). A) In the male/female combined group, SST expression is significantly inversely correlated with age in control subjects ($R = -0.357; p = 0.005$), but not in MDD subjects ($R = -0.104; p = 0.234$). B) In the male cohort SST expression is significantly inversely correlated with age ($R = -0.509; p = 0.004$), but not in MDD subjects ($R = -0.143; p = 0.243$). C) In the female cohort, SST expression is inversely correlated with age at the trend level in control subjects ($R = -0.278; p = 0.089$), and not in MDD subjects ($R = -0.116; p = 0.291$).](image2)
of infrared Odyssey Infrared imaging system captures the whole dynamic range secondary antibodies were used in signal detection. The Li-Cor parallel statistical approaches were applied. First, paired t-tests were different Western blots. To control for gel-to-gel variability, two signal ratios were calculated. Samples were processed in matched lane used here). Dual signals were detected and prepro-SST/Actin (Sibille et al., 2009). In brief, gel-transferred PVDF membrane were the Odyssey system (LI-COR Biosciences, Lincoln, NE) as described, age was a significant covariate in the ANCOVA model, subject group was statistically significant and sgACC SST transcript expression was reduced by 27% in male MDD subjects compared to controls ($F_{1,28} = 4.295, p = 0.044$) (Fig. 1B). In the female group ($n=25$ pairs), none of scale (including age) or nominal cofactors were significant by one-way ANOVA or Pearson correlation. sgACC SST transcript expression was significantly reduced by 38% in female MDD subjects compared to controls ($F_{1,28} = 7.771, p = 0.008$) by ANOVA (Fig. 1C). Hence, SST mRNA expression was significantly reduced in MDD subjects, and to a larger extent and greater statistical significance in female MDD subjects.

To investigate whether SST levels related to disease severity, we assessed correlations between SST qPCR levels and depressive symptoms, as determined by psychological autopsy (See Methods). We observed a moderate negative correlation between past depressive symptom score and SST expression ($R = -0.276, p = 0.025$). When segregated by sex, the effect was more profound in female MDD subjects ($R = -0.528, p = 0.003$) and absent in male MDD subjects ($R = 0.023, p = 0.456$). There was no correlation with symptom number at time of death and SST expression for the combined or sex-specific group (all $R<0.114$; all $p>0.215$).

**Reduced SST age regulation in subjects with MDD**

The expression of SST is significantly downregulated with age (Hoffman and Sladek, 1980; Hayashi et al., 1997; Erraji-Benchekroun et al., 2005), which we showed can explain some of the experimental variability that is observed in SST measures (Fig. 1; see also (Sibille et al., in press)). As described, age was a significant covariate by ANCOVA for all samples and in the male cohort. When subjects were subdivided into control and MDD groups, the age-SST correlation remained significant in controls ($R = -0.357, p = 0.005$), but not in the MDD group ($R = -0.104, p = 0.234$), as SST mRNA levels were lower at all ages in most subjects with MDD (75% cases)
compared to age-matched controls (Fig. 2A). Similarly, when segregated by sex, male control subjects displayed a statistically significant inverse correlation with age (R = −0.509, p = 0.004), but not MDD subjects (R = 0.143, p = 0.243) (Fig. 2B). In female subjects, decreased SST with increasing age was at the trend levels in controls (R = −0.278, p = 0.089) and not significant in MDD subjects (R = −0.116, p = 0.291).

Reduced prepro-SST protein levels in subjects with MDD

To assess whether decreased mRNA translated to decreased protein level, we investigated tissue content level of the prepro-peptide for SST. SST’s active form has been shown to rapidly degrade within the first few hours postmortem, which complicates its analysis in postmortem cohort (Hayes et al., 1991). However, we have now shown that the precursor protein is present in the postmortem tissue (Sibille et al., in press). The prepro-SST immunoreactive band (Fig. 3A) migrated at the expected size and was not correlated with PMI (R = −0.37, p = 0.38). Using Western blot analysis, the SST prepro-peptide was decreased by 19% in MDD subjects compared to control subjects (n = 42 pairs available, males, n = 26; females, n = 16; 3 replicate experiments; Stouffer’s z-score on paired T-test, p = 0.0001; Stouffer’s z-score test on ANCOVA results, p = 0.0005) (Fig. 3A). There was no statistically significant correlation between prepro-SST protein levels and age in control or depressed subjects, however this negative result may have been complicated by the increased variability in measures obtained across multiple gels (coefficient of variation (CV) across blots: CV = 0.47; and within blots: CV = 0.29). After segregation by sex, the reduction remained at 19% in male MDD subjects (3 replicates, Stouffer’s z-score on paired T-test, p = 0.002, and on ANCOVA results, p = 0.0373) (Fig. 3A). In female MDD subjects, SST prepro-peptide was similarly decreased by 19%, but at higher statistical significance (3 replicates, Stouffer’s z-score on paired T-test, p = 0.0001; Stouffer’s z-score test on ANCOVA results, p = 0.0056).

We observed a weak correlation or no correlation (0.04 < p-value < 0.46) between pre-proSST protein and mRNA levels in the combined or sex-specific groups, which may reflect the blot to blot variability in the assessment of protein levels, and/or additional processing regulation of the precursor protein into functional SST.

Discussion

Results from this study show that SST is downregulated by ~30% at the RNA level and by ~20% at the precursor protein level in the sgACC of male and female subjects with MDD compared to normal non-psychiatric control subjects. These results extend our prior findings of reduced SST mRNA expression from the dorsolateral prefrontal cortex (Sibille et al., 2011) to the subgenual ACC, a central brain area in a corticollumic circuitry of mood regulation, hence representing a robust and replicated molecular phenotype for major depression. Comparable results were obtained in male and female subjects with MDD, suggesting a similar pathological entity across sex groups, but the extent and/or statistical significance of the findings were more robust in female subjects (or alternatively more variable in males), both at the mRNA and protein levels. Results were independent of cofactors associated with clinical features of the illness or technical parameters of brain collection, with the exception of age and symptom number. Similar to our prior observation in the dorsolateral prefrontal cortex, we show that the characteristic downregulation of SST mRNA with age was blunted in MDD subjects, as SST was low at most ages in those subjects. Notably, the age effect was attenuated in both control and MDD female subjects, potentially explaining the less variable findings in this cohort, due to a decreased analytical confounding effect of age in that group. Together, these results establish low SST as a frequently observed pathological finding that is shared between the dorsolateral prefrontal cortex and the sgACC, and that corresponds with the elevated vulnerability and prevalence of MDD in female subjects. The findings were present regardless of the depressive syndrome was fully present or in full/partial remission at time of death, moderately and inversely correlated with symptom numbers, together suggesting that low SST may represent a critical vulnerability factor to develop MDD, and that additional factors may further determine the severity of the illness.

In this report, we also demonstrated a reduction in the level of the prepro-SST peptide. Since direct levels of SST are difficult to measure in postmortem tissue due to rapid postmortem peptide processing (Hayes et al., 1991), we speculate that low prepro-SST may represent an adequate proxy of SST level, although additional regulatory steps and effects of MDD on peptide processing likely occurred, as suggested by the lack of subject-wise correlation with RNA levels. The extent of the reduction was more robust in female subjects.

There is a historical literature associating low SST levels in cerebrospinal fluid (CSF) with depressed states (Post et al., 1988; Rubinow et al., 1988). SST was an early target of investigation for depression as the major neuropeptide that inhibits the hypothalamic–pituitary–adrenal (HPA) axis, inhibiting corticotrophin releasing hormone (CRH) and the stress response (Post et al., 1988). SST expression was also shown to be positively regulated by brain-derived neurotrophic factor (BDNF) and to inversely correlate with age (Hoffman and Sladek, 1980; Hayashi et al., 1997; Erraji-Benchekroun et al., 2005). The etiological factors leading to reduced SST are not known and may include decreased BDNF-mediated transcriptional activation, through decreased TrkB and/or TrkC receptors availability or signaling (Rage et al., 1999; Jin et al., 2003; Hashimoto et al., 2005; Glorioso et al., 2006) and/or through changes in methylation status at the SST promoter. In major unipolar depression or bipolar depression, SST was shown to be transiently decreased in CSF and normalized with recovery (Post et al., 1988; Pantazopoulos et al., 2007). In contrast other disorders, such as Alzheimer’s disease, showed an irreversible decrease in SST concentrations in the CSF (Post et al., 1988). Elevated CSF SST levels have also been reported in mania compared to subjects with MDD, schizoaffective disorder, or schizophrenia (Sharma et al., 1995). SST was also investigated in the context of its influence on sleep quality, as a potential therapeutic approach to sleep disturbances in MDD, although with inconsistent results (Kuperf et al., 1992; Frieboes et al., 1997; Spier and de Lecea, 2000). However, despite these earlier findings, interest in this neuropeptide in MDD has declined over time, potentially due to the difficulties in unraveling the complexity of neuroendocrine changes in MDD.

Low SST has also been reported across cortical layers in schizophrenia (Morris et al., 2008) in the context of reduced parvalbumin (Lewis et al., 2001; Beasley et al., 2002; Hashimoto et al., 2003, 2008; Sakai et al., 2008). In contrast, SST appears to be selectively downregulated in MDD, as parvalbumin and other GABA markers are unchanged in the dorsolateral prefrontal cortex of MDD subjects (Sibille et al., 2011). As suggested by the anatomical and functional diversity of GABA interneuron populations, changes in SST neurons, combined with other GABA- and disease-specific changes in related systems, may result in distinct pathophysiological outcomes. Hence, we speculate that the present findings reflect MDD-specific microcircuitry deficits, and that the consequences on associated information processing may vary across diseases, potentially underlying the prevalence of distinct symptom dimensions across diseases, i.e. working memory deficits in schizophrenia (Lewis and Gonzalez-Burgos, 2006) or altered mood regulation in MDD (Sibille et al., 2011). We believe that our replicated findings of low SST in brain areas that are relevant to a neural network implicated in the pathophysiology and treatment response in MDD (Seminowicz et al., 2004; Agid et al., 2007), provide a new perspective on SST as an inhibitory neuropeptidomodulatory peptide in the brain, in addition to its putative neuroendocrine-related dysfunction in MDD, and as a target for investigations with functional implication for local neuronal microcircuity in MDD. Notably, the fact that SST was downregulated in
dorsolateral prefrontal and cingulate cortices, despite variable functional changes in those areas (Seminowicz et al., 2004), suggesting low SST being a risk factor (of yet-unknown etiology), rather than a pathological consequence of the illness, as compensatory changes may show opposite patterns. SST is coexpressed and coreleased with GABA in interneurons in many parts of the human brain, including the sgACC. Thus low SST may provide a means to begin characterizing changes in the local microcircuitry that may be involved in the excitation/inhibition imbalance suggested in limbic brain areas in MDD (Maciag et al., 2010).

Specifically, the SST+ neocortical circuitry inhibits distal dendrites on target neurons, compared to the soma-targeting parvalbumin+ inhibitory circuitry for instance.

Other than age and symptom number of the subjects, none of the clinical, demographic and technical parameters had any detectable effects on SST expression. This includes particulars of brain tissue collection postmortem (PMI, pH, RNA ratio, and RIN), and clinical variables (race, remission status, antidepressants, and mode of death). The fact that antidepressant exposure in rodent models results in either increase (Pallis et al., 2009) or no change (Surget et al., 2009) in SST mRNA levels, suggesting that the reduction in SST mRNA expression observed here is instead associated with the disease process of MDD. Furthermore, the absence of change of SST reduction in depressed subjects with antidepressant medication suggests that this mechanism is independent of treatment response or drug mechanism. The moderate inverse correlation between SST levels and symptom numbers suggest that low SST may contribute to disease severity, in addition to being associated with disease state. Thus, low SST may represent a stable vulnerability factor involved in the development of the illness and may determine in concert with other factors the severity of MDD. Accordingly, the more robust SST-related findings in female subjects would also be consistent with the increased vulnerability to develop episodes of MDD in that population.

In relation to age, SST levels progressively decline throughout adult life in control subjects (Glorioso et al., 2011), but were low at most ages in MDD subjects, displaying non-significant correlations with age. This was consistent across areas (Sibille et al., 2011) and cohorts (Fig. 2). We previously discussed potential mechanisms and implications of consistently low SST in MDD subjects (Sibille et al., 2011). SST is expressed transiently (Violet et al., 2008) and progressively decreases during development (Fung et al., 2010), hence by extension earlier in life, constitutive low levels of SST expression could result in alteration of normal brain development resulting in a greater vulnerability to depression throughout one’s lifespan. At the other end of the lifespan, decreasing SST levels in normal subjects may reach critical threshold, below which the vulnerability to develop MDD increases; so age-dependent reduction in SST levels may represent a vulnerability factor underlying the increased risk for low mood symptoms in elderly subjects (Fiske et al., 2009). Finally, the reduced SST expression could be representative of an overall decrease in the structure and functional capacity of the SST+ subgroup of interneurons, and additional gene products and neurotransmitter present in these interneurons (e.g., neuropetide Y, GABA) may participate in mediating the cellular dysfunctions leading to altered brain function and depressive states.

In summary, we have established a robust reduction in SST mRNA and precursor peptide in MDD subjects, with age, symptom number, and sex modulating that deficit. Alterations in SST-bearing GABA neurons and/or in SST signaling may thus represent a pathophysiological entity that contributes to sgACC dysfunction in both male and female subjects with MDD.

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