Psychobiological Characteristics of Dissociative Identity Disorder: A Symptom Provocation Study

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Background: *Dissociative identity disorder (DID) patients function as two or more identities or dissociative identity states (DIS), categorized as 'neutral identity states' (NIS) and 'traumatic identity states' (TIS). NIS inhibit access to traumatic memories thereby enabling daily life functioning. TIS have access and responses to these memories. We tested whether these DIS show different psychobiological reactions to trauma-related memory.*

Methods: *A symptom provocation paradigm with 11 DID patients was used in a two-by-two factorial design setting. Both NIS and TIS were exposed to a neutral and a trauma-related memory script. Three psychobiological parameters were tested: subjective ratings (emotional and sensori-motor), cardiovascular responses (heart rate, blood pressure, heart rate variability) and regional cerebral blood flow as determined with $H_2{}^{15}O$ positron emission tomography.*

Results: *Psychobiological differences were found for the different DIS. Subjective and cardiovascular reactions revealed significant main and interactions effects. Regional cerebral blood flow data revealed different neural networks to be associated with different processing of the neutral and trauma-related memory script by NIS and TIS.*

Conclusions: *Patients with DID encompass at least two different DIS. These identities involve different subjective reactions, cardiovascular responses and cerebral activation patterns to a trauma-related memory script.*

Key Words: Neuroimaging, cardiovascular, physiologic, subjective, autobiographical memories

Traumatic stress studies have focused on posttraumatic stress disorder (PTSD). Characteristic cerebral, endocrine, and cardiovascular responses of patients with PTSD to external stress stimuli have been reported (e.g. Rauch et al 2003; Tanev 2003). Functional neuroimaging of PTSD has revealed abnormalities in functional connectivity, regional volume and regional cerebral blood flow (rCBF) in several brain structures (e.g. Yamasue et al 2003; Lanius et al 2004; Tanev 2003; Vermetten and Bremner 2003).

Dissociative Identity Disorder (DID; DSM-IV [1994], American Psychiatric Association 1994), is associated with chronic traumatization (Nijenhuis et al 2002). Some consider DID a controversial diagnostic and nosological entity (Piper and Merskey 2004; Merckelbach et al 2002). Nevertheless, patients with DID find themselves to be able to function as two or more identities. These identities are also referred to as 'different emotional states,' 'alters' or 'dissociative identity states' (DIS). Each of the DIS is characterized by its own pattern of perception, reaction and thinking (Nijenhuis et al 2002; Dorahy 2001) and displays different psychobiological characteristics that are generally not reproduced by DID-simulating controls (e.g. Miller and Triggiano 1992; Putnam 1997). Differential responses in DID have been reported in electrodermal activity (Ludwig et al 1972; Larmore et al 1977), EEG (Mesulam 1981; Coons et al 1982; Hughes et al 1990; Putnam 1993), visual evoked potentials (Putnam 1992), cerebral blood flow (CBF; Mathew et al 1985; Saxe et al 1992; Tsai et al 1999), autonomic nervous system variables (Putnam et al 1990), optical variables (Birnbaum and Thomann 1996), and arousal (Putnam et al 1990). Affected brain regions most consistently reported are directly or indirectly linked with emotional and memory processing (Nijenhuis et al 2002; Dorahy 2001). None of these studies, however, have compared the response to trauma-related stimuli in the same patients remaining in different DIS.

As a neutral identity state (NIS), DID patients concentrate on functioning in daily life. To that end, this protective identity state seems to apply a censor mechanism to avoid access to or subsequent processing of at least a part of the painful memories. Thus, NIS has a degree of amnesia for traumatic memories ranging from lack of personalization of the traumatic past to total amnesia. A traumatic identity state (TIS), i.e. the trauma-associated identity state, is fixated on, and has access and responses to, the traumatic memories (Van der Kolk and Fisler 1995). As the treatment progresses, DID patients learn to evoke switching between NIS and TIS in a controlled way.

A previous study (Reinders et al 2003) demonstrated specific changes in localized brain activity consistent with the ability to generate at least two mental states of self-awareness (Putnam 1997). The current study aims to assess how DID patients process autobiographical neutral and trauma-related memories as NIS and TIS, using a script-driven symptom provocation paradigm (Rauch et al 1996) in a two-by-two factorial design. This design allows us to test whether NIS and TIS involve different patterns of rCBF and if these patterns are dependent on subjective and autonomic reactions. In addition, our current data relates to the discussion of the neural basis of emotion regulation in normal controls and (traumatized) patients (e.g. Phelps 2004; Phan et al 2002; Tanev 2003) and/or emotion suppression (e.g. Mitchell et al 2005; Phan et al 2005; Anderson et al 2004).

We a priori hypothesized that psychobiological differences exist for NIS and TIS and expected that while listening to the trauma-related memory script, compared to NIS, TIS displays (i) rCBF patterns that mimic emotional processing in patients with PTSD who re-experience traumatizing events (brain areas as reported in trauma-related literature: Bremner et al 1999a, 1999b; Lanius et al 2001, 2002; Liberzon et al 1999; Osuch et al 2001;

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Pissiota et al 2002; Rauch et al 1996; Reiman et al 2000; Shin et al 1999, 2001; Simeon et al 2000) (ii) more emotional and sensorimotor reactions, (iii) higher heart rate and blood pressure and less heart rate variability. Furthermore, (iv) when listening to the trauma-related memory script, compared to TIS, NIS displays perfusion differences in brain areas associated with inhibition of emotional responses to trauma-related information and with depersonalization (Simeon et al 2000; Phillips et al 2001). Finally, we hypothesized that (v) NIS and TIS have similar psychobiological reactions to memory scripts involving neutral personal experiences.

Methods and Materials

Patients

Patients meeting the DSM-IV American Psychiatric Association (1994) criteria for DID, as operationalized in the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D; Steinberg 1993), were invited to participate in the positron emission tomography (PET) investigation, which was approved by the Medical Ethical Committee of the Groningen University Hospital. Their treatment had to have progressed to phase II (Brown et al 1998), which involves therapeutic exposure to trauma-related memories.

Patients were capable of self-initiated and self-controlled switching between DIS in an experimental situation with minimal guidance of their psychotherapist. The structure of the patients had to encompass at least one TIS with a subjective sense of age exceeding 10 years and one NIS (Nijenhuis et al 2002).

Exclusion criteria were pregnancy, traumatic experiences in a hospital setting, systemic or neurological illness, and no command of the Dutch language. Eleven female patients (age range 27–48 years) gave written informed consent and participated. The therapist and the patient selected the NIS and TIS (when other DIS did not object) for participation in the investigation. Both NIS and TIS gave informed oral consent.

Stimulus Scripts

Studies of PTSD suggest that the provocation stimulus needs to be individualized and specific for the patient to respond physiologically (Casada et al 1998). In the present study, the patients were exposed to neutral personal memories that both DIS regarded as personal experiences, and to memories of traumatizing events that only TIS experienced as a personal memory. The patient offered their specific memories and the therapist cast them in terms of stimulus descriptions. To limit suggestion, memories described in the second person singular and response descriptions were excluded. An autobiographical neutral and a trauma-related memory script (MS) were developed. The latter was constructed such that it would not likely trigger an extreme emotional response. This guideline was dictated by ethics and the interest that patients would be able to complete the experimental procedure. After approval of the scripts by one of the principal investigators, the therapist audiotaped the 120 sec scripts in a neutral tone of voice for playback during the PET investigation.

PET Procedure

Each patient habituated to the PET environment prior to the investigation. Approximately two hours prior to the PET investigation a continuous ECG registration was started. A urine sample was obtained to detect potential illegal drug and concealed medication use. From these urine tests we could not confirm substance abuse or fraud.

The patients underwent eight scans, except one patient, who was not able to complete the paradigm, and only underwent six scans. Four different conditions were obtained twice, resulting in eight scans. The scanning sequence was NISn, NISt, TISn, TISt, TISn, TISt, NISn and NISt. The last minor character (n or t) denotes the content of the MS (neutral or trauma-related). For patient comfort considerations, i.e. minimizing the number of DIS switches, a fixed condition order was used. The therapist invited the patient to switch from NIS to TIS before the third scan, and from TIS to NIS before the seventh scan. The time interval between each scan was 15 min with five additional min for the switching procedure. When the patient received the bolus injection, the therapist was instructed to start the audiotape and to mark the ECG to indicate the 120 sec of symptom provocation. The heart rate variability (HRV) measurements consisted of one time domain variable, i.e. the average of normal-to-normal time intervals (AVGNN), a high frequency domain (HF) and a high frequency domain in normalized units (HF nu) as well as a low frequency domain (LF) and a low frequency domain variable in normalized units (LF nu). These were calculated over two min segments and compared with a baseline measurement (see: HRV Guidelines; Malik 1996). Heart rate variability analysis was performed using discrete Fourier transformation (Haaksma et al 1994).

Immediately following the end of the script, blood pressure (systolic and diastolic) and discrete heart rate frequency were measured. Next, the therapist inquired for the subjective emotional and sensori-motor experiences of the patient during the MS. The severity of sixteen affects and sensori-motor modalities were recorded using 0 (complete absence) to 10 (maximum possible) point analog scales. The six emotional dimensions consisted of fear, sorrow, sadness, anger, shame and disgust. With regard to re-experiencing phenomena each patient was asked which sensorimotor modalities were involved. The questioned sensorimotor modalities pertained to visual, kinesthetic, auditory, olfactory, and gustatory reactions, as well as pain and physical numbness, body stiffening, paralysis and restlessness. The presence of the DIS under investigation and the interference among DIS were also debriefed.

Image Acquisition and Data Processing

Data acquisition, reconstruction, attenuation correction, spatial transformation, spatial smoothing (isotropic Gaussian kernel of 12 mm) and global normalization were performed as usual (Reinders et al 2002, 2003). In brief, all 120 sec scans were obtained, after a bolus injection of 500 MBq of $H_2{}^{15}O$ for each scan, in 3D acquisition mode using a Siemens ecat exact HR+ PET scanner (Siemens/CTI, Knoxville, Tennessee). The emission scans were reconstructed using standard filtered back reconstruction. Calculated attenuation correction was used as attenuation correction method (Reinders et al 2002). All scans were corrected for remaining activity using a 30-sec background correction frame, which was acquired immediately prior to $H_2{}^{15}O$ injection. SPM99 was used for spatial transformation (using heavy regularization) (Friston et al 1995a; Talairach and Tournoux 1988) and statistical analysis (Friston et al 1995b) of the data.

Data Analysis: Autonomic and Subjective Reactions

Statistical analysis, missing value analysis and principal component analysis were performed with SPSSPC 8.0 (1997, SPSS Inc., Chicago, Illinois). Results with $p < .05$ are reported as significant. Within SPSS the two-by-two factorial design was defined with the first factor DIS, consisting of the levels NIS and TIS, and the second factor was MS, consisting of the levels neutral and trauma-related. No statistically significant differences between the initial and repeated measurement were found for

Table 1. Subjective and Autonomic Reactions

	DIS	MS	DIS * MS
Subjective Ratings			
Emotional rating	<.001	<.001	<.001
Sensori-motor rating	.001	<.001	.001
Autonomic Reactions			
Heart rate frequency	.004	<.001	.009
Systolic blood pressure	.024	.007	.026
Diastolic blood pressure	.064	<.001	.135
HRV			
AVGNN	.002	.006	.007
HF	n.s.	n.s.	n.s.
LF	n.s.	n.s.	n.s.
HF_nu	n.s.	n.s.	n.s.
LF_nu	n.s.	n.s.	n.s.

Factorial statistical analyses of the subjective reactions (emotional and sensori-motor ratings) and autonomic (discrete heart rate, systolic and diastolic blood pressure and heart rate variability) measurements. The statistical analyses consist of the two main effects and the accompanying interaction effect. Statistical values are reported in *p* values.

DIS, dissociative identity state; MS, memory script; DIS * MS, interaction effect; HRV, heart rate variability; AVGNN, average of normal-to-normal time intervals; HF, high frequency domain; HF_nu, high frequency domain in normalized units; LF, low frequency domain; LF_nu, low frequency domain variable in normalized units.

the subjective (averaged over emotional and sensori-motor modalities, respectively) and autonomic reactions allowing a within subject condition effects testing using a repeated measures general linear model.

Data Analysis: PET-Data

A few patients reported interference among DIS during a small number of scans and three patients were not free of medication. One patient used fluoxetine, one patient used paroxetine, and one patient used a combination of levopromazine, promethazine and flurazepam. SPM was used to test interference and medication effects using extended linear models (see below for the definitive linear model). Interference effects were set up as a covariate of interest and tested with an *F* test. Medication effects were tested on an individual level (excluding one subject from the group) and on a group level (medication vs. no medication), with *t* tests. No significant rCBF effects were found when testing the interference effects, nor when testing effects of medication independently (data not shown). Although it could be argued that the effects did not reach statistical threshold due to insufficient power, the fact remains that, using SPM and the accompanying GLM, there is no significant contamination of the rCBF condition effects due to medication or interference effects. One patient's PET data were excluded from the analyses due to apparent neurological malformations. Due to head movements between scans, e.g. induced by a DIS switch, parts of the brain moved outside the field of view of the PET scanner. To maximize available brain volume for statistical testing, 11 scans with major nonscanned brain parts were discarded after visual inspection by two independent observers. Three scans with observed head movement during the PET data collection and one scan suffering a procedural error were also excluded from the data analyses. A total of 65 scans were statistically analyzed (17 NISn ($n = 10$), 17 NISt ($n = 10$), 19 TISn ($n = 10$) and 12 TISt ($n = 7$)).

The general linear model (GLM) consisted of three parts: the conditions (NISn, NISt, TISn and TISt), the subjective reactions and the autonomic reactions. To retain optimal statistical power of SPM, the 25 covariates (16 subjective ratings and 9 cardiovascular measurements) were condensed, using a principal component analysis (PCA). The variance in the subjective ratings could be described with the first two principal components (explaining 64% of the variance) and the variance in the autonomic reactions could be described with the first three principal components (explaining 85% of the variance) using a threshold of one for the eigenvalues. This gave the final GLM with the four conditions, the five principal components as covariate regressors (saving 20 degrees of freedom), and the global cerebral blood flow (CBF) as

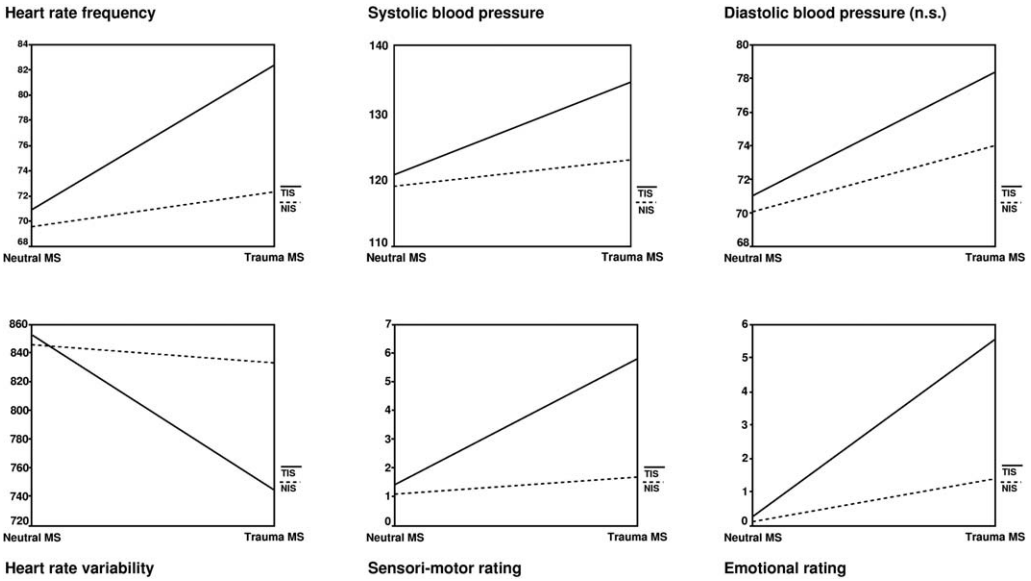

Figure 1. Graphical representation (as obtained from SPSS) of subjective emotional experiences, subjective sensori-motor experiences, and cardiovascular responses. Only significant or near significant interaction effects are depicted (see also Table 1). The dashed line depicts the response of the neutral identity state (NIS) when listening to the neutral or trauma-related memory script (MS). The solid line depicts the response of the traumatic identity state (TIS) when listening to the neutral or trauma-related MS.

Table 2. Main and Interaction Effects

			x	y	z	T^a	kE
Main Effect MS : t						n.s.	
Main Effect MS : n						n.s.	
Main Effect DIS : TIS							
Cortical Areas							
Lateral fissure/Postcentral gyrus	BA 43	R	69	−11	15	4.79	226
Precentral gyrus	BA 6	R	67	5	20	3.99	
Sub-cortical Areas							
Caudate nucleus		L	−18	−5	19	5.65	1024
Parietal operculum		L	−48	−19	16	5.54	
Caudate nucleus (caudal part)		L	−28	−36	13	4.86	
Caudate nucleus		R	24	3	18	5.40	560
Putamen		R	32	−1	20	4.47	
Parietal operculum		R	50	−3	22	4.22	
Amygdala		L	−6	−9	−23	4.51	61
Caudate nucleus		R	22	−24	18	4.49	94
Other Areas							
Cerebellum (ventral-medial part)		L	−6	−42	−26	5.15	113
Cerebellum (ventral-medial part)		R	14	−46	−25	4.22	24
						Total	2102
Main Effect DIS : NIS							
Cortical Areas							
IPS (transition SPL/IPL)	BA 7/40	R	28	−37	42	5.67	365
M. Occipital Gyrus	BA 19	L	−44	−74	30	5.66	213
IPS (transition SPL/IPL)	BA 7/40	L	−28	−47	39	5.60	408
Fusiform gyrus	BA 37/19	R	42	−63	−14	5.29	283
M. Frontal gyrus	BA 6	L	−30	−4	46	5.18	453
S. Parietal lobule	BA 7	R	26	−62	34	5.16	286
S. Frontal gyrus	BA 8	R	12	38	52	5.14	160
Cingulate gyrus	BA 32	R	2	43	3	5.11	900
Cingulate sulcus/S. Frontal gyrus	BA 6/24	R	18	−12	41	5.08	1165
I. Temporal gyrus	BA 37	R	48	−37	−8	4.51	105
(Pre-) Cuneus	BA 18	L	−14	−74	26	4.31	395
I. Parietal lobule	BA 40	L	−61	−41	43	4.29	68
Parahippocampal gyrus	BA 35	L	−8	−37	−8	4.25	101
M. Occipital gyrus	BA 19	L	−30	−90	17	4.24	81
Lingual gyrus	BA 18	R	14	−78	−8	4.21	207
Parahippocampal gyrus	BA 35	R	28	−39	−5	4.13	90
S. Temporal sulcus/M. Temporal Gyrus	BA 21	R	63	−8	−6	3.85	30
I. Temporal sulcus/M. Temporal Gyrus	BA 21	R	53	−26	−10	3.71	30
S. Occipital sulcus	BA 19	R	20	−85	41	3.66	14
Precuneus	BA 7	L	−6	−59	32	3.61	19
Parieto-occipital sulcus	BA 7	R	18	−76	37	3.52	18
Sub-cortical Areas							
Caudate nucleus (ventral part)		L	−6	6	0	4.07	46
External globus pallidus		R	22	0	−2	4.00	39
Thalamus/Hypothalamus		R	8	−8	0	3.82	27
						Total	5503
DIS and MS Interaction Effects						n.s.	

Overview of brain areas with statistically significant cerebral blood flow changes for the main effects as well as the interaction effect.

(x, y, z) = Talairach coordinates in mm. kE = clustersize in voxels (one voxel is 2 × 2 × 2 mm). DIS, dissociative identity state; MS, memory script; NIS, neutral identity state; TIS, traumatic identity state; n, neutral memory script; t, trauma-related memory script; n.s., no significant cerebral blood flow changes; BA, Brodmann area; I., inferior; M., middle; S., superior; IPS, intraparietal sulcus; SPL, superior parietal lobule; IPL, inferior parietal lobule.

[a]All reported statistical values: $p < .05$ corrected for multiple comparisons.

a nuisance variable. With inclusion of the five covariates of interest we were able to examine and account for the effect of the autonomic and subjective reactions on the rCBF. Using simple *F* contrasts, two variance maps were created showing the variance in rCBF which can be explained by the subjective ratings and autonomic reactions, respectively.

Study Design: Factorial Design

With two stimulus scripts, i.e. neutral and trauma-related MS, presented at two DIS, i.e. NIS and TIS, this study represents a two-by-two factorial design (Friston et al 1996, 1997; Friston 1997; Price et al 1997). The design allows the assessment of various effects, i.e. main effects (both comprising two levels: NIS

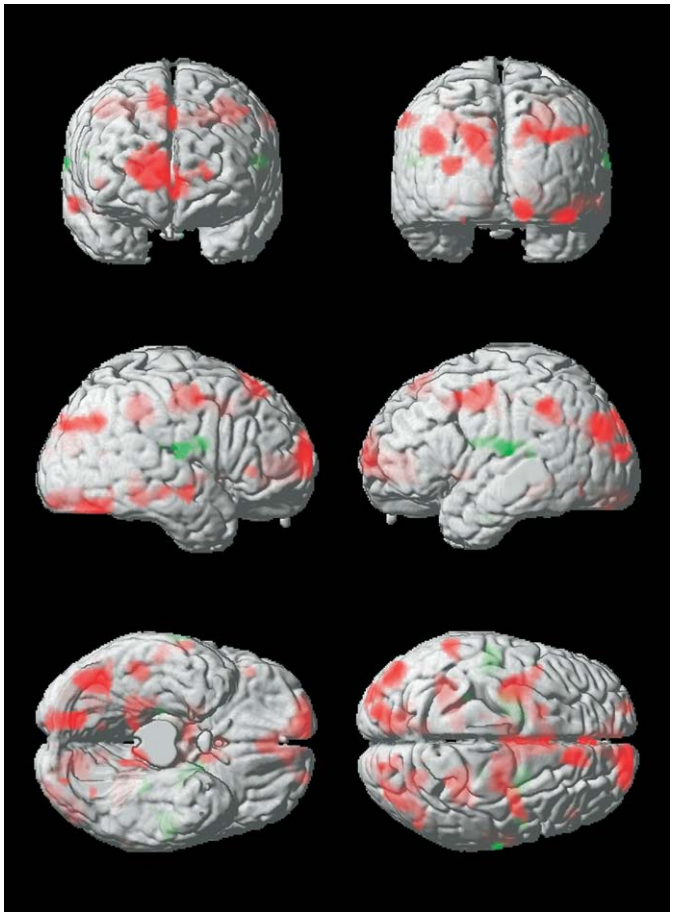

Figure 2. Brain areas are shown which display a significant increase in regional cerebral blood flow (rCBF) (see also Table 2) for the dissociative identity state (DIS) main effect. Brain activations depicted in green show regional cerebral blood flow changes for the traumatic identity state (TIS), while brain activations depicted in red show regional cerebral blood flow changes for the neutral identity state (NIS).

and TIS), interaction effects, several possibilities for simple subtraction analyses and conjunction analyses. Note that all tests are one-sided; only positive differences in rCBF are tested. Therefore, all tests were performed twice: a contrast to assess increases in rCBF and the inverse contrast to assess decreases in rCBF.

Main Effects

The DIS main effect examines brain areas for a significant difference in rCBF between NIS and TIS, irrespective of MS. Similarly, the MS main effect examines brain areas for a significant difference in rCBF between trauma-related and neutral MS, irrespective of DIS.

Interaction Effect

The main effects may exhibit an interaction effect. Observed changes in rCBF induced by the DIS, may very well be dependent on the MS. Changes in rCBF due to MS might be connected to the DIS. An interaction analysis aimed to identify brain areas for which the effect of one factor (DIS or MS) depends on the other. Provided that no significant interaction is observed, our design fulfills the criteria of pure insertion (Friston et al 1996; Friston 1997), which allows the use of simple subtraction analyses.

Simple Subtraction Analysis

Our main hypotheses were tested using simple subtraction analyses, consisting of MS effects within DIS and between DIS. The MS within DIS examines the existence of a significant change in rCBF between the trauma-related and neutral MS for either DIS. Similarly, the MS between DIS examines the existence of a significant change in rCBF between DIS for either MS.

Conjunction Analysis

Conjunction analysis (Price and Friston 1997; Price et al 1997) can identify the presence of conjointly activated neural networks. The within DIS conjunction analysis serves to find brain areas for which there is a consistent significant difference in rCBF between both MS for each of the DIS. By using this conjunction analysis we tested our hypothesis that NIS and TIS address two different neural networks when processing trauma-related information. The between DIS conjunction analysis serves to find brain areas for which there is a consistent significant difference in rCBF between both DIS for each of the MS.

Statistical Inference

For our a priori hypotheses we accepted uncorrected significance levels (i.e. voxel level of significance uncorrected for multiple testing for the whole brain) of $p < .001$ (Friston et al 1991). For the specific subtraction TISt - NISt the statistical threshold was lowered to $p < .005$ uncorrected for exploration of the a priori hypothesized amygdala regions. Otherwise, when no a priori hypothesis was available, for main effects and conjunction analysis, we only accepted (and report) significant areas (corrected p values $p < .05$). Corrected p values (corrected for whole brain multiple comparisons) are reported based on false discovery rate statistics as included in the SPM99 package (www.sph.umich.edu/~nichols/FDR/). Only clusters larger than eight voxels, the first peak voxel of large clusters, and only the most significant finding of a brain area are reported in the Tables. The coordinates were converted from MNI space to Talairach space (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) to be defined in Brodmann areas (BA) (Talairach and Tournoux 1988) and their location was anatomically compared to and described using a second brain atlas (Mai et al 1997).

Results

Autonomic and Subjective Reactions

Statistical results of the autonomic and subjective reactions are presented in Table 1. Significant changes in heart rate, systolic blood-pressure (diastolic blood-pressure approached significance), subjective ratings, and the AVGNN HRV variable were found for the DIS.

Similarly, MS showed significant changes in the heart rate, systolic and diastolic blood-pressure, subjective ratings, and the AVGNN HRV variable. Interaction effects (DIS * MS) were significant for heart rate, systolic blood pressure (diastolic blood pressure approached significance), subjective ratings, and the AVGNN HRV variable. Figure 1 depicts the significant or near significant interaction effect. The DIS and MS dependent effects, including the direction, and the averaged values of the effect are also shown.

Regional Cerebral Blood Flow Changes

Covariate Data. Variance statistics, using F contrast as applied to the two principal component sets, did not reveal any areas for which a significant amount of variance is explained by either the subjective ratings ($p > .5$) or the

Table 3. Memory Script Effects within Dissociative Identity State

			x	y	z	*T*	kE
NISt - NISn						n.s.	
NISn - NISt						n.s.	
TISt - TISn							
Sub-Cortical Areas							
Parietal operculum		L	−48	−19	16	5.54	786
Insular gyrus		L	−30	−3	20	3.92	
Caudate nucleus		R	22	1	22	4.32	62
Amygdala		L	−12	−7	−20	4.31	123
Caudate nucleus (caudal part)		L	−24	−32	16	4.31	40
Caudate nucleus		L	−10	1	17	4.11	24
Parietal operculum		R	42	−18	27	3.68	10
Other Areas							
Cerebellum (ventral-medial part)		L	−6	−42	−26	4.11	32
TISn - TISt							
Cortical Areas							
Fusiform gyrus	BA 19/37	R	40	−59	−16	4.84	276
IPS (transition SPL/IPL)	BA 7/40	R	28	−37	42	4.63	111
(Pre-) Cuneus	BA 7	L	−14	−74	26	4.39	266
IPS (transition SPL/IPL)	BA 7/40	L	−36	−47	34	4.22	38
S. Occipital sulcus	BA 19	R	32	−84	32	4.19	41
S. Temporal sulcus/M. Temporal gyrus	BA 21	R	63	−6	−13	4.07	46
Precentral gyrus/S. Frontal gyrus	BA 6	R	22	−9	52	3.97	92
M. Occipital gyrus	BA 19	L	−40	−74	30	3.94	24
S. Parietal lobule	BA 7	R	24	−64	35	3.91	62
I. Parietal lobule	BA 40	L	−61	−37	39	3.89	34
Precentral gyrus/S. Frontal gyrus	BA 6/4	L	−30	−7	48	3.88	51
I. Temporal gyrus	BA 20	R	48	−36	−12	3.76	31
IPS (transition SPL/IPL)	BA 7/40	L	−18	−45	32	3.72	21
Cingulate gyrus	BA 31	L	−8	−37	42	3.71	22
S. Occipital sulcus	BA 19	R	18	−85	41	3.64	11
Conjunction within DIS							
(TISt - TISn) and (NISt - NISn)						n.s.	
(TISn - TISt) and (NISn - NISt)						n.s.	

Overview of brain areas with statistically significant cerebral blood flow changes for the simple subtractions of memory script effects within the dissociative identity state as well as the corresponding conjunctions.

(x, y, z) = Talairach coordinates in mm. kE = clustersize in voxels (one voxel is 2 × 2 × 2 mm). NISn, neutral identity state exposed to the neutral memory script; NISt, neutral identity state exposed to the trauma memory script; TISn, traumatic identity state exposed to the neutral memory script; TISt, traumatic identity state exposed to the trauma-related memory script; n.s., no significant cerebral blood flow changes; BA, Brodmann area; I., inferior; M., middle; S., superior; IPS, intraparietal sulcus; SPL, superior parietal lobule; IPL, inferior parietal lobule.

cardiovascular measurements ($p > .5$). Hence, the rCBF condition effects were not contaminated by, and therefore independent of, suggestibility effects or the arousal of the cardiovascular system.

Main Effects and Interaction Effect. Results for the main effects are given in Table 2. Significant rCBF changes for both the NIS and the TIS levels of the DIS main effect, independent of MS, were found. The brain areas for the NIS level are shown in Figure 2 in red. The brain areas for the TIS level are shown in Figure 2 in green. No significant rCBF changes for the neutral or trauma-related levels of the MS main effect, independent of DIS, were found. In addition, no significant increase or decrease in rCBF was found due to an interaction effect between DIS and MS. Therefore, the requirements for pure insertion are satisfied validating the analysis by simple subtraction.

MS Effects within DIS. MS effects within DIS are given in Table 3. For NIS no significant increase or decrease in brain activity was found. However, TIS revealed MS dependent rCBF patterns. TIS showed significant regionally specific increases and decreases in blood flow when processing the trauma-related MS as compared to the neutral MS.

MS Effects between DIS. The MS effects between DIS are given in Table 4. The hypothesis that NIS and TIS process the neutral memory script in a similar way could not be rejected, because no significant increase or decrease in rCBF was found. Different rCBF patterns were found for NIS and TIS, when processing the trauma-related MS. The rCBF pattern for TIS, compared to NIS, in response to the trauma MS, is depicted in Figure 3 in green. The rCBF pattern for NIS, compared to TIS, in response to the trauma MS, is depicted in Figure 3 in red.

Conjunction Analyses. We found (see Table 3) that the two DIS are associated with functionally different neural networks. Applying a conjunction analysis on the within DIS MS effects, no significant commonalities in rCBF patterns were found between TIS and NIS. The between DIS conjunction (Table 4) analysis revealed several brain areas for which a consistent significant

Table 4. Memory Script Effects Between Dissociative Identity States

			x	y	z	*T*	kE
TISn - NISn						n.s.	
NISn - TISn						n.s.	
TISt - NISt							
Cortical Areas							
Lateral fissure/Postcentral gyrus	BA 43	R	69	−11	15	3.89	60
I. Temporal gyrus	BA 20	L	−55	−33	−29	3.88	18
M. Temporal gyrus	BA 21	L	−40	−1	−20	3.70	19
Sub-Cortical Areas							
Parietal operculum		L	−48	−19	16	5.94[a]	789
Insular gyrus		L	−26	−9	19	4.56[a]	
Caudate nucleus		L	−14	−1	18	4.51[a]	
Caudate nucleus		R	24	3	18	4.85[a]	138
Caudate nucleus (caudal part)		L	−28	−36	13	4.37	84
Lateral pulvinar nucleus		L	−18	−32	13	4.03	
Amygdala		L	−6	−9	−23	4.32	72
Amygdala[b]		R	12	−4	−26	3.15	53
Caudate nucleus		R	22	−24	18	4.02	26
Other Areas							
Cerebellum (ventral-medial part)		L	−6	−42	−26	5.16[a]	115
Cerebellum (lateral part)		L	−55	−48	−26	4.04	10
NISt - TISt							
Cortical Areas							
IPS (transition SPL/IPL)	BA 7/40	R	28	−37	42	5.20[a]	323
IPS (transition SPL/IPL)	BA 7/40	L	−24	−45	37	5.19[a]	432
M. Occipital gyrus	BA 18/19	L	−44	−74	30	5.14[a]	290
Fusiform gyrus	BA 37/19	R	42	−63	−14	5.09[a]	210
S. Parietal lobule	BA 7	R	26	−62	33	5.02[a]	456
S. Occipital sulcus	BA 19	R	18	−85	41	4.05[a]	
S. Frontal gyrus	BA 8	R	12	38	52	4.97[a]	169
(Pre-)cuneus	BA 7/18/19	L	−8	−76	24	4.95[a]	690
M. Frontal gyrus	BA 6	L	−30	−4	46	4.85[a]	289
Cingulate gyrus	BA 32	R	12	63	8	4.53[a]	388
Cingulate sulcus	BA 6/24	R	30	−11	47	4.52[a]	459
Cingulate gyrus	BA 31	R	4	19	38	4.48[a]	191
S. Temporal sulcus/M. Temporal gyrus	BA 21	R	63	−8	−11	4.36[a]	123
I. Temporal gyrus	BA 37	R	48	−37	−8	4.31[a]	65
Cingulate gyrus	BA 32	x	0	43	3	4.20[a]	76
Fusiform gyrus	BA 37	R	26	−55	−9	3.85[a]	21
I. Parietal lobule	BA 40	L	−61	−41	43	3.84[a]	28
Parahippocampal gyrus	BA 35	R	26	−35	−7	3.81[a]	29
Parahippocampal gyrus	BA 35	L	−10	−47	−3	3.79[a]	29
Cingulate gyrus	BA 24	L	−10	−8	39	3.71[a]	17
S. Frontal gyrus	BA 6	R	10	−12	78	3.70[a]	11
Cingulate sulcus/Cingulate gyrus	BA 32/24	L	−18	10	36	3.61[a]	12
Sub-Cortical Areas							
External globus pallidus		R	22	0	−2	3.91[a]	35
Caudate nucleus (ventral part)		L	−8	6	−2	3.70[a]	10
Conjunction between DIS (TISt - NISt) and (TISn - NISn)							
Cortical Areas							
Orbital gyrus (lateral part)	BA 11	L	−22	51	−19	2.78[a]	92
Inferior frontal gyrus	BA 47	L	−51	30	−17	2.53[a]	21
Sub-Cortical Areas							
Caudate nucleus		L	−18	−5	19	4.11[a]	331
Caudate nucleus		R	20	7	18	3.11[a]	1159
Caudate nucleus		R	20	−24	20	2.45[a]	13

Table 4. (continued)

			x	y	z	*T*	kE
Other Areas							
Cerebellum (ventral-medial part)		R	14	−46	−25	3.11[a]	59
(NISt - TISt) and (NISn - TISn)							
Cortical Areas							
Cingulate gyrus	BA 32	R	4	43	2	3.41[a]	927
IPS (transition SPL/IPL)	BA 7/40	L	−28	−48	41	3.37[a]	99
IPS (transition SPL/IPL)	BA 7/40	R	20	−37	42	3.18[a]	175
Lingual gyrus	BA 18	R	14	−78	−8	3.10[a]	342
Parahippocampal gyrus	BA 35	L	−8	−37	−8	2.93[a]	131
Cingulate gyrus	BA 24	x	0	−10	41	2.74[a]	524
Precentral sulcus	BA 6/9	L	−38	2	40	2.59[a]	100
M. Occipital gyrus	BA 19	L	−40	−80	32	2.49[a]	37
Fusiform gyrus	BA 37/19	R	48	−59	−11	2.47[a]	219
Parahippocampal gyrus	BA 35	R	32	−39	−6	2.44[a]	49
I. Parietal lobule	BA 40	L	−57	−44	46	2.43[a]	39
Cingulate gyrus	BA 32/24	L	−14	10	38	2.38[a]	71
Sub-Cortical Areas							
Thalamus/Hypothalamus		R	6	−8	0	2.62[a]	115
Caudate nucleus (ventral part)		L	−6	6	2	2.46[a]	52

Overview of brain areas with statistically significant cerebral blood flow changes for the simple subtractions of memory script effects between the dissociative identity states as well as the corresponding conjunctions.

(x, y, z) = Talairach coordinates in mm. kE = clustersize in voxels (one voxel is 2 × 2 × 2 mm). NISn, neutral identity state exposed to the neutral memory script; NISt, neutral identity state exposed to the trauma memory script; TISn, traumatic identity state exposed to the neutral memory script; TISt, traumatic identity state exposed to the trauma-related memory script; n.s., no significant cerebral blood flow changes; BA, Brodmann area; I., inferior; M., middle; S., superior; IPS, intraparietal sulcus; SPL, superior parietal lobule; IPL, inferior parietal lobule.

[a] $p < .05$ corrected for multiple comparisons.

[b] Clustersize at threshold $p < .005$ uncorrected.

difference in rCBF between both DIS independent of the MS is present.

Discussion

The current study tested several hypotheses in a two-by-two factorial design with two stimulus scripts presented to two dissociative identity states (DIS). The straightforward way of modeling the variance in rCBF is to include only the four experimental conditions in the GLM within SPM. However, the autonomic and subjective reactions showed significant differences, which consequently may cause, at least partly, rCBF changes. Therefore, the model had to be extended to remove rCBF variance that can be explained by the autonomic and subjective reactions. Inclusion of these covariates allows the GLM to fit with more parameters which gives a better overall model fit of the data. From the variance that is explained by the conditions, we found different rCBF patterns for different DIS. Furthermore, we found DIS dependent processing of the trauma-related MS.

Autonomic and Subjective Reactivity

The current results from the autonomic and subjective reactions are consistent with other studies on PTSD or DID (e.g. Rauch et al 2003; Tanev 2003). The significant interaction between the factors DIS and MS for the autonomic and subjective reactions was not replicated in the rCBF data. Inconsistency between psychophysiological and the neurophysiological data is known (e.g. Vuilleumier et al 2003). Only one among five HRV variables showed a significant decrease. A lack of power, due to the short time intervals in which this parameter was determined may explain why the other four HRV variables did not reach threshold.

Regional Cerebral Blood Flow Changes

Main Effects. The main effects analyses show significant differences in the rCBF patterns for the two DIS, but not for MS. The NIS level of the DIS main effect revealed a broad pattern of brain areas that showed an increase in rCBF relative to the TIS level. To function as a TIS, only few brain areas appear to be involved. Interestingly, no interaction effect was found, which shows that the rCBF patterns for the main effects of DIS are indifferent to MS. Therefore, we propose that functioning as a DIS is of a more general nature, i.e. maintaining in a different brain state, than the effect of MS.

Subtraction Analysis

MS Effects within DIS. Exposing TIS to trauma-related MS was associated with differences in rCBF in a wide range of subcortical areas. The insular cortex (included in the parietal operculum activation) is preferentially involved in the emotional response to potentially distressing thoughts, interoceptive sensory stimuli, and body sensations, and operates as an 'internal alarm center' (Reiman et al 2000). Alarming body sensations promote psychophysiological arousal, including increased heart rate frequency and blood pressure and decreased heart rate variability, consistent with our results. Notably, trauma-related scripts also evoked insular activity among PTSD patients (Rauch et al 1996). Thus, in TIS the trauma-related MS activates somatosensory and brain areas implicated in negative emotional states. In addition, differences in rCBF were found in the bilateral caudate nucleus when exposing TIS to trauma-related MS as compared to neutral MS. The basal ganglia, which include the caudate, play a critical role in motor planning and movement sequencing (Menon et al 2000). The basal ganglia are also involved in anxiety (Reiman 1997), and the amygdala in the

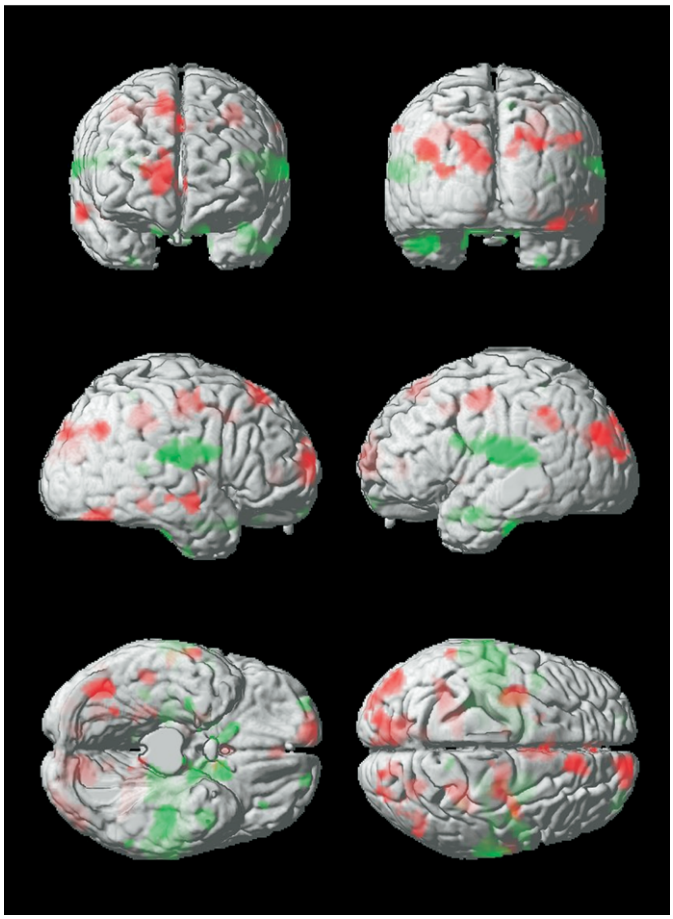

Figure 3. Brain activations are shown which display a significant increase in regional cerebral blood flow (rCBF) (see also Table 4) due to the processing of the trauma-related memory script (MS) in one dissociative identity state as compared to the other. Brain activations depicted in green show regional cerebral blood flow changes in the traumatic identity state (TIS), as compared to the neutral identity state (NIS), when listening to the trauma-related MS. Moreover, brain activations depicted in red show regional cerebral blood flow changes in the NIS due to listening to the traumatic MS as compared to TIS.

processing of fear (LeDoux 2000; Davis and Whalen 2001). Many brain areas showing significant changes in blood flow in the current study were also highlighted in women with PTSD exposed to reminders of their childhood sexual abuse (Shin et al 1999). In the latter study (Shin et al 1999), exposure to trauma-related MS was, among others, associated with changes in rCBF in visual association cortex, middle temporal gyrus, inferior and superior parietal lobule, and superior frontal gyrus.

In contrast to TIS, NIS processed the trauma-related MS in a similar way as the neutral MS since no significant changes in rCBF were detected. Therefore, we conclude that NIS processed trauma-related MS as if they pertained to neutral(ized) memories.

MS Effects between DIS. During exposure to trauma-related MS, TIS showed more rCBF in areas which are consistent with subjective reactions and suggests the activation of a neural network involving traumatic memory-related somatosensory body representations (right lateral fissure, BA 43), aversive sensations and emotions including pain, fear, and panic (amygdala and insula) and effects of classical conditioning (left cerebellum; Fischer et al 2000).

During exposure to trauma-related MS, NIS displayed a pattern of CBF that mimics the pattern displayed by patients with depersonalization disorder (Hollander et al 1992; Sar et al 2000; Simeon et al 2000; Phillips et al 2001) and patients with PTSD who had negative dissociative symptoms when exposed to a trauma-related MS (Lanius et al 2004, 2005). Compared with healthy controls, patients with depersonalization disorder and PTSD patients with negative dissociative symptoms had more rCBF in two unimodal association areas, i.e., precuneus (BA 19, visual association cortex) and parietal area BA 7 which probably is central to higher order somato-sensory integration (Lanius et al 2004; Simeon et al 2000). Thus, NIS showed parietal and occipital blood flow alterations that suggest a relatively low level of somato-sensory awareness and integration. These findings match the clinical features of NIS, as well as their subjective responses and the lack of sympathetic arousal in the current experiment.

Consistent with our hypothesis, no significant voxels could be found when testing whether NIS and TIS process the neutral MS differently. Hence, both DIS processed the neutral MS in a similar manner.

Conjunction Analysis. The within DIS conjunction analysis did not reveal any brain areas which are consistently (de-)activated in NIS and TIS when comparing the processing of the neutral and trauma-related MS. These results indicate that the neural networks subserving the two different identity states are to a great extent separate. Therefore, we propose that the two DIS (NIS and TIS) are associated with two functionally different neural networks (Edelman and Tononi 2000).

This is consistent with the between DIS conjunction analysis, assessing conjoint differences between NIS and TIS independent of text, which revealed several brain areas. Our interpretation is that these areas are involved in the establishment of functioning as two dissociative identity states.

General Remarks

It is unlikely that the current results reflect an experimental artifact considering the high degree of comorbidity between DID and PTSD (Boon and Draijer 1993). In fact, it is very difficult for nonPTSD patients to simulate physiological responses of PTSD patients (Gerardi et al 1989; Orr and Pitman 1993). Therefore, our results support the idea that DID and PTSD are related disorders because both involve psychobiological structures associated with detachment (NIS) and re-experiencing traumatic memories (TIS). Considering this close relation between DID and PTSD it would have been interesting to have information on the specific psychiatric co-morbidities of the DID patients. The absence of this information may, despite the fact that all patients met the SCID-D (Steinberg 1993) criteria, be considered as a shortcoming of the current study. During the PET investigation no validated quantitative trait and state (e.g. Kruger and Mace 2002) dissociative symptom measures were obtained, which may be regarded as a limitation of this study.

Skeptics could argue that the current findings result from suggestion and role-playing (e.g. Deeley 2003; Piper and Merskey 2004; Merckelbach et al 2002). Consequently, suggestibility would most likely affect the subjective ratings. Interestingly, the variance in the PET data which is explained by these suggestibility effects did not reach statistical threshold. Therefore, rCBF differences are condition specific and are not induced by suggestibility effects. This is in accordance with DID-simulating controls who were not able to produce psychophysiological effects equivalent to those in DID patients (Putnam 1997). Symptom provocation studies exploring changes in rCBF patterns in PTSD and DID simulating controls are unavailable to

date. Although we consider it unlikely that the current results would be replicated in such experiments, it would enable further quantification and objectification of these disorders. Nevertheless, our findings of differential processing of trauma-related information by two DIS, holds.

The integrative capacity of the women involved in our study had increased to allow them to be in phase II (Steele et al 2005) of the treatment, which is dedicated to the integration of traumatic memories (Brown et al 1998; Steele et al 2001). This evolvement to phase II was determined by the personal therapist. One of the characteristics of phase II is that the two identity states are aware of each others existence and may sometimes have some degree of co-consciousness, which is neither complete nor permanent. Our findings therefore probably underestimate, rather than overestimate, the degree of dissociation between NIS and TIS. Nevertheless, our results may not be generalizable to patients who can not readily switch, to males or to patients who do not have the two types of identities which are included in our study.

As Freud already mentioned (Freud 1891), studying abnormalities in the field of psychology and psychiatry, can provide us with valuable information about the brain areas and networks involved in normal functioning subjects (Frith et al 1998). Therefore, the present study may also be discussed in view of the psychoanalytical concepts of Freud. He proposed that the brain may suppress traumatic memories (Freud 1966), which is in line with our indication that NIS processes trauma-related information as if it pertains neutral information, i.e. thereby protecting the ego. Furthermore, our study can be regarded as an extension of a recent study in normal volunteers (Anderson et al 2004) showing that suppression of memory can be transferred to other apparent unrelated memories. In the present study we show that such mechanisms may have psychopathological consequences.

We conclude that dissociative identity disorder is characterized by at least two types of dissociative identity states. Dissociative identity states that inhibit access and responses to traumatic memories to be able to function in daily life and dissociative identity states fixated on (with access and responses to) traumatic memories. These types of dissociative identity states exhibit different regional cerebral blood flow patterns as well as autonomic and subjective reactions when exposed to identical trauma-related stimuli.

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