Regenbogen C, Kellermann T, Seubert, J, Schneider, DA, Gur, RE, Derntl B, Schneider, F, Habel, U. Neural responses to dynamic multimodal stimuli and pathology-specific impairments of social cognition in schizophrenia and depression. SUPPLEMENT

Supplemental Methods and Materials

Study participants

The experiment conformed to the Code of Ethics of the World Medical Association. The study was approved by the local institutional review board. Participants gave written consent to the study protocol and received 35€ after completion.

A neuropsychological battery was carried out assessing crystallized intelligence (WST[1]), processing speed and cognitive flexibility (Trail Making Test TMT[2]), word fluency (Regensburger Word Fluency Test RWT[3], and short-term/working memory (Wechsler Adult Intelligence Scale, Revised, WAIS-R[4]). To test static face recognition accuracy, participants were tested with the Vienna Emotion Recognition Task-short version (VERT-K[5]). All PSZ received antipsychotics (butyrophenones: n=2, atypical antipsychotics: n=17, partial agonists/antagonists: n=6). All PMD received antidepressants (selective serotonin reuptake inhibitors: n=6, serotonin-norepinephrine reuptake inhibitors: 12, noradrenaline reuptake inhibitors: n=1, tricyclic antidepressants: n=2, tetracyclic antidepressants: n=5), two patients were additionally medicated with a benzisoxazole derivative). Patients with a life-time psychiatric comorbidity other than substance abuse were excluded.

Table DS1. Mean values (SD) of neuropsychological data and questionnaires and one-way ANOVA results testing for differences between the groups.

	HC	n	PMD	n	PSZ	n	F	p
Demographics								
Age	35.25 (9.80)	24	36.42 (12.01)	24	37.30 (8.44)	20	0.22	.80
Edu	12.38 (1.24)	24	11.58 (1.61)	24	12.35 (1.27)	20	2.44	.10
Parental edu	10.44 (1.78)	24	10.04 (1.58)	23	10.68 (2.50)	20	0.57	.60
Neuropsychology								
IQ	110.17 (7.60)	24	102.38 (8.26)	24	107.60 (12.43)	20	4.19	.02*
Word fluency (percentile)	54.18 (14.75)	24	47.59 (21.29)	23	35.33 (22.79)	18	4.80	.01*
TMT-A (sec)	20.30 (5.43)	23	23.62 (7.94)	24	27.47 (12.83)	20	3.37	.04*
TMT-B (sec)	33.74 (9.54)	23	47.03 (21.54)	24	47.10 (25.71)	20	3.40	.04*
Short-term memory	9.21 (1.44)	24	8.38 (2.04)	24	8.53 (2.12)	19	1.33	.27
Working memory	7.58 (1.44)	24	7.38 (1.88)	24	6.32 (1.49)	19	3.58	.03*
Psychopathology								
Illness duration			7.31 (8.38)	24	9.58 (9.58)	19	0.68	.41
GAF			51.00 (12.14)	20	49.89 (11.35)	19	0.09	.77
PANSS total					75.58 (23.11)	19		
- psychopathology					38.26 (13.32)	19		
- positive symptoms					14.21 (4.53)	19		
- negative symptoms					23.11 (8.52)	19		
HAMA total					13.23 (3.32)	13		
- soma					3.46 (2.26)	13		
- psych					9.77 (2.65)	13		
HAMD			14.45 (6.67)	20				
BDI			27.55 (11.77)	22				
Static face recognition								
VERT (% corr)	83.46 (8.06)	22	82.99 (6.41)	24	79.86 (8.64)	16	1.17	.32
VERT RT (ms)	5193 (4100)	22	5095 (4422)	24	4177 (1327)	16	0.40	.68
Alexithymia screening								
TAS-20	43.42 (8.21)	24	52.79 (11.92)	24	45.26 (11.99)	19	5.03	.01*
Empathy questionnaires								
E-scale	3.25 (0.41)	24	3.15 (0.61)	24	3.19 (0.70)	20	0.18	.83
SPF (IRI)	33.75 (5.88)	24	34.46 (5.76)	24	30.00 (4.93)	20	3.92	.03*

Note. HC=Healthy controls, PMD=Patients with major depression, PSZ=Patients with schizophrenia, Edu=education, IQ=Intelligence quotient of crystallized intelligence, GAF=Global assessment of functioning, PANSS=positive and negative symptom scale for schizophrenia, HAMA=Hamilton anxiety rating scale, HAMD=Hamilton depression rating scale, BDI=Beck depression inventory, SPF(IRI) = German version of the Interpersonal Reactivity Index, *significant on a p<.05 threshold, but not corrected for the total number of tests carried out. N = number of participants.

Correlation analyses

In controls, 'Empathy' was significantly associated with working memory (r=0.605, p=.002). In MD and SZ, no correlation survived Bonferroni-correction. For exploratory purposes, we chose to report correlations that emerged between 'Empathy', 'Other', and 'Self', respectively, and psychopathology ratings: In MD, negative correlations were found between 'Empathy' and 'Self' and alexithymia (TAS) (SOMT: r=-0.487, p=.016; SMT: r=-.498, p=.013) as well as between 'Other' and depression severity (BDI, r=-0.427, p=.048). In SZ, 'Other' correlated negatively with the negative symptom scale (r=-0.564, p=.01) and the global scale (r=-0.565, p=.01).

Task

Participants were comfortably placed in the MR scanner. The hand's index- and middle fingers were positioned on fMRI compatible response buttons (LUMItouch™, Lightwave Technologies, Richmond, Canada) through which the empathy ratings were carried out after each video clip. Clips were presented in pseudo-random order via the presentation program Presentation® (Neurobehavioral Systems Inc., San Francisco, CA) and presented via MR-compatible goggles and headphones (VisuaStimDigital, Resonance Technology, RT, Northridge, CA, USA). During the interstimulus interval a white fixation cross on black background was displayed (M=4.53 s, SD=2.26, jittered in steps of 500ms with respect to the MR trigger) (Figure S1).

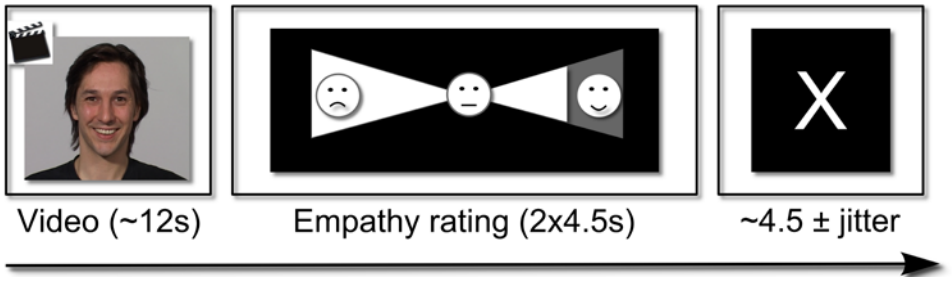

Figure DS1. One of 96 study trials.

Participants were presented with short video clips displaying actors which they were instructed to regard as personally familiar. In this example, the participant chose the extreme positive valence with three button presses with the right middle finger.

Functional magnetic resonance imaging

Functional imaging data were obtained on a 3 Tesla Tim Trio® MR scanner (Siemens Medical Systems, Erlangen, Germany) with a standard 12-channel head matrix coil using a T2* weighted echo-planar imaging (EPI) sequence sensitive to blood oxygenation level dependent (BOLD) changes (voxel size: 3.125×3.125×3.1mm^3, matrix size: 64×64, field of view (FoV): 200×200 mm^2, 36 axial (AC-PC) slices, 0.465 mm-gap, TR/TE=2000/30 ms, flip angle: 76°, 1180 volumes, duration: 39.33 min).

Several participants were excluded from further analysis due to excessive head motion (>3 mm, n=2), scanner artifacts (n=4) and non-compliance (n=1). The final sample consisted of 20 PSZ (7 females), 24 PMD (11 females), and 24 HC (11 females, Table S1).

Data analysis was carried out with SPM8 (Wellcome Department of Cognitive Neurology, London). The functional images were realigned to the first image of the time-series and the functional mean image was coregistered into the Montreal Neurologic Institute (MNI) image space, which delivered the priors for a unified segmentation process[6]. The mean image was non-linearly segmented into grey matter, white matter, and cerebrospinal fluid (CSF). The fitting of the mean image's grey matter with the corresponding tissue probability map yielded the normalization parameters which were applied to the whole time series and included resampling to a voxel size of 1.5×1.5×1.5 mm3. Spatial smoothing on normalized images was carried out with an isotropic 8 mm FWHM (full width at half maximum) Gaussian kernel.

Supplemental results

The components of empathy

The analysis of emotion recognition ('Other', Table S2) resulted in a significant main effect of COND (Wald $\chi2(4)=235.02$, $p<.001$). Neither GRP nor the interaction term was significant (GRP: Wald $\chi2(2)=1.82$, $p=.40$; GRP by COND, Wald $\chi2(8)=6.33$, $p=.61$).

Post-hoc tests for the main effect of COND showed highest emotion recognition in 'trimdoal emotional' when comparing with all other conditions ('neutral prosody': $t(67)=3.48$, $p=.003$, 'neutral facial expression': $t(67)=6.74$, 'neutral speech': $t(67)=8.07$, 'foreign language': $t(67)=11.00$, ps<.001). 'Neutral speech' showed the lowest emotion recognition rates, significantly lower compared to 'neutral prosody' ($t(67)=-7.33$, $p<.001$) and 'neutral facial expression' ($t(67)=-3.64$, $p=.003$), followed by 'foreign language' (significantly lower compared to 'neutral prosody': $t(67)=10.08$, $p<.001$ and 'neutral facial expression': $t(67)=3.09$, $p=.02$) and 'neutral facial expression'. 'Neutral facial expression' was significantly lower compared to 'neutral prosody' ($t(67)=5.04$, $p<.001$).

The analysis of affective responses ('Self') resulted in a significant main effect of COND (Wald $\chi^2(4)=208.49$, $p<.001$). The main effect of GRP (Wald $\chi^2(2)=0.05$, $p=.97$) was not significant, the interaction effect showed a trend (GRP by COND: Wald $\chi^2(8)=13.64$, $p=.09$).

Table DS2. Results (% M±SD) for emotion recognition ('Other') and affective response ('Self') ratings.

	HC		PMD		PSZ	
	M	SD	M	SD	M	SD
Other						
Trimodal emotional	98.44	2.76	95.31	8.29	97.19	5.54
Neutral prosody	95.31	8.50	93.23	10.08	94.38	6.69
Neutral face	88.80	12.22	85.16	18.04	85.00	14.25
Neutral speech	68.49	25.83	69.53	28.69	74.38	28.74
Foreign language	79.43	15.69	76.82	13.60	80.31	11.87
Self						
Trimodal emotional	74.74	27.67	75.00	25.14	73.75	27.10
Neutral prosody	70.57	28.70	64.32	27.18	65.94	28.42
Neutral face	57.29	28.47	59.90	28.43	61.25	30.73
Neutral speech	30.99	28.04	33.85	28.01	33.75	29.41
Foreign language	51.82	29.34	45.57	26.29	43.13	22.39

Note. For abbreviations concerning the different conditions, please refer to the main document. M=Mean, SD=Standard deviation, HC=Healthy controls, PMD=Patients with major depression, PSZ=Patients with schizophrenia.

Post-hoc tests for the main effect COND showed that condition 'trimodal emotional' showed higher affective response rates compared to any other condition ('neutral prosody': $t(67)=4.84$; 'neutral facial expression': $t(67)=6.94$; 'neutral speech': $t(67)=13.10$; 'foreign language': $t(67)=11.86$, all ps<.001), and all other conditions showed significant differences between each other (all ps ≤.001).

Channel-sensitive contrasts

Within each participant group, T-contrasts comparing the trimodal emotional condition with each bimodal emotional condition revealed activation in areas responsible for processing the respective sensory modality (Figure DS2, Tables DS3-DS5).

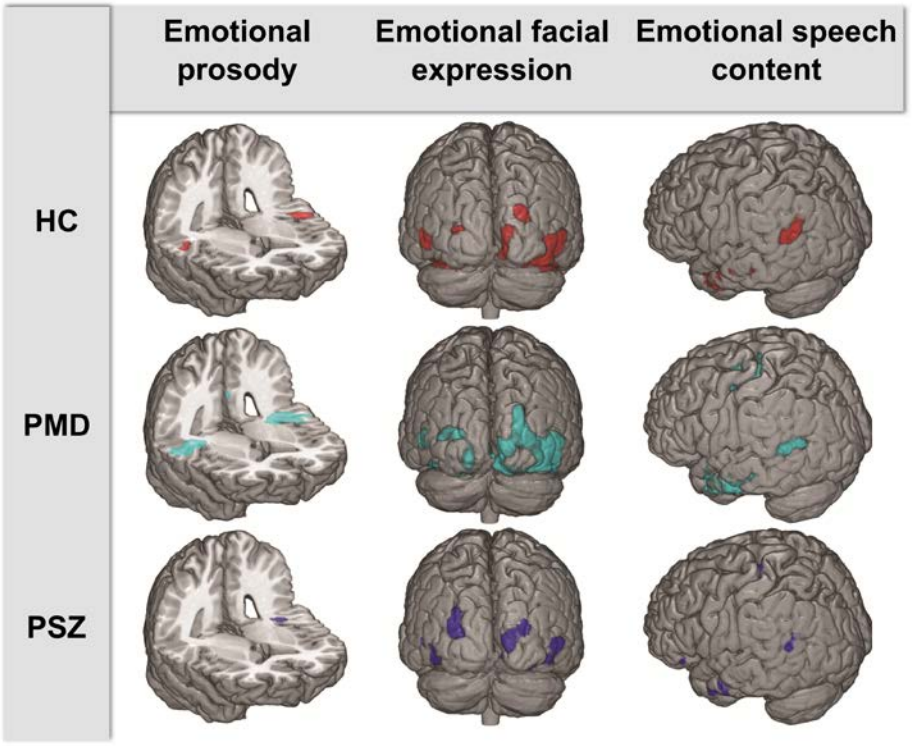

Figure DS2. Areas responsible for processing emotional prosody, facial expressions, and speech.

Planned 'channel-contrasts' within each participant group (random-effects general linear model, Ts>4.78, Monte-Carlo-cluster-level corrected, p<.05, k>125) as well as the F-contrast (F>7.03, Monte-Carlo-cluster-corrected, masked inclusively with contrast 1).

Table DS3. Activation patterns in the contrast 'emotional prosody'.

	Anatomical label	Anatomy toolbox	H	Size	T	p	x	y	z
HC	Heschls gyrus	TE1.0, TE1.2, OP4, TE3	L	593	6.96	<.001	-51	-15	2
	Heschls gyrus	TE1.0, TE1.1, TE1.2	R	148	5.21	.008	57	-18	5
	Inferior parietal lobule	hIP1, hIP3, IPC	L	107	5.35	.004	-38	-54	42
	Precuneus	SPL, (7A, 7M, 7P), Area 18	L	107	5.19	.009	-9	-68	36
PMD	Heschls gyrus	TE1.1, TE1.0, Insula (Ig2, Ig1)	L	2059	8.22	<.001	-35	-24	9
	Heschls gyrus	TE1.1, TE1.0, Insula (Ig1), OP1	R	1468	7.94	<.001	41	-26	8
	Posterior cingulate cortex	-	L	632	6.37	<.001	-2	-24	30
	Precuneus	SPL (7M, 7A, 7P)	R	485	5.50	.002	9	-65	36
	IFG (orbitalis)	-	R	275	6.23	<.001	39	24	-14
	Angular gyrus	IPC (PGa, PGp), hIP3, hIP1	R	236	5.19	.009	39	-65	38
	Inferior parietal lobule	hIP1, hIP3, SPL (7A), IPC	L	233	5.89	<.001	-36	-53	45
	IFG (orbitalis)	-	L	66	5.30	.005	-44	18	-3
	Middle orbital gyrus	-	L	56	5.32	.009	-44	47	-2
PSZ	Superior temporal gyrus	TE1.1, TE1.0, Insula (Id1, Ig2)	L	265	6.08	<.001	-41	-27	8
	White matter	-	L	103	5.54	.002	-3	-23	27

Table DS4. Activation patterns in the contrast 'emotional facial expression'.

	Anatomical label	Anatomy toolbox	H	Size	T	p	x	y	z
HC	Fusiform gyrus	hOC4v(V4), hOC3v(V3v), Area17, Area18	R	9336	8.75	<.001	51	-72	-9
	Fusiform gyrus	hOC4v(V4), Lobule VIIa Crus I, hOC3v(V3v), Area18	L	1887	6.32	<.001	-26	-87	-15
	Middle occipital gyrus	hOC5	L	968	7.70	<.001	-51	-74	0
	Middle occipital gyrus	Area18, hOC3v	L	291	6.28	<.001	-26	-96	9
	Hippocampus, amygdala	Hipp(CA), Amyg(CM), Hipp(SUB), Th-Temporal	R	246	6.41	<.001	27	-15	-11
	Precentral gyrus	Area4a, Area4p, Area6, Area3b	L	157	5.62	.001	-38	-24	59
	Superior medial gyrus	-	L	78	5.31	.005	-9	54	6
	Brainstem	-	L	67	6.58	<.001	-9	-23	-15
PMD	Fusiform gyrus	Area17, hOC4v (V4), hOC4v (V4), Area18	R	19519	9.82	<.001	47	-75	-6
	SMA	Area6	L	1639	6.31	<.001	-3	-5	53
	Cerebellar vermis	Lobule VIIIa, IX, VI	R	711	6.13	<.001	3	-57	-39
	Precentral gyrus	Area6, Area4a, Area4p, Area3b	L	528	5.60	.001	-32	-18	63
	Thalamus	Th-Parietal, Hipp (SUB), Th-Visual, Th-Temporal	R	424	6.25	<.001	8	-27	-8
	Precentral gyrus	Area6, Area4a	R	255	6.13	<.001	54	-2	39
	Hippocampus	Hipp(SUB, CA, FD), Th-Parietal	L	110	5.60	.001	-24	-21	-18
	Angular gyrus	SPL, hIP3, SPL	R	104	5.62	<.001	29	-59	53
	Anterior cingulate cortex	-	L	61	5.28	.006	-3	6	30
	Anterior cingulate cortex	-	L	60	5.39	.004	-2	17	23
PSZ	Fusiform gyrus	hOC4v (V4), hOC3v (V3v), hOC5 (V5), Area18	R	1846	7.61	<.001	50	-72	0
	Inferior occipital gyrus	hOC4v (V4), hOC5v (V5)	L	800	6.12	<.001	-41	-78	-12
	Middle occipital gyrus	Area18, hOC3v, IPC	L	709	5.96	<.001	-29	-92	17
	Calcarine gyrus	Areaa17, Area18, hOC3v (V3v)	R	686	6.16	<.001	15	-101	5
	Fusiform gyrus	hOC4v (V4)	R	365	5.75	.001	38	-60	-17
	Middle cingulate cortex	Area4a, SPL (5M), Area6	L	153	5.48	.002	-2	-30	39
	Lingual gyrus	hOC4v (V4), Area18, hOC3v (V3v)	L	148	5.43	.003	-23	-89	-14
	Fusiform gyrus	hOC4v (V4), hOC3v (V3v)	L	104	5.38	.004	-24	-71	-6
	Brainstem	-	R	102	6.16	<.001	8	-27	-11
	Precuneus	SPL (7M)	R	69	5.18	.009	0	-65	33
	Precentral gyrus	Area3a, Area4p	R	57	5.40	.003	38	-9	36
	Precentral gyrus	Area6, Area4a, Area1, Area3b	L	54	5.20	.008	-30	-29	66

Table DS5. Activation patterns in the contrast 'emotional speech'.

	Anatomical label	Anatomy toolbox	H	Size	T	p	x	y	z
HC	Middle temporal gyrus	TE3	L	2781	8.13	<.001	-56	-27	-11
	Superior medial gyrus	-	L	2499	6.99	<.001	-11	53	5
	Middle temporal gyrus	IPC(PGa), IPC(PGp), IPC(PFm), IPC(PF)	L	2062	7.36	<.001	-56	-59	21
	Cerebellum	Lobule VII Crus I, Lobule VI	R	647	7.45	<.001	29	-75	-33
	Postcentral gyrus	Area4a, Area6, Area4p, Area3b	L	498	6.48	<.001	-36	-21	54

	IFG (p. triangularis)	Area45, Area44	L	305	5.64	<.001	-44	21	15
	Precuneus	-	L	254	5.67	.001	-6	-54	30
	Precentral gyrus	Area6	L	182	5.64	.001	-41	5	47
	SMA	Area6	L	121	5.56	.002	-5	-8	57
	Superior frontal gyrus	-	L	55	5.48	.002	-21	-3	50
PMD	SMA	Area6, Area4p, Area3b	L	8449	8.64	<.001	-18	-2	60
	Middle temporal gyrus	IPC(PGa), IPC(PGp), IPC(PFm), IPC(PFcm)	L	6539	8.13	<.001	-65	-8	-23
	Superior medial gyrus	-	L	2761	8.57	<.001	-11	56	27
	Posterior cingulate cortex	-	L	1130	7.14	<.001	-6	-51	32
	Cerebellum	Lobule VIIa Crus I, Lobule VI	R	735	7.00	<.001	26	-77	-33
	Superior frontal gyrus	Area6	R	520	6.65	<.001	26	2	57
	Hippocampus	Hipp(SUB), Hipp(CA), Th-Parietal, Hipp(FD)	L	490	6.48	<.001	-26	-21	-17
	Middle frontal gyrus	-	L	343	6.93	<.001	-29	17	38
	Medial temporal pole	-	R	262	6.12	<.001	54	9	-20
	Inferior temporal gyrus	-	R	250	6.25	<.001	53	-17	-18
	Thalamus	Th-Prefrontal, Th-Temporal	L	169	5.39	<.001	-12	0	8
	Cerebellar vermis	Lobule VI	L	133	5.74	.001	-2	-75	-12
	Insula	-	L	99	5.32	.002	-30	6	11
	White matter	-	R	79	5.48	.002	23	8	15
	Cerebellum	Lobule VIIa Crus I, Lobule VI	R	77	5.32	.004	42	-57	-33
	ParaHippocampal gyrus	Hipp(CA), Hipp(SUB), hIP1	R	67	6.07	.005	35	-12	-29
	Putamen	-	L	60	5.56	.005	-26	-2	0
PSZ	Precuneus	SPL(7A), SPL(5M9, SPL(5L), Area4a	L	1723	7.15	<.001	-6	-54	30
	Middle temporal gyrus	IPC(PGa), IPC(PGp), IPC(PFm), IPC(PFcm)	L	1530	6.45	<.001	-48	-48	23
	Postcentral gyrus	Area6, Area4a, Area3b, Area4p	L	1284	6.34	<.001	-32	-30	65
	Middle cingulate cortex	Area6		506	5.67	<.001	0	-5	51
	Middle temporal gyrus	-	L	441	6.06	<.001	-65	-8	-20
	Hippocampus/amygdala	Hipp(CA), Hipp(FD), Hipp(SUB), Amyg(LB)	L	397	6.50	<.001	-36	-20	-20
	Superior frontal gyrus	-	L	378	6.39	<.001	-14	42	42
	Caudate nucleus	Th-Prefrontal/Premotor/Parietal/and Temporal	R	250	6.89	<.001	21	-14	20
	Thalamus	Th-Prefrontal/Premotor/Parietal, OP3	L	142	5.65	.001	-18	-9	15
	Caudate nucleus	-	R	124	5.66	.001	15	15	6
	Middle frontal gyrus	Area 45	L	108	5.30	.005	-33	35	15
	Middle frontal gyrus	-	L	95	5.51	.002	-33	41	27
	SMA	Area6	R	89	5.48	.002	3	-15	71
	Thalamus	Th-Prefrontal/Temporal	L	88	5.31	.002	-8	-3	-2
	Thalamus	Th-Prefrontal/Temporal	L	79	5.67	.001	-54	-29	-8
	Middle temporal gyrus	-	L	79	5.47	.002	-5	-14	5
	IFG	Area45	L	70	5.41	.003	-53	29	-9
	Superior parietal lobe	SPL(7PC), Area1, SPL(7A), Area2	L	68	5.31	.005	-32	-48	62

Note. Tables DS3-DS5 present 'Channel-sensitive' activation patterns resulting from a subtraction of a bimodal emotional from a trimodal emotional contrast. Contrasts resulted from a random-effects GLM, Ts>4.78, ps<.05, FWE-corrected for multiple comparisons, k>50). Stereotaxic coordinates of local maxima of activation are expressed as x;y;z values in proper MNI space. HC=healthy controls, PMD=patients with major depression, PSZ=patients with schizophrenia, H=hemisphere, R=right, L=left. The column Anatomy toolbox gives cytoarchitectonical labels[7].

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