Data supplement for Dugré et al., Limbic Hyperactivity in Response to Emotionally Neutral Stimuli in Schizophrenia: A Neuroimaging Meta-Analysis of the Hypervigilant Mind. Am J Psychiatry (doi: 10.1176/appi.ajp.2019.19030247)

TABLE S1. PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #				
TITLE	TITLE						
Title	1	Identify the report as a systematic review, meta- analysis, or both.	1				
ABSTRACT							
Structured summary	2						
INTRODUCTION							
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-6				
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6				
METHODS							
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA				
Eligibility criteria	Eligibility criteria 6 Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.		6				
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6				
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6				

(Continued)

Section/topic	#	Checklist item	Reported on page #
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7-8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-11 Supp T2 to T6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-11, Supp T2 to Supp T6

(Continued)

Section/topic	#	Checklist item	Reported on page #		
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-111 Supp T2 to T6		
DISCUSSION					
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15		
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15		
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16		
FUNDING					
Funding	27	NA			

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TABLE S2. Description of the studies included in the meta-analysis (n = 23)

First Author, Date	n=	HC (n=)	TR (ms)	Explicit/ Implicit		Stimuli type	Task indications	Contrast selected (1st-level)
Dowd, 2010 (18)	40	32	3000	Explicit	No	Emotional pictures, words and faces	Arousal and Valence Ratings	Neutral > Baseline
Ferri, 2014 (25)	22	22	2400	Implicit	No	Dynamic stimuli of human emotionaction	Passive observation	Neutral Action & Emotion > Intertrial fixation Baseline
Habel, 2010 (26)	17	17	3000	Explicit	Yes	Emotional recognition (fear, happiness, anger or sadness)	Selecting target emotion or non-target/neutral face)	Neutral face > baseline condition (blank screen)
Hall, 2008 (12)	19	24	2500	Implicit	Yes	Facial expression (fear and neutral)	Gender identification	Neutral > Baseline (fixation cross)
Holt, 2006 (16)	15	16	2800	Implicit	Yes	Facial expression (happy, fearful, neutral faces)	Passive observation	Neutral > Baseline (visual crosshair)
Jensen, 2008 (27)	13	13	2240	Implicit	No	Classical passive Pavlovian learning paradigm (Aversive acoustic stimulus)	Passive hearing	Unconditioned Stimulus (Colored circles) only
Lakis, 2013 (28)	27	37	3000	Implicit	No	Positive, Negative and Neutral Pictures	Passive observation	Neutral > Rest
Lee, 2014 (29)	15	14	2000	Explicit	No	Positive, Negative and Neutral Pictures (IAPS)	Subjective emotional rating	Neutral > Null events (crosshair fixation)
Mier, 2010 (30)	16	16	3000	Implicit	Yes	Neutral Task (Statement + Neutral Face)	Physical feature detection	Neutral Task > Baseline (fixation cross)
Modinos, 2015 (17)	18	22	3000	Explicit	No	Emotional pictures (IAPS: Positive, Negative, Neutral)	Emotional Arousal Ratings	Neutral > Baseline (Fixation cross)
Mothersill, 2014 (31)	25	21	2200	Implicit	Yes	Dynamic facial emotional expression (Angry, Neutral)	Passive observation	Neutral > Baseline (dynamic circles)
(Conti	nued)							

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First Author, Date	n=	HC (n=)	TR (ms)	Explicit/ Implicit	Facial expressions	Stimuli type	Task indications	Contrast selected (1st-level)
Pankow, 2013 (32)	35	36	2300	Implicit	No	Emotional pictures (IAPS: Positive, Negative, Neutral)	Active viewing (i.e. confirming each viewed picture)	Neutral > Baseline (overall mean)
Rauch, 2010 (33)	12	12	3000	Explicit	Yes	Facial stimuli (sad, happy, neutral, erased face)	Valence ratings	Neutral > Erased face
Reske, 2009 (34)	18	18	3000	Explicit	Yes	Facial expressions (happy, sad, neutral)	Emotional recognition matching verbal categories	Neutral > Baseline
Shin, 2015 (35)	16	16	2000	Implicit	Yes	Facial emotional expression (fearful, happy, neutral)	Gender identification	Neutral > baseline (fixation cross)
Spilka, 2015 (36)	28	27	2500	Implicit	Yes	Facial expressions (happy, sad, angry, neutral or scrambled faces)	Passive observation	Neutral > Scrambled faces
Surguladze, 2006 (37)	15	11	2000	Implicit	Yes	Facial expression (sad, happy, neutral)	Gender identification	Neutral > Baseline (fixation cross)
Suslow, 2013 (38)	30	35	2000	Explicit	Yes	Facial expressions (Angry, Happy, Neutral)	Emotional Valence Ratings	Neutral > Baseline (Erased Face)
Taylor, 2002 (39)	14	13	NA	Explicit	No	Emotional pictures (aversives, non- aversives)	Arousal Ratings	Non-aversive > Baseline (Blank screen with fixation cross)
Taylor, 2007 (40)	23	15	2000	Explicit	No	Emotional pictures (IAPS: Positive, Aversives, Neutral)	Arousal and Valence Ratings	Neutral > Baseline (Blank images of a colored polygon on a textured, gray-toned background)
Taylor, 2011 (41)	21	21	2000	Implicit	Yes	Facial emotional expression (happy, fearful, sad, neutral)	Gender identification and preference indication (yes/no)	Neutral > Baseline (fixation cross)

(Continued)

First Author, Date	n=		TR (ms)	Explicit/ Implicit		Stimuli type	Task indications	Contrast selected (1st-level)
Ursu, 2011 (42)	20	20	2500	Explicit	No	Affective pictures (IAPS: pleasant, unpleasant, neutral)	Valence and Arousal ratings	Neutral > Baseline (fixation cross)
Whalley, 2009 (43)	15	14	2500	Explicit	No	Affective scenes (IAPS: Positive, Neutral)	Arousal Ratings	Neutral > Baseline (Fixation cross)

Note. HC = Healthy Controls; WB = Whole Brain; ROI = Region of Interest; CPZ = Chlorpromazine equivalents; FWHM = Full Width at Half Maximum kernel size. Positive Psychotic Symptoms refer to the Positive subscale score of the PANSS.

TABLE S3. Brain responses to emotionally neutral stimuli in individuals with schizophrenia versus healthy controls: Jackknife analyses (n=23)

	Increased activ	rations $(SZ > HC)$	Decreased activation (HC > SZ)
	L Putamen (-28, -6, -12)	R Amygdala (32, 0, -24)	R Middle Frontal Gyrus (48, 16, 34)
<u>Jackknife analysis</u>			
All studies but Dowd, 2010	Yes	Yes	Yes
All studies but Ferri, 2014	Yes	Yes	No
All studies but <i>Habel</i> , 2010	Yes	Yes	Yes
All studies but <i>Hall</i> , 2008	Yes	Yes	Yes
All studies but <i>Holt</i> , 2006	Yes	Yes	Yes
All studies but <i>Jensen</i> , 2008	Yes	Yes	Yes
All studies but <i>Lakis</i> , 2013	Yes	Yes	Yes
All studies but <i>Lee</i> , 2014	Yes	Yes	Yes
All studies but <i>Mier</i> , 2010	Yes	Yes	Yes
All studies but <i>Modinos</i> , 2015	Yes	Yes	Yes
All studies but <i>Mothersill</i> , 2014	Yes	Yes	Yes
All studies but <i>Pankow</i> , 2013	Yes	Yes	Yes
All studies but Rauch, 2010	Yes	Yes	Yes
All studies but <i>Reske</i> , 2009	Yes	Yes	Yes
All studies but Shin, 2015	Yes	Yes	Yes
All studies but <i>Spilka</i> , 2015	Yes	Yes	Yes
All studies but <i>Surguladze</i> , 2006	Yes	Yes	Yes
All studies but Suslow, 2013	Yes	Yes	Yes
All studies but <i>Taylor</i> , 2002	Yes	Yes	Yes
All studies but <i>Taylor</i> , 2007	Yes	Yes	Yes
All studies but <i>Taylor</i> , 2011	Yes	Yes	Yes
All studies but <i>Ursu</i> , 2011	Yes	Yes	No
All studies but Whalley, 2009	Yes	Yes	Yes
	23 out of	23 out of	21 out of
	23 studies	23 studies	23 studies

TABLE S4. Brain responses to emotionally neutral stimuli in individuals with schizophrenia versus healthy controls: whole-brain studies (n=14)

Main Peaks	MNI Coordinates	SDM z-value ^(a)	P Value (b)	No. of voxels (c)	Breakdown (No. of voxels) (c)
Increased activations L Putamen	-30, 2, -2	1.52	0.000005	1338	L Insula (346) L Putamen (279) L Hippocampus (87) L Amygdala (22)
R Putamen	32,2,2	1.34	0.0001	924	R Putamen (379) R Insula (215)
L Postcentral gyrus	-46, -12, 34	1.05	0.0012	212	L Postcentral (145) L Precentral (11)
<u>Decreased activations</u> R Middle Frontal Gyrus	48, 20, 38	-1.33	0.0002	360	R Middle Frontal Gyrus (83) R Inferior frontal gyrus, opercular (215) R Inferior frontal gyrus, triangular (62)
R Fusiform gyrus	36,-70,-10	-1.15	0.0006	300	R Fusiform gyrus (110) R Inferior occipital gyrus (34)

⁽a) Voxel probability threshold: p = 0.005

⁽b) Peak height threshold: z = 1

⁽c) Cluster extent threshold: 100 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

TABLE S5. Brain responses to emotionally neutral stimuli in individuals with schizophrenia versus healthy controls: studies studies using region of interest (n=9)

Main Peaks	MNI Coordinates	SDM z-value ^(a)	P Value (b)	No. of voxels (c)	Breakdown (No. of voxels) (c)
Increased activations R Amygdala	34, 0, -22	1.65	0.0004	636	R Amygdala (89) R Superior Temporal Gyrus (123) R Parahippocampal gyrus (158)
R Middle Temporal Gyrus	56, -56, 20	1.65	0.0004	424	R Middle Temporal Gyrus (178) R Angular Gyrus (145) R Superior Temporal Gyrus (66)
L Parahippocampal gyrus	-24, 8, -24	1.59	0.0006	269	L Parahippocampal gyrus (27) L Superior Temporal Gyrus (49) L Insula (11)
Decreased activations					
R Precentral gyrus	44, -2, 46	-1.22	0.0005	363	R Precentral gyrus (205) R Postcentral gyrus (105)

⁽a) Voxel probability threshold: p = 0.005

⁽b) Peak height threshold: z = 1

⁽c) Cluster extent threshold: 100 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

TABLE S6. Brain responses to emotionally neutral stimuli in individuals with schizophrenia versus healthy controls: studies using only facial expressions stimuli (n=12)

Main Peaks	MNI Coordinates	SDM z-value ^(a)	P Value (b)	No. of voxels	Breakdown (No. of voxels) (c)
Increased activations L Putamen	-26, 4, -6	2.56	~0	2329	L Putamen (315) L Insula (270) L Hippocampus (207) L Amygdala (186) L Parahippocampal gyrus (106) L Superior temporal gyrus (32)
R Putamen Decreased activations	34, 4, 2	1.44	0.0008	381	R Putamen (247) R Insula (65)
L Lingual gyrus	-18, -82, 0	-1.06	0.0002	142	L lingual gyrus (87)

⁽a) Voxel probability threshold: p = 0.005

⁽b) Peak height threshold: z = 1

⁽c) Cluster extent threshold: 100 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

TABLE S7. Brain responses to emotionally neutral stimuli in individuals with schizophrenia versus healthy controls: studies with other stimuli than facial expressions (i.e. scenes, pictures, words, auditory stimuli) (n=11)

Main Peaks	MNI Coordinates	SDM z-value ^(a)	P Value (b)	No. of voxels (c)	Breakdown (No. of voxels) (c)
Increased activations					
R Angular Gyrus	54, -52, 24	1.13	0.0006	309	R Angular Gyrus (143) R Superior Temporal Gyrus (67) R Middle Temporal Gyrus (42) R Supramarginal Gyrus (39)
R Amygdala	32, 0, -26	1.06	0.0009	183	R. Amygdala (107) R Superior Temporal Gyrus (37)
Decreased activations					
R Inferior Frontal Gyrus opercular part.	46, 10, 38	-1.72	0.00007	1072	R Precentral gyrus (530)
put					R Inferior Frontal Gyrus, Opercular (287) R Middle Frontal Gyrus (152) R Inferior Frontal Gyrus, Triangular (42)

⁽a) Voxel probability threshold: p = 0.005

⁽b) Peak height threshold: z = 1

⁽c) Cluster extent threshold: 100 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

TABLE S8. Brain responses to emotionally neutral stimuli in individuals with schizophrenia versus healthy controls: studies with an explicit emotional task (n=11)

Main Peaks	MNI Coordinates	SDM z-value ^(a)	P Value (b)	No. of voxels (c)	Breakdown (No. of voxels) (c)
Increased activations					
L Putamen	-24, 4, -2	1.29	0.00014	601	L Putamen (439) BA 48 (116)
Decreased activations					
R Fusiform Gyrus	36, -70, -10	-1.29	0.0003	688	R Fusiform Gyrus (587) R Inferior Occipital Gyrus (53) R Inferior Temporal Gyrus (10)

Note. L = Left; R = Right; BA = Brodmann Area

⁽a) Voxel probability threshold: p = 0.005

⁽b) Peak height threshold: z = 1

⁽c) Cluster extent threshold: 100 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

TABLE S9. Brain responses to emotionally neutral stimuli in individuals with schizophrenia versus healthy controls: studies with an implicit emotional task (n=12)

Main Peaks	MNI Coordinates	SDM z-value ^(a)	P Value (b)	No. of voxels (c)	Breakdown (No. of voxels) (c)	
Increased activations						
R Uncus	30, -2, -30	1.85	0.00004	1529	R Parahippocampal gyrus (354) R Middle Temporal Gyrus (119) R Amygdala (93) R Fusiform (60)	
L Amygdala	-24, -8, -16	2.33	~0	1181	L Amygdala (170) L Hippocampus (332) L Parahippocampal gyrus (76)	
Decreased activations						
R Precentral gyrus	46, 4, 42	-1.32	0.0003	976	R Precentral gyrus (455) R Inferior Frontal Gyrus, Opercular (192) R Postcentral (196) R Middle Frontal Gyrus (16)	

Note. L = Left; R = Right
(a) Voxel probability threshold: p = 0.005

⁽b) Peak height threshold: z = 1

⁽c) Cluster extent threshold: 100 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

TABLE S10. Brain responses to emotionally neutral stimuli in individuals with schizophrenia versus healthy controls: studies a FWHM <= 8mm (n=17)

Main Peaks	MNI SDM Coordinates z-value (a)		P Value (b)	No. of voxels (c)	Breakdown (No. of voxels) (c)		
Increased activations L Putamen	-26, 4, -10	1.75	~0	2068	L Putamen (269) L Insula (175) L Amygdala (182) L Hippocampus (229) L Parahippocampal gyrus (103) L Olfactory cortex (34) L Superior Temporal Gyrus (32)		
R Parahippocampal gyrus	32, 2, -26	1.11	0.0007	414	R Parahippocampal Gyrus (83) R Amygdala (76) R Superior temporal Gyrus (51)		
<u>Decreased activations</u> R Middle Frontal Gyrus	48, 14, 32	-1.47	0.00002	1118	R Inferior Frontal Gyrus, Opercular (395) R Precentral Gyrus (227) R Postcentral Gyrus (147) R Middle Frontal Gyrus (124) R Inferior Frontal Gyrus, Triangular (85)		

⁽a) Voxel probability threshold: p = 0.005(b) Peak height threshold: z = 1

⁽c) Cluster extent threshold: 100 voxels. Regions with less than 10 voxels are not reported in the cluster breakdown.

TABLE S11. Description of the studies included in the meta-analysis: Emotionally Negative Stimuli versus Neutral (SZ versus HC) (n=16)

		Studies with	Type of		
Study	Contrasts	Significant results	Stimuli	WB/ROI	Explicit/Implicit
Dowd, 2010 (18)	Negative > Neutral	X	Others	WB	Explicit
Hall, 2008 (12)	Fear > Neutral	X	Faces	ROI	Implicit
Holt, 2006 (16)	Fearful > Neutral	-	Faces	ROI	Explicit
Jensen, 2008 (27)	CS+	-	Others	ROI	Implicit
Lakis, 2013 (28)	Negative > Neutral	X	Others	ROI	Implicit
Modinos, 2015 (17)	Emotional scenes > Neutral	-	Others	WB	Explicit
Mothersill, 2014 (31)	Angry > Neutral	-	Faces	WB	Implicit
Pankow, 2013 (32)	Main effect: Negative > Positive+Neutral	X	Others	WB	Implicit
Rauch, 2010 (33)	Sad > Neutral	X	Faces	ROI	Explicit
Reske, 2009 (34)	Main effect: Sad > Happy+neutral	X	Faces	WB	Explicit
Spilka, 2015 (36)	Fearful > Neutral	-	Faces	WB	Implicit
Surguladze, 2006 (37)	Fearful > Neutral	-	Faces	ROI	Implicit
Suslow, 2013 (38)	Angry> initial phase	-	Faces	ROI	Explicit
Taylor, 2002 (39)	Aversive > Non-aversive	X	Others	WB	Explicit
Taylor, 2007 (40)	Aversive > Neutral	X	Others	ROI	Explicit
Whalley, 2009 (41)	Emotional scenes > Neutral	X	Others	ROI	Explicit

Note. X = Significant Results reported; - = no peaks reported. WB = Whole Brain; ROI = Region-of-Interest