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Ribosomal DNA transcription in dorsal raphe nucleus neurons is increased in residual schizophrenia compared to depressed patients with affective disorders

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ABSTRACT

The central serotonergic system is implicated differentially in the pathogenesis of depression and schizophrenia. The dorsal raphe nucleus (DRN) is the main source of serotonergic innervation of forebrain limbic structures disturbed in both disorders. The study was carried out on paraffin-embedded brains from 27 depressed (15 major depressive disorder, MDD and 12 bipolar disorder, BD) and 17 schizophrenia (9 residual and 8 paranoid) patients and 28 matched controls without mental disorders. The transcriptional activity of ribosomal DNA (rDNA) in DRN neurons was evaluated by the AgNOR silver staining method. A significant effect of diagnosis on rDNA activity was found in the cumulative analysis of all DRN subnuclei. Further analysis revealed an increase in this activity in residual (but not paranoid) schizophrenia compared to depressed (both MDD and BD) patients. The effect was most probably neither confounded by suicide nor related to antidepressant and antipsychotic medication. Our findings suggest that increased activity of rDNA in DRN neurons is a distinct phenomenon in residual schizophrenia, related presumably to differentially disturbed inputs to the DRN and/or their local transformation compared with depressive episodes in patients with affective disorders.

1. Introduction

The central serotonergic system is implicated in the aetiology of numerous mental disorders, including depression (for a review see: Altieri et al., 2012) and schizophrenia (for reviews see: Abi-Dargham, 2007; Meltzer, 2012; de Bartolomeis et al., 2013). As revealed by neuropathological research on depression and suicide, abnormalities in the serotonergic system may be structurally restricted to a specific brain region, the dorsal raphe nucleus (DRN), which affects brain circuits (for a review see: Bach and Arango, 2012). DRN neurons provide the major serotonergic innervation to the prefrontal cortex (PFC) (Wilson and Molliver, 1991; Jacobs and Azmitia, 1992; Van Bockstaele et al., 1993). Limbic regions of the PFC (i.e. the anterior cingulate cortex and the orbitofrontal cortex) in turn may reciprocally regulate DRN function through direct pyramidal input (Peyron et al., 1998; Jankowski and Sesack, 2004) disturbed in both depression and schizophrenia with an involvement of dysfunctional serotonergic modulation of PFC neuronal networks (for reviews see: Marek, 2007; Meltzer and Massey, 2011).

Compared with the number of postmortem studies on the DRN in affective disorders and suicide (Lloyd et al., 1974; Stockmeier et al., 1998; Underwood et al., 1999; Bligh-Glover et al., 2000; Arango et al., 2001; Baumann et al., 2002; Austin et al., 2003; Bonkale et al., 2004, 2006; Bielau et al., 2005; Boldrini et al., 2005, 2008; Bach-Mizrachi et al., 2006, 2008; Gos et al., 2008; Matthews and Harrison, 2012), reports on the DRN in schizophrenia are scanty (Craven et al., 2005; Matthews and Harrison, 2012; Krzyżanowska et al., 2015; for a review of older studies see: Harrison, 1999). Discrepancies in these studies result from various factors. Inconsistencies in psychiatric diagnosis and treatment, cause of

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Table 1
Demographic data of patients with schizophrenia ($n=17$), depression ($n=27$) and healthy control subjects ($n=28$). *Abbreviations:* PMI – postmortem interval, f – female, m – male, Sz – schizophrenia, MDD – major depressive disorder, BD – bipolar disorder, *q1* and *q3* – quartile 1 and 3.

Case ID	Diagnosis (DSM-IV)	Sex	Age [yr]	Illness duration [yr]	PMI [h]	Cause of death
1	Sz, paranoid	f	49	2	72	Fall from the high
2	Sz, paranoid	m	47	16	24	Strangulation
3	Sz, paranoid	f	52	28	24	Drowning
4	Sz, paranoid	f	55	6	48	Overdose of medication
5	Sz, paranoid	m	34	5	5	Hanging
6	Sz, paranoid	m	45	20	72	Tracheobronchitis
7	Sz, paranoid	m	38	38	24	Self-strangulation
8	Sz, paranoid	m	27	5	24	Hanging
9	Sz, residual	m	46	18	48	Pulmonary embolism
10	Sz, residual	m	51	28	48	Ileus
11	Sz, residual	m	57	23	72	Cardiac insufficiency
12	Sz, residual	f	64	0	12	Pulmonary embolism
13	Sz, residual	m	48	32	48	Acute respiratory failure
14	Sz, residual	m	58	25	24	Cardio-respiratory insufficiency
15	Sz, residual	m	54	34	48	Cardio-respiratory insufficiency
16	Sz, residual	f	54	18	24	Pulmonary embolism
17	Sz, residual	m	76	26	12	Self-strangulation
Schizophrenia: ratio/median (q1;q3)		*12m/5f*	*51 (46; 55)*	*18 (6; 26)*	*24 (24; 48)*	
18	Depressed, MDD	f	63	2	17	Pulmonary embolism
19	Depressed, MDD	f	61	11	70	Sudden cardiac death
20	Depressed, MDD	f	41	2	20	Pulmonary embolism
21	Depressed, MDD	f	39	7	48	Overdose of medication
22	Depressed, MDD	f	47	11	24	Overdose of medication
23	Depressed, MDD	f	53	2	46	Hanging
24	Depressed, MDD	f	46	11	48	Hanging
25	Depressed, MDD	f	53	–	47	Self-electrocution
26	Depressed, MDD	f	26	–	22	Fall from the height
27	Depressed, MDD	m	35	2	15	Incision of the radial artery
28	Depressed, MDD	m	36	1	42	Hanging
29	Depressed, MDD	f	60	–	24	Hanging
30	Depressed, MDD	f	62	11	72	Pulmonary embolism
31	Depressed, MDD	f	60	10	14	Bronchopneumonia
32	Depressed, MDD	m	39	2	14	Pulmonary embolism
33	Depressed, BD	m	39	14	56	Coronary failure
34	Depressed, BD	m	69	26	48	Pulmonary embolism
35	Depressed, BD	m	69	18	24	Bronchopneumonia
36	Depressed, BD	f	52	–	24	Pulmonary embolism
37	Depressed, BD	f	65	25	52	Heart failure
38	Depressed, BD	m	57	–	48	Hanging
39	Depressed, BD	m	60	–	24	Self-strangulation
40	Depressed, BD	f	46	13	4	Overdose of medication
41	Depressed, BD	f	59	24	72	Overdose of medication
42	Depressed, BD	m	47	9	24	Stab wound
43	Depressed, BD	m	42	16	17	Hanging
44	Depressed, BD	m	53	–	24	Self-strangulation
Depressed: ratio/median (q1;q3)		*11m / 16f*	*53 (41; 60)*	*11 (2; 15)*	*24 (20; 48)*	
45	Control	m	56	–	48	Retroperitoneal haemorrhage
46	Control	m	47	–	24	Respiratory insufficiency
47	Control	f	52	–	24	Ovarian carcinoma
48	Control	f	48	–	48	Pulmonary embolism
49	Control	m	47	–	24	Coronary failure
50	Control	f	64	–	24	Sepsis
51	Control	f	33	–	72	Coronary failure
52	Control	m	40	–	96	Myocardial infraction
53	Control	m	64	–	35	Heart failure
54	Control	f	48	–	26	Pulmonary embolism
55	Control	f	65	–	24	Heart failure
56	Control	f	30	–	48	Pulmonary embolism
57	Control	m	56	–	24	Pulmonary embolism
58	Control	f	64	–	26	Heart failure
59	Control	m	63	–	48	Heart failure
60	Control	f	61	–	8	Sudden cardiac death
61	Control	f	61	–	24	Heart failure
62	Control	f	38	–	24	Heart failure
63	Control	m	39	–	4	Peritonitis
64	Control	f	61	–	24	Heart failure
65	Control	f	67	–	24	Sudden cardiac death
66	Control	m	54	–	24	Right heart failure
67	Control	m	46	–	24	Lymphoma
68	Control	f	63	–	24	Heart failure