

## Supplementary Online Content

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**eTable 1.** 5-HT<sub>1A</sub> Receptor Binding in the Medullary 5-HT System in SIDS Cases Compared With Controls in the Current (2010) and 2006<sup>11</sup> Data Sets Combined

**eFigure.** 5-HT<sub>1A</sub> Receptor Binding Correlations Among Nuclei of the Medullary 5-HT System in SIDS Cases in the 2006 and 2010 Data Sets Combined

**eTable 2.** Risk Factors for SIDS in the 2010 Data Set

**eTable 3.** Association Between SIDS Risk Factors and 5-HT Tissue Markers in the Raphé Obscurus and Paragigantocellularis Lateralis in the SIDS Group

This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1.** 5-HT<sub>1A</sub> Receptor Binding in the Medullary 5-HT System in SIDS Cases Compared With Controls in the Current (2010) and 2006<sup>11</sup> Data Sets Combined

	Age-Adjusted Mean [95% CI]		Diagnosis	PCA		Age-Diagnosis Interaction p-value
	SIDS N=51	Controls N=11	p-value	Slope	p-value	
HG*	-	-	-	-	-	0.006
NTS*	8.35 [7.36, 9.33]	13.72 [11.46, 15.99]	<0.001	-0.10	0.01	0.10
MAO	11.15 [9.11, 13.20]	22.38 [17.80, 26.95]	<0.001	-0.20	0.02	0.99
ROb	-	-	-	-	-	0.003
GC*	-	-	-	-	-	0.002
PGCL*	-	-	-	-	-	<0.001
IRZ*	-	-	-	-	-	0.002
ARC	4.48 [3.56, 5.41]	6.58 [4.77, 8.39]	0.04	-0.05	0.19	0.46

Measurements in fmol/mg tissue.

\*Nuclei in which there were significant differences in 5-HT<sub>1A</sub> receptor binding levels between SIDS and controls in both the 2006 and 2010 dataset when analyzed separately. With a significant age-diagnosis interaction, no means are given because the difference in means between SIDS and control cases varies by age. When the age-diagnosis interaction was not significant, it was dropped from the final model. Abbreviations: HG, hypoglossal nucleus; NTS, nucleus of the solitary tract; MAO, medial accessory nucleus; ROb, raphé obscurus; GC, gigantocellularis; PGCL, paragigantocellularis lateralis; IRZ, intermediate reticular zone; ARC, arcuate nucleus; CI, confidence interval.

**eFigure.** 5-HT<sub>1A</sub> Receptor Binding Correlations Among Nuclei of the Medullary 5-HT System in SIDS Cases in the 2006 and 2010 Data Sets Combined

A) The corresponding sample size, correlation coefficient, and p-values for the correlations among the SIDS cases (n=51). B) Correlations for the controls. The sample size varies due to missing data for each particular nucleus. Abbreviations: DAO, dorsal accessory olive; DMX, dorsal motor nucleus of the vagus; HG, Hypoglossal nucleus; NTS, nucleus of the solitary tract; MAO, medial accessory olive; ROb, raphé obscurus; GC, gigantocellularis; PGCL, paragigantocellularis lateralis; IRZ, intermediate reticular zone; Arc, arcuate nucleus.

**eFigure A. 5-HT<sub>1A</sub> Correlations in the SIDS Cases of 2006<sup>11</sup> and 2010 Data Sets Combined**

Correlation p-value N	HG	DMX	NTS	MAO	Rob	GC	PGCL	IRZ	DAO	Arc	pio
HG	1.00000 46	0.81019 <.0001 31	0.76791 <.0001 46	0.38029 0.0109 44	0.45103 0.0021 44	0.51127 0.0004 44	0.58628 <.0001 44	0.53606 0.0002 43	0.40550 0.0950 18	0.36490 0.0287 36	0.66776 0.1472 6
DMX	0.81019 <.0001 31	1.00000 32	0.67225 <.0001 32	0.25486 0.1665 31	0.49750 0.0052 30	0.49282 0.0057 30	0.56149 0.0012 30	0.54649 0.0022 29	0.44835 0.0620 18	0.01804 0.9303 26	. . 0
NTS	0.76791 <.0001 46	0.67225 <.0001 32	1.00000 47	0.70762 <.0001 45	0.71861 <.0001 45	0.78889 <.0001 45	0.79050 <.0001 45	0.82953 <.0001 44	0.76877 0.0002 18	0.52163 0.0009 37	0.30807 0.5525 6
MAO	0.38029 0.0109 44	0.25486 0.1665 31	0.70762 <.0001 45	1.00000 45	0.71545 <.0001 43	0.74522 <.0001 43	0.73811 <.0001 43	0.74984 <.0001 42	0.66274 0.0027 18	0.38562 0.0202 36	0.46757 0.3498 6
Rob rob L678	0.45103 0.0021 44	0.49750 0.0052 30	0.71861 <.0001 45	0.71545 <.0001 43	1.00000 49	0.87029 <.0001 49	0.83713 <.0001 49	0.77357 <.0001 48	0.82332 <.0001 19	0.33654 0.0388 38	-0.16595 0.7534 6
GC	0.51127 0.0004 44	0.49282 0.0057 30	0.78889 <.0001 45	0.74522 <.0001 43	0.87029 <.0001 49	1.00000 49	0.95494 <.0001 49	0.90350 <.0001 48	0.87545 <.0001 19	0.42211 0.0083 38	0.45223 0.3679 6
PGCL	0.58628 <.0001 44	0.56149 0.0012 30	0.79050 <.0001 45	0.73811 <.0001 43	0.83713 <.0001 49	0.95494 <.0001 49	1.00000 49	0.92251 <.0001 48	0.89427 <.0001 19	0.47771 0.0024 38	0.43489 0.3888 6
IRZ	0.53606 0.0002 43	0.54649 0.0022 29	0.82953 <.0001 44	0.74984 <.0001 42	0.77357 <.0001 48	0.90350 <.0001 48	0.92251 <.0001 48	1.00000 48	0.83063 <.0001 19	0.34911 0.0342 37	0.55087 0.2573 6
DAO	0.40550 0.0950 18	0.44835 0.0620 18	0.76877 0.0002 18	0.66274 0.0027 18	0.82332 <.0001 19	0.87545 <.0001 19	0.89427 <.0001 19	0.83063 <.0001 19	1.00000 19	0.53236 0.0229 18	. . 0
Arc	0.36490 0.0287 36	0.01804 0.9303 26	0.52163 0.0009 37	0.38562 0.0202 36	0.33654 0.0388 38	0.42211 0.0083 38	0.47771 0.0024 38	0.34911 0.0342 37	0.53236 0.0229 18	1.00000 38	0.97798 0.1338 3
pio	0.66776 0.1472 6	. . 0	0.30807 0.5525 6	0.46757 0.3498 6	-0.16595 0.7534 6	0.45223 0.3679 6	0.43489 0.3888 6	0.55087 0.2573 6	. . 0	0.97798 0.1338 3	1.00000 6

**eFigure B.** 5-HT<sub>1A</sub> Correlations in the Controls of 2006<sup>11</sup> and 2010 Data Sets Combined

Correlation  
p-value  
N

	HG	DMX	NTS	MAO	Rob	GC	PGCL	IRZ	DAO	Arc	pio
HG	1.00000 0.65789	-0.51208 0.86203	0.06801 0.86209	-0.42075 0.25949	0.37162 0.32479	0.26364 0.49319	0.80852 0.00839	0.20241 0.60159	1.00000 .2	-0.39072 0.33858	0.39606 0.60394
DMX	-0.51208 0.65783	1.00000 0.48563	0.99992 0.00833	0.72293 0.48563	0.98832 0.09743	0.97604 0.13963	-0.12081 0.92293	0.43670 0.71233	1.00000 .2	0.75102 0.45913	.0
NTS	0.06801 0.86209	0.99992 0.00833	1.00000 0.02299	0.73919 0.02299	0.62793 0.07029	0.15427 0.69199	0.08287 0.83219	0.43240 0.24519	1.00000 .2	0.91934 0.00128	0.69639 0.30364
MAO	-0.42075 0.25949	0.72293 0.48563	0.73919 0.02299	1.00000 0.02299	0.47491 0.19649	0.02888 0.94129	-0.33946 0.37159	0.18744 0.62929	-1.00000 .2	0.83183 0.01048	0.47498 0.52504
Rob rob L678	0.37162 0.32479	0.98832 0.09743	0.62793 0.07029	0.47491 0.19649	1.00000 0.1111	0.78379 0.004311	0.82131 0.001911	0.87787 0.000411	0.97398 0.14563	0.61809 0.056810	0.32665 0.67334
GC	0.26364 0.49319	0.97604 0.13963	0.15427 0.69199	0.02888 0.94129	0.78379 0.004311	1.00000 0.1111	0.82427 0.001811	0.84769 0.001011	0.99778 0.04243	0.25900 0.469910	-0.15482 0.84524
PGCL	0.80852 0.00839	-0.12081 0.92293	0.08287 0.83219	-0.33946 0.37159	0.82131 0.001911	0.82427 0.001811	1.00000 0.1111	0.89282 0.000211	0.93103 0.23783	0.20079 0.578110	0.26057 0.73944
IRZ	0.20241 0.60159	0.43670 0.71233	0.43240 0.24519	0.18744 0.62929	0.87787 0.000411	0.84769 0.001011	0.89282 0.000211	1.00000 0.1111	0.79930 0.41043	0.41287 0.235710	0.34898 0.65104
DAO	1.00000 .2	1.00000 .2	1.00000 .2	-1.00000 .2	0.97398 0.14563	0.99778 0.04243	0.93103 0.23783	0.79930 0.41043	1.00000 0.3	0.57451 0.61043	.0
Arc	-0.39072 0.33858	0.75102 0.45913	0.91934 0.00128	0.83183 0.01048	0.61809 0.056810	0.25900 0.469910	0.20079 0.578110	0.41287 0.235710	0.57451 0.61043	1.00000 0.10	0.93637 0.22833
pio	0.39606 0.60394	.0	0.69639 0.30364	0.47498 0.52504	0.32665 0.67334	-0.15482 0.84524	0.26057 0.73944	0.34898 0.65104	.0	0.93637 0.22833	1.00000 0.4

**eTable 2.** Risk Factors for SIDS in the 2010 Data Set\*

Variable	SIDS n=41
Male sex	56% (23/41)
Race/ethnicity	
White	39% (15/39)
African American	13% (5/39)
Hispanic	39% (15/39)
Other	10% (4/30)
Minor illness	
Within 1 week of death	44% (17/39)
<48 hours of death	33% (13/40)
Position in which found at death	
Prone	49% (17/35)
Supine	26% (9/35)
Side	14% (5/35)
Other, eg, car seat	11% (4/35)
Face down	37% (11/30)
Face covered	10% (3/31)
Bed sharing	20% (8/41)
Prematurity**	29% (12/41)

\*The variation between known SIDS risk factors and 5-HT tissue markers in the raphé obscurus and paragigantocellularis lateralis, the key raphé, and extraraphé components of the medullary 5-HT system.

\*\*Prematurity defined as <37 gestational weeks at birth.

**eTable 3.** Association Between SIDS Risk Factors and 5-HT Tissue Markers in the Raphé Obscurus and Paragigantocellularis Lateralis in the SIDS Group

A. 5-HT Levels in the Raphé Obscurus

Risk Factor	Yes		No		t-test p-value
	N	Mean [95% CI]	N	Mean [95% CI]	
Male	17	60.99 [51.65, 70.34]	18	53.83 [44.25, 63.42]	0.27
Black [vs White/Hispanic/Asian]	3	60.04 [39.36, 80.71]	26	59.17 [51.86, 66.48]	0.94
Premature	9	62.22 [50.83, 73.61]	26	55.61 [47.53, 63.69]	0.37
Position in which found at death					
Prone [vs supine]	13	58.47 [48.73, 68.21]	8	57.18 [37.95, 76.42]	0.88
Side [vs supine]	5	41.57 [35.89, 47.24]	8	57.18 [37.95, 76.42]	0.10
Car Seat [vs supine]	2	64.04 [-50.89, 179.0]	8	57.18 [37.95, 76.42]	0.70
Prone+side [vs supine]	18	53.78 [45.93, 61.62]	8	57.18 [37.95, 76.42]	0.66
Face down	9	53.19 [43.28, 63.11]	17	53.68 [43.46, 63.90]	0.95
Bed-sharing	8	48.55 [34.39, 62.71]	27	59.91 [52.45, 67.37]	0.14
Adult bed [vs crib]	13	59.71 [45.89, 73.53]	12	58.50 [48.11, 68.90]	0.88
Illness within last week	16	56.87 [46.59, 67.15]	19	57.68 [48.55, 66.81]	0.90
Illness within last 48 hours	13	60.38 [48.42, 72.35]	21	55.98 [47.43, 64.52]	0.52

B. 5-HT Levels in the Paragigantocellularis Lateralis

Risk Factor	Yes		No		t-test p-value
	N	Mean [95% CI]	N	Mean [95% CI]	
Male	17	30.01 [25.10, 34.93]	18	31.54 [25.71, 37.37]	0.68
Black [vs White/Hispanic/Asian]	3	27.33 [19.87, 34.80]	26	32.53 [28.17, 36.90]	0.42
Premature	9	33.39 [26.96, 39.81]	26	29.90 [25.35, 34.46]	0.40
Position in which found at death					
Prone [vs supine]	13	28.06 [23.84, 32.28]	8	30.99 [22.50, 39.49]	0.44
Side [vs supine]	5	26.52 [10.15, 42.89]	8	30.99 [22.50, 39.49]	0.50
Car Seat [vs supine]	2	30.61 [29.34, 31.88]	8	30.99 [22.50, 39.49]	0.92
Prone+side [vs supine]	18	27.64 [23.31, 31.97]	8	30.99 [22.50, 39.49]	0.40
Face down	9	24.29 [20.46, 28.13]	17	30.09 [25.10, 35.08]	0.11
Bed-sharing	8	29.07 [16.98, 41.16]	27	31.31 [27.57, 35.05]	0.61
Adult bed [vs crib]	13	29.82 [22.41, 37.23]	12	31.58 [23.74, 39.42]	0.73
Illness within last week	16	30.73 [26.30, 35.16]	19	30.86 [24.87, 36.85]	0.97
Illness within last 48 hours	13	31.30 [26.62, 35.98]	21	30.38 [24.72, 36.03]	0.81

C. TPH2 Levels in the Raphé Obscurus

Risk Factor	Yes		No		t-test p-value
	N	Mean [95% CI]	N	Mean [95% CI]	
Male	17	145.29 [130.4, 160.2]	17	155.12 [134.8, 175.4]	0.41
Black [vs White/Hispanic/Asian]	3	148.00 [23.79, 272.2]	26	143.81 [133.4, 154.2]	0.81
Premature	9	146.89 [116.7, 177.1]	25	151.40 [137.6, 165.2]	0.74
Position in which found at death					
Prone [vs supine]	13	157.15 [134.6, 179.7]	7	147.86 [116.5, 179.3]	0.59
Side [vs supine]	5	127.80 [108.3, 147.3]	7	147.86 [116.5, 179.3]	0.25
Car Seat [vs supine]	2	121.50 [-177.1, 420.1]	7	147.86 [116.5, 179.3]	0.36
Prone+side [vs supine]	18	149.00 [131.6, 166.4]	7	147.86 [116.5, 179.3]	0.94
Face down	9	156.11 [121.6, 190.6]	16	145.94 [130.1, 161.7]	0.50
Bed-sharing	8	134.88 [111.9, 157.8]	26	154.92 [140.6, 169.3]	0.15
Adult bed [vs crib]	12	136.08 [120.6, 151.6]	12	153.58 [127.9, 179.2]	0.21
Illness within last week	15	165.67 [143.3, 188.0]	19	138.00 [126.6, 149.4]	<b>0.03</b>
Illness within last 48 hours	12	165.42 [139.6, 191.2]	21	138.14 [127.8, 148.4]	<b>0.05</b>

D. 5-HT<sub>1A</sub> Receptor Binding in the Raphé Obscurus

Risk Factor	Yes		No		t-test p-value
	N	Mean [95% CI]	N	Mean [95% CI]	
Male	16	45.34 [32.63, 58.04]	17	33.95 [25.30, 42.59]	0.12
Black [vs White/Hispanic/Asian]	5	33.55 [9.44, 57.66]	22	41.72 [32.52, 50.93]	0.43
Premature	10	36.69 [24.50, 48.88]	23	40.68 [30.84, 50.52]	0.62
Position in which found at death					
Prone [vs supine]	14	44.18 [33.84, 54.51]	7	26.76 [15.64, 37.88]	<b>0.03</b>
Side [vs supine]	3	62.00 [55.36, 68.63]	7	26.76 [15.64, 37.88]	<b>0.001</b>
Car Seat [vs supine]	2	21.66 [15.94, 27.38]	7	26.76 [15.64, 37.88]	0.59
Prone+side [vs supine]	17	47.32 [38.23, 56.38]	7	26.76 [15.64, 37.88]	<b>0.01</b>
Face down	10	47.03 [33.21, 60.84]	15	34.97 [25.91, 44.03]	0.11
Bed-sharing	7	51.94 [27.21, 76.67]	26	36.11 [28.69, 43.53]	0.08
Adult bed [vs crib]	12	49.06 [34.20, 63.92]	12	32.76 [21.38, 44.14]	<b>0.07*</b>
Illness within last week	14	32.12 [22.67, 41.57]	19	44.88 [33.92, 55.85]	0.08
Illness within last 48 hours	12	31.60 [22.76, 40.44]	20	45.69 [35.19, 56.19]	0.06

\*p=0.04 on adjusting for postconceptional age.