Supplemental Tables

Table S1. Mediation analysis of microglial M1/M2 phenotype, pro-inflammatory/anti-inflammatory cytokines and the proteins of the BDNF signaling system on the association of Clostridia with spatial learning and memory ability

Mediator	Outcome	Total effect	ACME	Mediation proportion
M1 microglia and pro-inflammatory cytokines				
M1	EL	91.2% (52.6%, 122.0%)	47.5% (-4.1%, 117.0%)	47.2%
IL-1 β	EL	86.8% (50.2%, 117.0%)	88.1% (-8.1%, 156.0%)	112.4%
IL-6	EL	86.7% (47.0%, 123.0%)	43.9% (9.4%, 106.0%)	47.9%
M1	NPC	-87.2% (-118.8%, -61.0%)	-23.3% (-73.8%, 33.0%)	22.6%
IL-1 β	NPC	-94.2% (-132.7%, -63.0%)	-52.4% (-132.2%,19.0%)	51.8%
IL-6	NPC	-88.9% (-127.6%, -46.0%)	-13.5% (-62.5%, 21.0%)	12.8%
M1	TSTQ	-90.9% (-133.2%, -59.0%)	-45.6% (-101.7%, 1.0%)	48.5%
IL-1 β	TSTQ	-89.8% (-121.9%, -63.0%)	-79.1% (-140.6%, -9.0%)	85.9%
IL-6	TSTQ	-89.4% (-125.9%, -55.0%)	-24.7% (-64.9%, 16.0%)	30.2%
M2 microglia, anti-inflammatory cytokines, and the proteins of the BDNF signaling system				
M2	EL	86.8% (49.2%, 121.0%)	42.9% (-0.4%, 86.0%)	49.2%
IL-4	EL	91.0% (44.3%, 119.0%)	12.5% (-25.0%, 69.0%)	11.0%
IL-10	EL	87.9% (49.7%, 116.0%)	-11.6% (-68.3%, 38.0%)	-6.8%
TGF- β	EL	88.8% (60.3%, 124.0%)	38.2% (-2.1%, 83.0%)	44.6%
mBDNF	EL	87.0% (57.8%, 118.0%)	16.4% (-43.1%, 66.0%)	19.8%
TrkB	EL	91.0% (59.7%, 135.0%)	37.0% (3.3%, 90.0%)	41.7%
proBDNF	EL	88.1% (57.2%, 117.0%)	45.6% (17.0%, 86.0%)	54.7%
$p75^{NTR}$	EL	90.2% (55.3%, 121.0%)	17.6% (-27.7%, 74.0%)	15.9%
t-PA	EL	86.4% (57.0%, 114.0%)	60.2% (13.1%, 127.0%)	70.3%
M2	NPC	-84.2% (-119.3%, -60.0%)	-42.3% (-75.2%, -9.0%)	47.3%
IL-4	NPC	-91.3% (-121.2%, -55.0%)	-3.6% (-38.5%, 34.0%)	1.9%
IL-10	NPC	-88.8% (-125.0%, -62.0%)	15.7% (-23.3%, 56.0%)	-20.6%

TGF-β	NPC	-88.0% (-114.8%, -57.0%)	-42.5% (-108.8%, 1.0%)	45.2%
mBDNF	NPC	-87.4% (-110.8%, -53.0%)	-8.2% (-69.6%, 42.0%)	12.8%
TrkB	NPC	-89.8% (-114.5%, -60.0%)	-14.4% (-55.0%, 42.0%)	17.8%
proBDNF	NPC	-87.4% (-136.2%, -50.0%)	-51.1% (-95.5%, -19.0%)	54.9%
$p75^{NTR}$	NPC	-91.2% (-121.8%, -60.0%)	-21.3% (-79.7%, 21.0%)	18.5%
t-PA	NPC	-88.2% (-118.1%, -58.0%)	-12.8% (-87.1%, 60.0%)	20.4%
M2	TSTQ	-94.5% (-125.1%, -60.0%)	-62.1% (-99.9%, -26.0%)	62.7%
IL-4	TSTQ	-88.7% (-119.7%, -52.0%)	-13.8% (-56.8%, 24.0%)	13.4%
IL-10	TSTQ	-92.7% (-132.7%, -62.0%)	1.9% (-45.2%, 68.0%)	1.3%
TGF-β	TSTQ	-95.9% (-133.9%, -65.0%)	-45.0% (-97.4%, 7.0%)	47.9%
mBDNF	TSTQ	-88.2% (-128.1%, -54.0%)	-16.2% (-87.2%, 30.0%)	14.9%
TrkB	TSTQ	-89.5% (-126.0%, -60.0%)	-33.1% (-78.1%, 15.0%)	39.3%
proBDNF	TSTQ	-92.6% (-134.1%, -55.0%)	-47.0% (-101.8%, -13.0%)	50.9%
$p75^{NTR}$	TSTQ	-87.8% (-128.0%, -50.0%)	-16.3% (-67.5%, 29.0%)	15.5%
t-PA	TSTQ	-87.8% (-116.3%, -57.0%)	-38.6% (-98.4%, 43.0%)	50.8%

Note: Data are shown as percent changes and 95% confidence intervals. EL: escape latency; NPC: number of platform crossings; TSTQ: time spent in the target quadrant (% of total time). EL is the indicator of spatial learning ability. NPC and TSTQ are indicators of spatial memory ability.

Table S2. Mediation analysis of microglial M1/M2 phenotype, pro-inflammatory/anti-inflammatory cytokines and the proteins of the BDNF signaling system on the association of *muribaculaceae* with spatial learning and memory ability

Mediator	Outcome	Total effect	ACME	Mediation proportion
M1 microglia and pro-inflammatory cytokines				
M1	EL	-78.6% (-123.2%, -32.0%)	-42.6% (-82.1%, -11.0%)	53.4%
IL-1 β	EL	-83.5% (-132.7%, -47.0%)	-57.5% (-109.7%, -22.0%)	69.0%
IL-6	EL	-85.7% (-136.1%, -49.0%)	-59.4% (-117.4%, -21.0%)	69.2%
TNF- α	EL	-79.3% (-136.9%, -41.0%)	-36.5% (-95.3%, -1.0%)	44.7%
M1	NPC	77.5% (20.4%, 126.0%)	42.3% (2.5%, 78.0%)	55.7%
IL-1 β	NPC	73.1% (31.8%, 143.0%)	62.5% (16.4%, 147.0%)	87.3%
IL-6	NPC	76.3% (38.6%, 112.0%)	50.1% (-18.6%, 117.0%)	62.5%
TNF- α	NPC	71.2% (19.9%, 125.0%)	50.0% (10.3%, 129.0%)	69.0%
M1	TSTQ	73.1% (25.1%, 113.0%)	39.9% (5.7%, 92.0%)	54.6%
IL-1 β	TSTQ	71.6% (24.0%, 113.0%)	59.6% (8.8%, 115.0%)	82.7%
IL-6	TSTQ	76.1% (38.9%, 121.0%)	41.9% (0.3%, 100.0%)	60.2%
TNF- α	TSTQ	72.4% (19.0%, 114.0%)	33.4% (-3.2%, 84.0%)	43.2%
M2 microglia, anti-inflammatory cytokines, and the proteins of the BDNF signaling system				
M2	EL	-82.6% (-116.6%, -42.0%)	-43.2% (-84.4%, -11.0%)	50.4%
IL-4	EL	-81.5% (-121.0%, -39.0%)	-28.1% (-70.5%, 2.0%)	33.6%
TGF- β	EL	-79.8% (-122.9%, -43.0%)	-48.9% (-99.0%, -13.0%)	61.2%
mBDNF	EL	-81.0% (-115.9%, -33.0%)	-32.1% (-72.1%, 1.0%)	38.4%
TrkB	EL	-83.7% (-130.2%, -42.0%)	-73.9% (-136.9%, -21.0%)	84.4%
proBDNF	EL	-81.2% (-123.5%, -36.0%)	-79.6% (-165.1%, -28.0%)	99.0%
$p75^{NTR}$	EL	-84.8% (-123.7%, -47.0%)	-22.3% (-61.5%, 19.0%)	23.7%
t-PA	EL	-81.5% (-124.7%, -40.0%)	-43.8% (-81.8%, -9.0%)	53.0%
M2	NPC	66.7% (25.8%, 101.0%)	44.9% (13.4%, 96.0%)	62.8%
IL-4	NPC	75.4% (21.5%, 128.0%)	22.1% (-27.7%, 85.0%)	29.5%

TGF-β	NPC	71.4% (30.9%, 114.0%)	52.8% (10.3%, 119.0%)	69.9%
mBDNF	NPC	81.1% (26.6%, 141.0%)	35.7% (0.2%, 91.0%)	46.1%
TrkB	NPC	73.9% (29.0%, 128.0%)	53.7% (-39.9%, 159.0%)	64.3%
proBDNF	NPC	72.1% (21.6%, 125.0%)	101.8% (57.9%, 192.0%)	144.4%
$p75^{NTR}$	NPC	77.0% (26.8%, 134.0%)	23.5% (-25.0%, 86.0%)	32.9%
t-PA	NPC	74.6% (31.5%, 124.0%)	42.9% (4.8%, 97.0%)	51.7%
M2	TSTQ	79.1% (41.3%, 121.0%)	53.4% (12.2%, 99.0%)	62.6%
IL-4	TSTQ	71.4% (14.6%, 125.0%)	26.3% (-15.9%, 76.0%)	40.2%
TGF-β	TSTQ	81.1% (47.5%, 136.0%)	60.4% (16.0%, 116.0%)	75.5%
mBDNF	TSTQ	71.9% (32.8%, 135.0%)	27.9% (2.8%, 77.0%)	38.7%
TrkB	TSTQ	75.3% (36.6%, 117.0%)	66.5% (-8.9%, 150.0%)	97.7%
proBDNF	TSTQ	83.4% (36.1%, 125.0%)	93.5% (32.1%, 152.0%)	107.4%
$p75^{NTR}$	TSTQ	81.6% (32.6%, 122.0%)	26.2% (-11.0%, 60.0%)	32.2%
t-PA	TSTQ	71.9% (24.5%, 112.0%)	37.8% (3.8%, 71.0%)	48.3%

Note: Data are shown as percent changes and 95% confidence intervals. EL: escape latency; NPC: number of platform crossings; TSTQ: time spent in the target quadrant (% of total time). EL is the indicator of spatial learning ability. NPC and TSTQ are indicators of spatial memory ability.

Table S3. Mediation analysis of microglial M1/M2 phenotype, pro-inflammatory/anti-inflammatory cytokines and the proteins of the BDNF signaling system on the association of *bacteroides* with spatial learning and memory ability

Mediator	Outcome	Total effect	ACME	Mediation proportion
M1 microglia and pro-inflammatory cytokines				
M1	EL	93.0% (63.9%, 128.0%)	74.4% (-40.4%, 186.0%)	82.3%
IL-1 β	EL	88.9% (61.5%, 132.0%)	50.8% (19.9%, 103.0%)	54.8%
IL-6	EL	93.8% (56.7%, 127.0%)	49.5% (7.6%, 96.0%)	50.4%
M1	NPC	-86.9% (-133.5%, -49.0%)	-62.4% (-185.5%, 99.0%)	73.4%
IL-1 β	NPC	-89.5% (-126.1%, -62.0%)	-60.8% (-125.5%, -18.0%)	65.8%
IL-6	NPC	-84.8% (-119.6%, -38.0%)	-27.1% (-90.1%, 45.0%)	31.0%
M1	TSTQ	-88.1% (-130.0%, -50.0%)	-55.2% (-172.9%, 50.0%)	80.2%
IL-1 β	TSTQ	-85.8% (-115.4%, -45.0%)	-51.3% (-84.8%, -22.0%)	58.9%
IL-6	TSTQ	-84.3% (-126.8%, -48.0%)	-24.7% (-74.2%, 48.0%)	26.3%
M2 microglia, anti-inflammatory cytokines, and the proteins of the BDNF signaling system				
M2	EL	92.0% (66.4%, 127.0%)	46.8% (1.0%, 98.0%)	51.7%
IL-4	EL	87.4% (45.3%, 127.0%)	14.7% (-17.2%, 46.0%)	17.2%
TGF- β	EL	92.0% (52.5%, 120.0%)	41.0% (7.3%, 103.0%)	39.1%
mBDNF	EL	96.2% (53.8%, 131.0%)	10.5% (-53.6%, 71.0%)	16.9%
TrkB	EL	89.3% (60.7%, 128.0%)	34.4% (8.5%, 75.0%)	34.1%
proBDNF	EL	92.7% (58.4%, 120.0%)	46.1% (18.9%, 85.0%)	49.4%
$p75^{NTR}$	EL	88.5% (58.5%, 134.0%)	22.2% (-10.0%, 78.0%)	24.5%
t-PA	EL	90.6% (53.0%, 125.0%)	66.8% (-12.4%, 147.0%)	80.9%
M2	NPC	-87.8% (-124.9%, -53.0%)	-73.4% (-155.8%, -3.0%)	86.8%
IL-4	NPC	-82.0% (-115.6%, -35.0%)	-17.0% (-69.6%, 33.0%)	21.4%
TGF- β	NPC	-83.8% (-116.7%, -42.0%)	-52.2% (-97.5%, -13.0%)	62.7%
mBDNF	NPC	-86.9% (-125.4%, -49.0%)	-17.7% (-107.9%, 71.0%)	17.3%
TrkB	NPC	-82.8% (-122.6%, -50.0%)	-28.1% (-90.0%, 35.0%)	32.0%

proBDNF	NPC	-88.2% (-118.5%, -46.0%)	-50.6% (-85.5%, -18.0%)	58.8%
$p75^{NTR}$	NPC	-84.9% (-114.1%, -47.0%)	-36.9% (-105.5%, -2.0%)	40.9%
t-PA	NPC	-81.9% (-123.0%, -47.0%)	-32.0% (-148.4%, 71.0%)	26.6%
M2	TSTQ	-90.3% (-144.2%, -58.0%)	-74.9% (-142.0%, -34.0%)	82.1%
IL-4	TSTQ	-90.7% (-122.8%, -56.0%)	-19.6% (-76.5%, 16.0%)	18.4%
TGF-β	TSTQ	-92.7% (-126.1%, -58.0%)	-43.9% (-86.4%, -14.0%)	43.5%
mBDNF	TSTQ	-91.0% (-130.8%, -59.0%)	-9.5% (-66.5%, 59.0%)	9.9%
TrkB	TSTQ	-86.8% (-123.3%, -49.0%)	-35.9% (-82.3%, -6.0%)	43.2%
proBDNF	TSTQ	-86.7% (-125.7%, -47.0%)	-44.2% (-75.5%, -12.0%)	49.9%
$p75^{NTR}$	TSTQ	-87.2% (-122.2%, -59.0%)	-19.8% (-61.5%, 9.0%)	22.3%
t-PA	TSTQ	-89.4% (-122.5%, -52.0%)	-39.9% (-130.9%, 63.0%)	51.6%

Note: Data are shown as percent changes and 95% confidence intervals. EL: escape latency; NPC: number of platform crossings; TSTQ: time spent in the target quadrant (% of total time). EL is the indicator of spatial learning ability. NPC and TSTQ are indicators of spatial memory ability.

Table S4. Mediation analysis of microglial M1/M2 phenotype, pro-inflammatory/anti-inflammatory cytokines and the proteins of the BDNF signaling system on the association of *lactobacillus* with spatial learning and memory ability

Mediator	Outcome	Total effect	ACME	Mediation proportion
M1 microglia and pro-inflammatory cytokines				
M1	EL	88.9% (51.8%, 115.0%)	62.9% (3.4%, 147.0%)	69.2%
IL-1 β	EL	91.5% (66.1%, 125.0%)	67.2% (14.8%, 112.0%)	71.4%
IL-6	EL	90.2% (54.5%, 128.0%)	49.4% (-30.7%, 146.0%)	53.6%
M1	NPC	-79.7% (-126.1%, -34.0%)	-90.2% (-215.5%, 17.0%)	116.7%
IL-1 β	NPC	-80.9% (-122.4%, -45.0%)	-86.8% (-173.7%, -26.0%)	107.6%
IL-6	NPC	-78.3% (-116.8%, -22.0%)	-35.6% (-146.7%, 108.0%)	59.9%
M1	TSTQ	-87.9% (-137.5%, -47.0%)	-77.8% (-160.4%, 11.0%)	90.2%
IL-1 β	TSTQ	-86.2% (-124.8%, -49.0%)	-83.6% (-152.4%, -22.0%)	98.8%
IL-6	TSTQ	-83.0% (-118.9%, -37.0%)	-5.4% (-96.3%, 86.0%)	10.8%
M2 microglia, anti-inflammatory cytokines, and the proteins of the BDNF signaling system				
M2	EL	88.6% (53.6%, 120.0%)	43.9% (9.7%, 81.0%)	48.4%
IL-4	EL	92.1% (65.6%, 128.0%)	16.4% (-28.2%, 65.0%)	14.6%
TGF- β	EL	94.1% (58.3%, 134.0%)	44.7% (2.5%, 96.0%)	49.2%
mBDNF	EL	85.4% (58.8%, 107.0%)	23.1% (-20.6%, 78.0%)	29.4%
TrkB	EL	88.8% (51.1%, 129.0%)	36.8% (-9.0%, 98.0%)	38.9%
proBDNF	EL	88.4% (49.0%, 120.0%)	49.9% (20.8%, 87.0%)	55.9%
$p75^{NTR}$	EL	93.5% (60.9%, 126.0%)	25.5% (-31.2%, 73.0%)	28.4%
t-PA	EL	93.1% (57.3%, 129.0%)	60.6% (-5.9%, 144.0%)	66.0%
M2	NPC	-77.9% (-115.3%, -30.0%)	-58.6% (-94.9%, -8.0%)	75.7%
IL-4	NPC	-77.8% (-119.5%, -31.0%)	-25.2% (-88.0%, 16.0%)	26.4%
TGF- β	NPC	-78.8% (-125.3%, -36.0%)	-69.1% (-153.4%, -14.0%)	90.8%
mBDNF	NPC	-75.4% (-126.2%, -30.0%)	-38.3% (-131.0%, 17.0%)	44.6%
TrkB	NPC	-79.9% (-127.4%, -22.0%)	-35.5% (-112.5%, 25.0%)	37.3%

proBDNF	NPC	-75.9% (-118.1%, -34.0%)	-59.6% (-115.0%, -15.0%)	80.2%
$p75^{NTR}$	NPC	-83.4% (-122.2%, -43.0%)	-40.9% (-96.3%, 21.0%)	51.5%
t-PA	NPC	-73.1% (-120.2%, -22.0%)	-49.1% (-150.0%, 27.0%)	54.7%
M2	TSTQ	-89.8% (-131.5%, -39.0%)	-70.2% (-124.5%, -23.0%)	78.9%
IL-4	TSTQ	-87.1% (-130.7%, -42.0%)	-17.4% (-68.7%, 42.0%)	21.1%
TGF- β	TSTQ	-88.8% (-130.5%, -54.0%)	-55.4% (-103.1%, 1.0%)	62.6%
mBDNF	TSTQ	-83.3% (-130.2%, -35.0%)	-27.4% (-101.9%, 36.0%)	27.1%
TrkB	TSTQ	-88.0% (-140.0%, -43.0%)	-48.6% (-111.5%, -3.0%)	58.9%
proBDNF	TSTQ	-82.7% (-121.5%, -46.0%)	-52.4% (-89.8%, -18.0%)	65.5%
$p75^{NTR}$	TSTQ	-81.6% (-126.6%, -43.0%)	-32.0% (-91.5%, 18.0%)	37.7%
t-PA	TSTQ	-88.3% (-134.1%, -52.0%)	-58.4% (-158.9%, 15.0%)	58.7%

Note: Data are shown as percent changes and 95% confidence intervals. EL: escape latency; NPC: number of platform crossings; TSTQ: time spent in the target quadrant (% of total time). EL is the indicator of spatial learning ability. NPC and TSTQ are indicators of spatial memory ability.