Supplementary Material

Supplementary methods

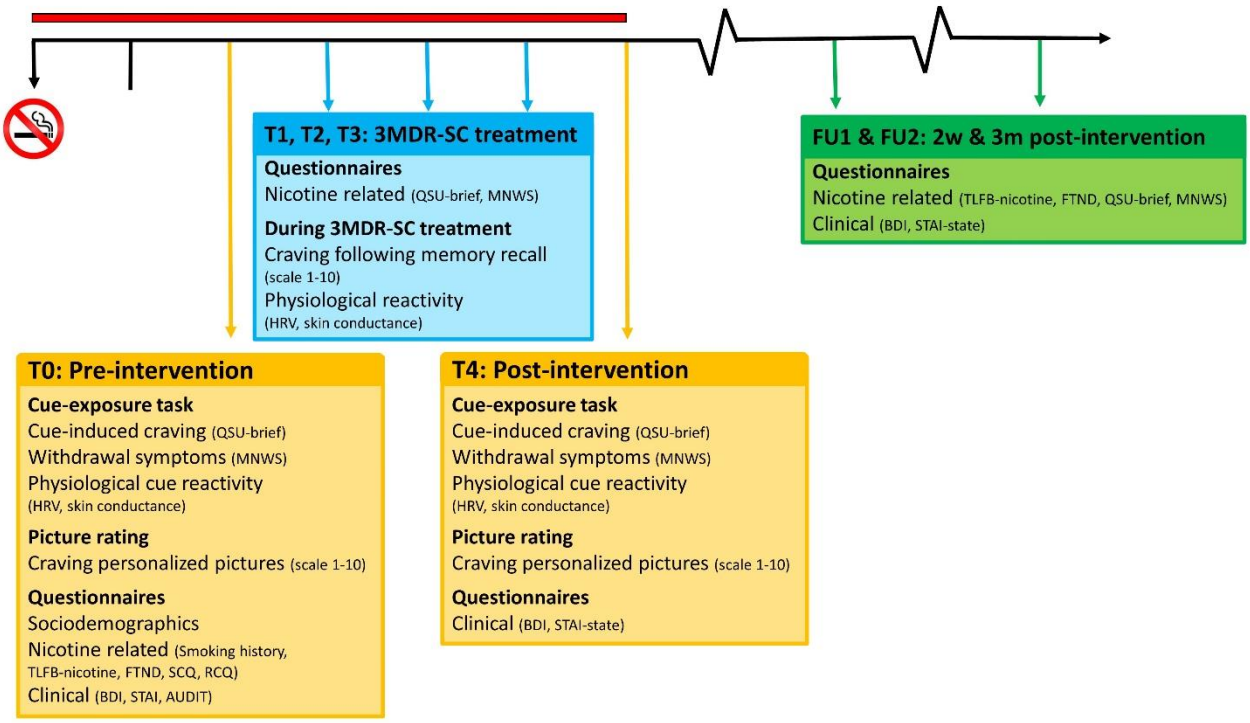

Figure S1. Overview of study procedures. Shown are the general study procedures pre-intervention at T0, during the three-day treatment at T1, T2 and T3, post-intervention at T4 and at 2-week (2w) and 3-month (3m) follow-up (FU1 and FU2). Forty-eight hours before the start of T0, participants were asked to stop smoking and to remain abstinent until T4.

3MDR-SC = smoking cessation motion-assisted memory desensitization and reprocessing, AUDIT = Alcohol Use Disorders Identification Test, BDI = Beck Depression Inventory, FTND = Fagerström Test for Nicotine Dependence, HRV = heart rate variability, MNWS = Minnesota Nicotine Withdrawal Scale, QSU-brief = brief Questionnaire on Smoking Urges, RCQ = Readiness to Change Questionnaire, SCQ = Smoking Consequence Questionnaire, STAI = State-Trait Anxiety Inventory, TLFB = Timeline Follow-Back method over last 14 days.

Smoking cue-exposure task blocks

The smoking cue-exposure paradigm was modified from a protocol by Kaag *et al.* (2018) and Germeroth *et al.* (2017) and programmed in E-prime (version 2). The 8 items from the Minnesota Nicotine Withdrawal (MNWS) followed the QSU-brief, to measure last 24-hour nicotine withdrawal symptoms (Hughes, 1992). First, an audio with guided relaxation was played for 75 seconds. The task then continued with two blocks of visual nicotine cues, with a 5-minute duration in total. Participants were instructed to look carefully at the images by trying to imagine themselves in the situations. In the first block, five video clips of 30 seconds were shown, depicting situations involving people smoking (adapted from Germeroth *et al.*, 2017). The second block consisted of a random presentation of 20 smoking-related pictures (adapted from Gorey *et al.*, 2023), 7.5 seconds each. Different pictures and video clips were shown to each participant per session. The task was followed by the handling of smoking paraphernalia, that was guided through four instructions shown on the computer screen for

30 seconds each (table 1). The lighter and package of cigarettes used during the handling block were taken from a closed white box on the table in front of the participant and were adjusted to the favorite brand of each participant.

Table S1. Instructions of handling smoking paraphernalia in the smoking cue-exposure task.

	Instruction
1	Open the box in front of you, put the lighter on the table in front of you and take the pack of cigarettes in your hands.
2	Take a cigarette out of the package and hold it between your fingers as you normally would when you start smoking.
3	Bring the cigarette to your face and give it a good sniff a few times.
4	Take the lighter and turn it on as you normally would if you were smoking, without actually lighting the cigarette.

HRV and skin conductance measurement details

HRV and *skin conductance* were measured by recording the participants electrocardiogram (ECG) and electrodermal activity (EDA) respectively, using the VU-AMS hardware and VU-DAMS software (version 5.4.13). During the 3MDR-SC intervention, the VU-AMS was attached to a belt worn by the participants to be able to record the EDA and ECG, and a VU-AMS remote device was used to manually place markers in the data at the moment current cigarette craving was assessed. After connecting the VU-AMS to an ECG V- lead electrode placed at the suprasternal notch, ECG V+ lead electrode between the bottom left third and fourth rib and ECG ground electrode between the right lower two ribs, ECG was acquired with a sampling frequency of 1000 Hz and -20 to 20 mV signal range. The EDA signal was measured on a 10 Hz sample frequency and 0-95 µS signal range utilizing a 16 bit A/D converter connected to an EDA electrode placed at the thenar eminence and an ECG electrode placed on the wrist bone. Disposable 55 mm diameter round ECG electrodes with an Ag/AgCl sensor and solid hydrogel (Kendall H98SG) and EDA electrodes of 27x36 mm with an Ag/AgCl sensor (Biopac EL507) were used. HRV was a derived parameter from the ECG signal and skin conductance from the EDA signal.

HRV and skin conductance processing

Physiological data recorded during the smoking cue-exposure task was processed using VU-DAMS software (version 5.4.13). R-peaks and suspicious inter-beat intervals in the raw ECG signal were automatically detected and marked by the software, as well as artefacts due to clipping or signal loss in the raw ECG and EDA signal. All data was visually inspected and manually corrected; artefacts and noisy data were removed, and R-peaks and beats were added, removed or adjusted if they were omitted or misplaced.

Thereafter, the data recorded during the smoking cue-exposure task was labeled by a relaxation, video presentation, picture presentation and handling phase, based on the corresponding blocks of the cue-exposure task. Each label was manually added between the two markers that were automatically placed by E-prime during data acquisition at the start and end of each task block.

The ECG and EDA data recorded during 3MDR-SC was manually labeled by a baseline, recall and task treatment phase for the three cues (cigarette, first and second picture). The baseline label was

placed during the 30 seconds in prior to the baseline memory recall marker. The recall labels were placed 20 seconds before and 10 seconds following memory recall of smoking cues before the task marker, a time window wherein the addiction memory was recalled. The task labels were placed 90 seconds prior to the memory recall after the distractor marker for a duration of 40 seconds, a time window wherein the distractor or non-distracting task was performed.

Per label, the RMSSD in ms, a time-based measure of HRV, and the mean SCL in µS, a tonic measure of EDA, was calculated by the VU-DAMS. Data of less than 10s per label was considered missing.

Additional questionnaires

At T0

Sociodemographic information, including age, sex assigned at birth (female or male), gender-identity (woman, man or none of both), country of origin, education (eight categories ranging from primary education to scientific education), work situation (5 categories, e.g. paid employment or unemployed), income (13 categories ranging from less than 500 to more than 10,000 euro/month gross) family situation (6 categories, e.g. married or single) and number of children (living at home) were assessed, as well as smoking history (e.g. onset age of regular smoking and number of quit attempts). The Smoking Consequence Questionnaire (SCQ) was used to assess smoking outcome expectancies (Myers *et al.*, 2003), and the valence of expectancies was provided for each scale of the SCQ, being negative consequences, positive reinforcement, negative reinforcement and appetite/weight control. To determine the stage of readiness to change, scores on the precontemplation, contemplation and action scales of the Readiness to Change Questionnaire (RCQ) were used (Rollnick *et al.*, 1992). Last 7-day depression symptoms were measured with the Beck Depression Inventory (BDI; Beck *et al.*, 1961), state and trait anxiety with the State-Trait Anxiety Inventory (STAI; Spielberger *et al.*, 1983) and alcohol use severity with the AUDIT.

At T1, T2 and T3

After the smokerlyzer breath test and before start of the 3MDR-SC treatment at T1, T2 and T3, the QSU-brief and MNWS were filled out with pen and paper by the participants to measure state-dependent craving and last 24-hour nicotine withdrawal symptom changes.

At T4

At the end of the last session, participants received online questionnaires that were filled out outside of the study location. These questionnaires included the BDI to measure last 7-day depression symptoms and the STAI-state to measure state-dependent anxiety.

At FU1 and FU2

State-dependent craving, last 7-day nicotine withdrawal symptoms, last 7-day depression symptoms and state anxiety were assessed using the QSU-brief, MNWS, BDI and STAI-state respectively.

At study completion

After the FU2 assessments of the last participant, all participants received an online survey asking if they had an idea what treatment they had received to assess treatment group awareness. The possible answers options were *1)* yes, the treatment that is expected to be most effective (interpret as active 3MDR-SC), *2)* yes, the treatment that may be less effective (interpret as control 3MDR-SC), or *3)* no, I do not know.

3MDR-SC treatment details

During the treatment, participants walked on the treadmill at a self-chosen and comfortable pace. A virtual landscape was projected on three 4x2.5 m screens surrounding the participant, creating a 180° panorama view, and passed by at the same speed as the treadmill. In this virtual landscape, participants walked through a tunnel with a visual stimulus at the end of it that enlarged to its maximum size when walking towards it. During the first cue exposure, this visual stimulus consisted of a grey plane as an in vivo cigarette instead of a visual stimulus was used to activate smoking memory. Specifically, participants were briefly taken off the treadmill and asked to light and take two puffs of the cigarette and to exhale the smoke in a fume hood. Thereafter, when the original walking speed on the treadmill was reached again, the participants were asked to recall the cigarette from a moment ago. A distractor or non-distractor task of 90 seconds then started while participants were asked to keep recalling the cigarette. After this task, participants walked out of the virtual tunnel and were asked to recall the cigarette from a moment ago again. This cue-exposure and distractor sequence was then repeated twice, but then the self-chosen pictures were used instead of the smoked cigarette to activate smoking memory. Participants were asked to explain why this picture was associated with their smoking behavior while walking through the tunnel towards the pictures, and were asked to recall the memory from the picture when the picture reached its maximum size.

The distractor task consisted of a red ball oscillating in a horizontal plane at 1Hz on the screen in the middle over the visual stimulus (grey plane or picture) and contained random changing numbers. Participants were instructed to follow the ball with their eyes while keeping their head still and simultaneously calling out the numbers on the ball. This was accompanied by binaural auditory stimulation (beeps) enabled by a surround sound system. The non-distractor task consisted of a stationary red ball that was presented in the middle of the screen over the presented visual stimulus. In this task, participants were instructed to keep their eyes on the ball.

Statistical analyses

Baseline differences between the active and control 3MDR-SC group were determined with t-tests (or non-parametric Mann-Whitney U test) and chi-square tests.

Main and secondary outcome analyses details

A paired sample t-test (or non-parametric Wilcoxon Signed-Ranks test) was performed for QSU-brief total sum score before and after cue exposure at T0 to check whether craving was induced by the nicotine cue-exposure task. The effect of active 3MDR-SC on cue-induced craving directly following treatment was tested with a rmANOVA on total (and reward- and relief-related) cue-induced craving

with session (T0 and T4) as a within-subject variable and group (active and control 3MDR-SC) as a between-subject factor.

A linear mixed model on HRV (in RMSSD) and skin conductance (in mean SCL) was performed with a random intercept and block (relax, video, picture and handling) as fixed effect at T0 to check whether physiological cue reactivity was present during the nicotine cue-exposure task. To investigate the effect of active 3MDR-SC on physiological cue-reactivity directly following treatment, a linear mixed model was performed on HRV and skin conductance with a random intercept and session (T0 and T4), block (relax, video, picture and handling), group and all interactions as fixed effects.

The effect of active 3MDR-SC on nicotine dependence severity and daily cigarette use at follow-up was tested with a rmANOVA on FTND sum scores and daily cigarette use, with time (T0, FU1 and FU2) as a within-subject variable and group as a between-subject factor.

Relapse rates were compared between the active and control 3MDR-SC group at FU1 and FU2 with chi-square tests.

Exploratory analyses details

To investigate the effect of active 3MDR-SC on craving following treatment for personalized pictures that were and were not selected during treatment, a rmANOVA on mean craving ratings (on a scale from 1 to 10) with session (T0 and T4) and picture type (selected and non-selected) as within-subject variables and group as a between-subject factor was performed.

A rmANOVA on craving (on a scale from 1 to 10) with session (T1, T2 and T3) and treatment phase (at baseline, following memory recall before and after the task for three cues) as within-subject variables and group as a between-subject factor was done to see the effect of active 3MDR-SC on craving following memory recall during the three-day treatment.

The effect of active 3MDR-SC on craving and withdrawal symptoms during treatment was investigated with a rmANOVA on QSU-brief and MNWS sum score, with time (T0, T1, T2, T3, T4, FU1 and FU2) as a within-subject variable and group (active and control 3MDR-SC) as a between-subject factor.

A rmANOVA on BDI and STAI-state sum score with time (T0, T4, FU1 and FU2) as a within-subject variable and group as a between-subject factor was performed, to determine whether there was an effect of active 3MDR-SC on depression symptoms and state-dependent anxiety following treatment and follow-up.

To assess the relationship between depression and withdrawal symptoms and between state-dependent anxiety and withdrawal symptoms, a one-tailed Pearson correlation test was performed with either the BDI or STAI-state sum scores and MNWS sum scores assessed at multiple time points (T0, T4, FU1 and FU2) for both groups (active and control 3MDR-SC) combined. A Kendall's tau-b correlation was done in case the assumption of normality and/or homoscedasticity was violated.

A linear mixed model on HRV (RMSSD) and skin conductance (mean SCL) with a random intercept and session (T1, T2 and T3), treatment phase (baseline, during memory recall before task and during task for three cues), group and all interactions as fixed effects was performed to investigate the effect of active 3MDR-SC on physiological cue- and task-reactivity during treatment was investigated.

SPSS (version 28) was used to perform the data-analyses and a $p < 0.05$ was considered significant. A $\eta_{(p)}^2 < 0.06$ was considered a small effect, a $0.06 \leq \eta_{(p)}^2 < 0.14$ was considered a medium effect and $\eta_{(p)}^2 \geq 0.14$ a large effect. A Greenhouse-Geisser or Huynh-Feldt correction was applied in case the

violation of sphericity was violated in all rmANOVAs. Imputation was applied when a single item was missing in a multiple-item questionnaire. Figures were created with GraphPad Prism (version 9.3.1).

Supplementary results

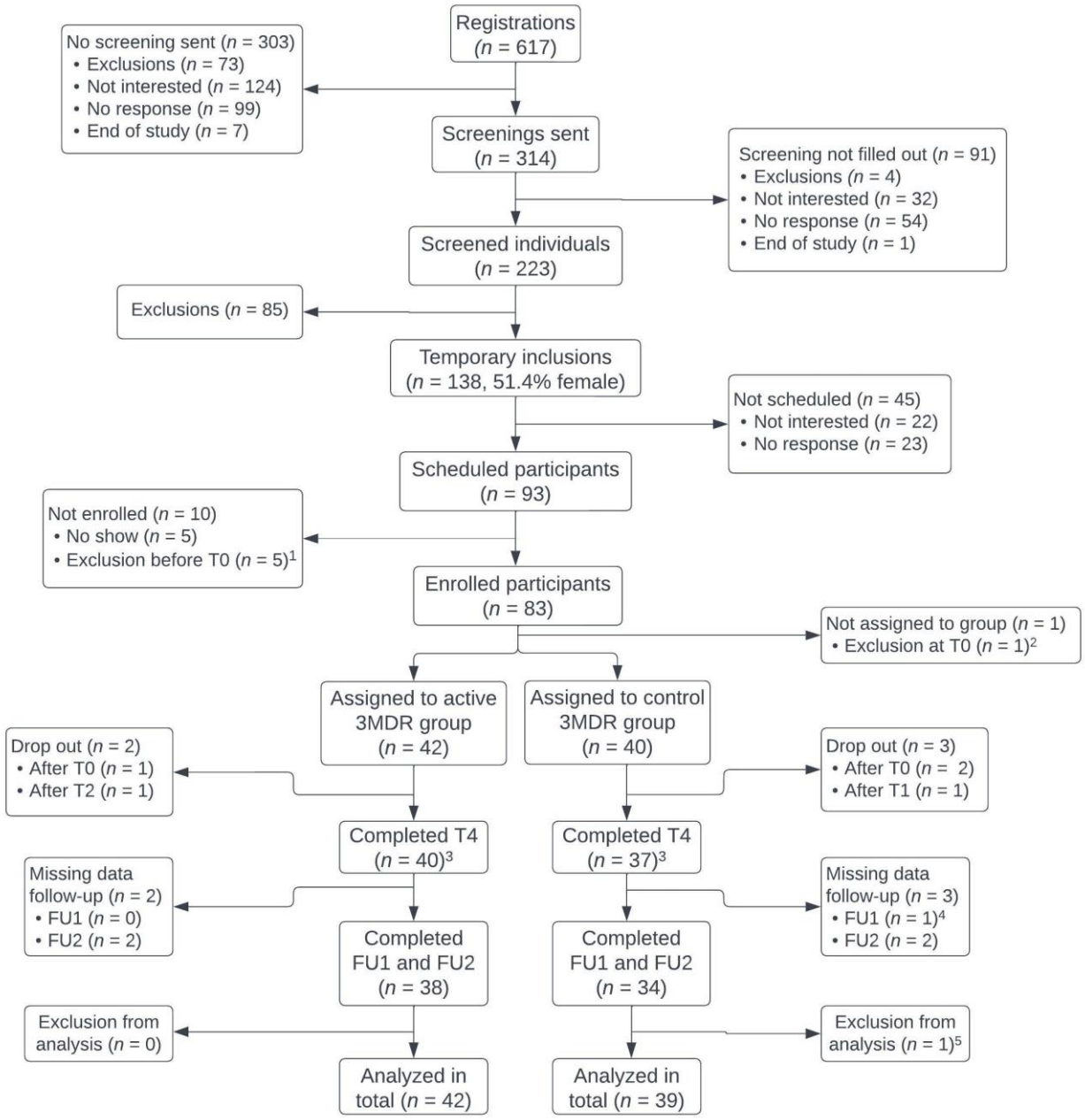

Figure S2. Flow-chart of individuals involved in study. Shown are the number of registered individuals and those that eventually did and did not get screened, included, scheduled, enrolled, randomly assigned, completed the treatment, completed the follow-up phases and got analyzed.

Note: 1) Exclusion before T0 (*n* = 5) was due to not being able to remain abstinent from smoking 48 hours before T0 as self-indicated by the participants. *2)* Exclusion at T0 (*n* = 1) was due to exhaled carbon monoxide levels exceeding 10 parts per million. *3)* Of the T4 completers, a participant from the control group (*n* = 1) did not perform the cue-exposure task at T4 and a participant from the active group (*n* = 1) did not complete the questionnaires at T4 (also not at FU2; therefore considered lost to follow-up). *4)* Participant from control group with missing data at FU1 (*n* = 1) did not have missing data at FU2. *5)* Exclusion from analysis (*n* = 1) was due to current use of psychotropic medication (an exclusion criterion) declared by the participant at T2. Analyses of the main and secondary outcomes revealed the same significant results when this participant was not excluded from the dataset.

Table S2. Baseline sociodemographic, nicotine-related, clinical and study-related characteristics from the active 3MDR-SC and control 3MDR-SC group.

		Active 3MDR-SC (n = 42)	*Control 3MDR-SC (n = 39)*	*Test statistics*
Sociodemographics				
Age		43.5, 14.0[a]	42.0, 13.0[a]	U = 797.500, p = .839
Sex assigned at birth[1]	Male	45.2% (n = 19)	53.8% (n = 21)	χ^2_1 = .599, p = .439
	Female	54.8% (n = 23)	46.2% (n = 18)	
Country of origin	Netherlands	97.6% (n = 41)	87.2% (n = 34)	χ^2_5 = 6.551, p = .256
	Other countries	2.4% (n = 1)	12.8% (n = 5)	
Education	Primary/secondary education	47.6% (n = 20)	41.0% (n = 16)	U = 800.500, p = .855
	Higher education	52.4% (n = 22)	59.0% (n = 23)	
Work situation	Paid employment	59.5% (n = 25)	71.8% (n = 28)	χ^2_5 = 3.868, p = .569
	Other (freelancer, unemployed, volunteer work or in education)	40.5% (n = 17)	28.2% (n = 11)	
Income	≤€3000-4000 per month	54.8% (n = 23)	43.6% (n = 17)	U = 673.0, p = .163
	>€3000-4000 per month	45.2% (n = 19)	56.4% (n = 22)	
Family situation	Married or living together	52.4% (n = 22)	56.4% (n = 22)	χ^2_5 = 6.852, p = .232
	Other (unmarried, divorced, single or widowed)	47.6% (n = 20)	43.6% (n = 17)	
Number of children		1, 2[a]	1, 2[a]	U = 802.500, p = .868
Number of children living at home		1, 1[a]	0, 1[a]	U = 773.500, p = .637
Nicotine related				
Daily current cigarette use		14.7, 6.1[b]	14.4, 5.9[b]	t_{79} = .174, p = .862
Years since regular cigarette use		24.9, 9.0[b]	24.4, 7.2[b]	t_{79} = .246, p = .806
Daily cigarette use at onset		5.0, 5.0[a]	8.0, 5.0[a]	U = 694.000, p = .229
Years since onset cigarette use		27.5, 16.0[a]	27.0, 11.0[a]	U = 791.500, p = .795
Weekly cigarette expenses		36.4, 18.3[b]	38.3, 20.8[b]	t_{79} = -.426, p = .671
Number of quit attempts		4, 3[a]	4, 6[a]	U = 748.500, p = .503
Number of quit attempt >24h		3, 3[a]	3, 4[a]	U = 797.500, p = .837
Days of quit attempt last 10 years[2]		55, 245[a]	90, 215[a]	U = 668.000, p = .210
FTND		5.0, 3.0[a]	5.0, 3.0[a]	U = 761.000, p = .580
SCQ	Negative consequences	35.0, 3.0[a]	36.0, 1.0[a]	U = 645.500, p = .079
	Positive reinforcement	28.0, 11.0[a]	27.0, 17.0[a]	U = 802.500, p = .876
	Negative reinforcement	39.5, 15.0[a]	41.0, 25.0[a]	U = 796.000, p = .828
	Appetite-weight control	21.5, 22.0[a]	25.0, 22.0[a]	U = 741.500, p = .463
RCQ[3]	Action	38.1% (n = 16)	30.8% (n = 12)	χ^2_1 = .480, p = .488
	Contemplation	61.9% (n = 26)	69.2% (n = 27)	

QSU-brief		27.0, 19.0[a]	33.0, 20.0[a]	U = 703.000, p = .273
MNWS		16.3, 6.2[b]	17.1, 5.9[b]	t_{79} = -.591, p = .556
Clinical				
BDI		6.5, 7.0[a]	6.0, 9.0[a]	U = 766.000, p = .615
STAI-trait		41.1, 8.3[b]	42.4, 8.7[b]	t_{79} = -.659, p = .512
STAI-state		43.7, 9.8[b]	42.4, 8.5[b]	t_{79} = .625, p = .534
AUDIT		7.0, 5.0[a]	6.0, 7.0[a]	U = 743.000, p = .471
Study related				
Group awareness[4]	Active 3MDR-SC	11.4% (n = 4)	16.0% (n = 4)	χ^2_2 = 3.093, p = .213
	Control 3MDR-SC	25.7% (n = 9)	8.0% (n = 2)	
	Do not know	62.9% (n = 22)	76.0% (n = 19)	
Missing data FU1		4.8% (n = 2)	10.3% (n = 4)	χ^2_1 = .890, p = .345
Missing data FU2		9.5% (n = 4)	12.8% (n = 5)	χ^2_1 = .223, p = .637
Days late of filling out FU1		0.0, 2.0[a]	0.0, 1.0[a]	U = 687.000, p = .873
Days late of filling out FU2		1.0, 2.0[a]	0.0, 1.0[a]	U = 519.000, p = .117
Days since last cigarette		2.0, 1.0[a]	2.0, 1.0[a]	U = 816.000, p = .975

Shown per group, with number of participants (n), are the [a]mean and standard deviation (SD) of parametric values, the [b]median and interquartile range (IQR) of non-parametric values and percentages of categorical values, as well as the corresponding test statistics of the t-test (t), Mann-Whitney U test (U) or chi-square test (χ^2) assessing group differences for these values.

Note: 1) Although missing data of gender-identity was present for participants in the active (n = 19) and control 3MDR-SC (n = 16) group, all questioned participants had a gender-identity that matched their sex assigned at birth. *2)* Missing data of days of quit attempts last 10 years for a participant in the control 3MDR-SC group (n = 1). *3)* No participants were allocated to the RCQ pre-contemplation stage. *4)* Missing data of group awareness for participants in the active (n = 7) and control 3MDR-SC (n = 14) group.

Table S3. Results of the rmANOVA on the main study outcome: cue-induced craving at T0 and T4.

Source	*SS*	*df*	*MS*	*F*	*p*	η_p^2
Between-subjects effects on total cue-induced craving						
Intercept	1491.669	1	1491.669	41.931	**<.001****	.365
Group	32.069	1	32.069	.901	.346	.012
Error	2596.918	73	35.574			
Within-subjects effects on total cue-induced craving						
Session * group	59.002	1	59.002	1.171	.283	.016
Session	770.469	1	770.469	15.293	**< .001****	.173
Error	3677.771	73	50.380			
Between-subjects effects on reward-related cue-induced craving						
Intercept	527.886	1	527.886	38.254	**<.001****	.344
Group	7.459	1	7.459	.541	.465	.007
Error	1007.361	73	13.799			
Within-subject effects on reward-related cue-induced craving						
Session * group	41.440	1	41.440	2.430	.123	.032
Session	180.107	1	180.107	10.561	**.002***	.126
Error	1244.893	73	17.053			
Between-subjects effects on relief-related cue-induced craving						
Intercept	244.809	1	244.809	30.676	**<.001****	.296
Group	8.595	1	8.595	1.077	.303	.015
Error	582.571	73	7.980			
Between-subject effects on relief-related cue-induced craving						
Session * group	1.547	1	1.547	.125	.724	.002
Session	205.547	1	205.547	16.670	**< .001****	.186
Error	900.093	73	12.330			

Shown is the source, sum of squares (SS), degrees of freedom (df), mean square (MS), F-value (*F*), p-value (*p*), and partial eta squared (η_p^2) of within-subjects effects. *, $p < 0.05$. **, $p < 0.001$.

Table S4. Results of the linear mixed models on the secondary study outcome: HRV and skin conductance cue-reactivity at T0, and at T0 and T4.

Source	df_{num}	df_{den}	*F*	*p*	η^2
Fixed effects on HRV at T0					
Block	3	210.203	40.857	**<.001****	0.368
Intercept	1	68.070	436.549	**<.001****	
Fixed effects on skin conductance at T0					
Block	3	233.057	47.735	**<.001****	0.381
Intercept	1	78.004	140.325	**<.001****	

Comparison	*M difference*	*SE*	*df*	*P*	*95% CI*
Pairwise comparisons on HRV at T0					
R-V	-11.592	1.330	210.317	**<.001****	-14.801, -8.383
R-P	-13.694	1.336	210.477	**<.001****	-16.919, -10.469
R-H	-8.760	1.342	210.552	**<.001****	-11.999, -5.520
Pairwise comparisons on skin conductance at T0					
R-V	.000	.205	233.052	1.000	-.494, .495
R-P	-.311	.205	233.052	.394	-.805, .184
R-H	1.892	.206	233.061	**<.001****	1.395, 2.388

Source	df_{num}	df_{den}	*F*	*p*	η^2
Fixed effects on HRV at T0 and T4					
Session * block * group	3	483.892	.070	.976	< .001
Session * group	1	495.766	.009	.925	< .001
Block * group	3	483.885	.642	.588	.003
Session * block	3	483.892	.301	.824	.002
Group	1	78.700	.015	.903	< .001
Session	1	495.766	9.604	**.002***	.019
Block	3	483.885	38.253	**< .001****	.192
Intercept	1	78.700	387.918	**< .001****	
Fixed effects on skin conductance at T0 and T4					
Session * block * group	3	508.139	.045	.987	< .001
Session * group	1	512.897	.446	.505	< .001
Block * group	3	508.139	.425	.736	.003
Session * block	3	508.139	.176	.913	< .001
Group	1	79.128	1.949	.167	.024
Session	1	512.897	.103	.749	< .001
Block	3	508.139	18.171	**< .001****	.096
Intercept	1	79.128	218.921	**< .001****	

Comparison	*M difference*	*SE*	*df*	*P*	*95% CI*
Pairwise comparisons on HRV at T0 and T4					
T0-T4	3.166	1.022	495.766	**.002***	1.159, 5.173
R-V	11.659	1.368	483.895	**< .001****	8.034, 15.284
R-P	13.314	1.364	483.864	**< .001****	9.701, 16.927
R-H	9.636	1.369	483.915	**< .001****	6.010, 13.262
Pairwise comparisons on skin conductance at T0 and T4					
R-V	-.076	.372	508.132	1.000	-1.060, .909
R-P	.236	.372	508.132	1.000	-.748, 1.220
R-H	-2.177	.372	508.147	**< .001****	-3.162, -1.191

Shown is the source, degrees of freedom of the numerator (df_{num}) and denominator (df_{den}), F-value (*F*), p-value (*p*), and eta squared (η_p^2) of fixed effects, and the mean (M) difference, standard error (SE), degrees of freedom (df), p-value (*p*), and 95% confidence interval (CI) of pairwise comparisons. *, $p < 0.05$. **, $p < 0.001$. *R = relaxation, V = video, P = picture, H = handling.*

Table S5. Results of the rmANOVA on the secondary outcome: FTND sum score and daily cigarette use at T0, FU1 and FU2.

Source	*SS*	*df*	*MS*	*F*	*p*	η_p^2
Between-subject effects on FTND sum score						
Intercept	951.130	1	951.130	298.348	**<.001****	.812
Group	1.903	1	1.903	.597	.442	.009
Error	219.971	69	3.188			
Within-subject effects on FTND sum score						
Time * group	2.949	1.865	1.582	.960	.380	.014
Time	75.099	1.865	40.276	24.450	**< .001****	.262
Error	211.934	128.659	1.647			
Simple within-subject contrasts on FTND sum score						
Time: FU1 vs. T0	121.721	1	121.721	33.366	**< .001****	.326
Error	251.716	69	3.648			
Time: FU2 vs. T0	102.777	1	102.777	50.619	**< .001****	.423
Error	140.096	69	2.030			

Between-subject effects on daily cigarette use						
Intercept	4626.816	1	4626.816	208.699	**<.001****	.752
Group	10.373	1	10.373	.468	.496	.007
Error	1529.714	69	22.170			
Within-subjects effects on daily cigarette use						
Time * group	.785	2	.393	.019	.981	.000
Time	4717.684	2	2358.842	115.397	**< .001****	.626
Error	2820.872	138	20.441			
Simple within-subject contrasts on daily cigarette use						
Time: FU1 vs. T0	9153.820	1	9153.820	207.875	**< .001****	.751
Error	3038.431	69	44.035			
Time: FU2 vs. T0	3889.915	1	3889.915	90.888	**< .001****	.568
Error	2953.127	69	42.799			

Shown is the source, sum of squares (SS), degrees of freedom (df), mean square (MS), F-value (*F*), p-value (*p*), and partial eta squared (η_p^2) of within-subjects effects and contrasts. *, $p < 0.05$. **, $p < 0.001$.

Table S6. Results of the rmANOVA on craving for personalized pictures at T0 and T4.

Source	***SS***	***df***	***MS***	***F***	***p***	η_p^2
Between-subject effects						
Intercept	2082.730	1	2082.730	1282.341	**<.001****	.945
Group	.721	1	.721	.444	.507	.006
Error	120.188	74	1.624			
Within-subject effects						
Session * picture type * group	.036	1	.036	.120	.730	.002
Session * picture type	18.943	1	18.943	63.070	**<.001****	.460
Error	22.226	74	.300	22.226	74	.300
Session * group	5.238	1	5.238	1.269	.264	.017
Error	305.543	74	4.129			
Picture type * group	1.970	1	1.970	2.338	.131	.031
Error	62.343	74	.842			
Within-subject effects per picture type						
Selected: session	516.404	1	516.404	219.436	**<.001****	.745
Error	176.499	75	2.353			
Non-selected: session	274.730	1	274.730	131.623	**<.001****	.637
Error	156.544	75	2.087			
Within-subject effects per session						
T0: Picture type	176.552	1	176.552	266.499	**<.001****	.780
Error	49.686	75	.662			
T4: Picture type	50.947	1	50.947	103.586	**<.001****	.580
Error	36.888	75	.492			

Shown is the source, sum of squares (SS), degrees of freedom (df), mean square (MS), F-value (*F*), p-value (*p*), and partial eta squared (η_p^2) of within-subjects effects. *, $p < 0.05$. **, $p < 0.001$.

Table S7. Results of the rmANOVA on craving following memory recall of cigarette-related cues during at T1, T2 and T3.

Source	*SS*	*df*	*MS*	*F*	*p*	η_p^2
Between-subject effects						
Intercept	1444.900	1	1444.900	451.087	**<.001****	.859
Group	.430	1	.430	.134	.715	.002
Error	237.033	74	3.203			
Within-subject effects						
Session * treatment phase * group	39.164	7.739	5.061	2.163	**.030***	.028
Error	1340.029	572.671	2.340			
Within-subject effects per treatment phase…						
B: session * group	9.640	1.899	5.076	1.904	.155	.025
Error	374.737	140.549	2.666			
C: session * group	12.248	2.000	6.124	1.859	.159	.025
Error	487.447	148.000	487.447			
T(C): session * group	12.913	1.703	7.580	3.398	**.044***	.044
Error	281.228	126.055	2.231			
Repeated within-subject contrasts for T(C) treatment phase						
Session * group: T1-T2	21.783	1	21.783	6.652	**.012***	.082
Error	242.322	74	3.275			
Session * group: T2-T3	.351	1	.351	.134	.715	.002
Error	193.281	74	2.612			
Continuation of within-subject effects per treatment phase						
P1: session * group	1.651	1.870	.883	.253	.762	.003
Error	483.831	138.412	3.496			
T(P1): session * group	5.957	1.825	3.264	1.487	.230	.020
Error	296.420	135.066	2.195			
P2: session * group	3.306	2	1.653	.731	.483	.010
Error	334.826	148	2.262			
T(P2): session * group	8.835	2	4.417	3.164	**.045***	.041
Error	206.654	148	1.396			
Repeated within-subject contrasts for T(P2) treatment phase						
Session * group: T1-T2	10.976	1	10.976	3.969	**.050***	.051
Error	204.656	74	2.766			
Session * group: T2-T3	.341	1	.341	.128	.722	.002
Error	197.148	74	2.664			

Shown is the source, sum of squares (SS), degrees of freedom (df), mean square (MS), F-value (*F*), p-value (*p*), and partial eta squared (η_p^2) of within-subjects effects and contrasts. *, $p <$ (and ≤) 0.05. **, $p < 0.001$. *B = baseline, C = puffed cigarette, T(C) = puffed cigarette after the (non-)distractor task, P1 = first personalized picture, T(P1) = first personalized picture after the (non-)distractor task, P2 = second personalized picture, T(P2) = second personalized picture after the (non-)distractor task.*

Results from exploratory analyses

Craving (QSU-brief) and withdrawal scores

There was no significant interaction between time (T0, T1, T2, T3, T4, FU1 and FU2) * group (active and control) for the QSU-brief sum score and MNWS sum score, but both sum scores showed a significant large main effect of time, independent of group. Polynomial contrasts showed that this main effect of time on the QSU-brief sum score was primarily quadratic and on the MNWS sum score was primarily linear. Moreover, simple contrasts for the QSU-brief and MNWS sum score revealed a

significant reduction from T0 to all other study session and follow-up time points. See figure S3 and table S8 for all statistics.

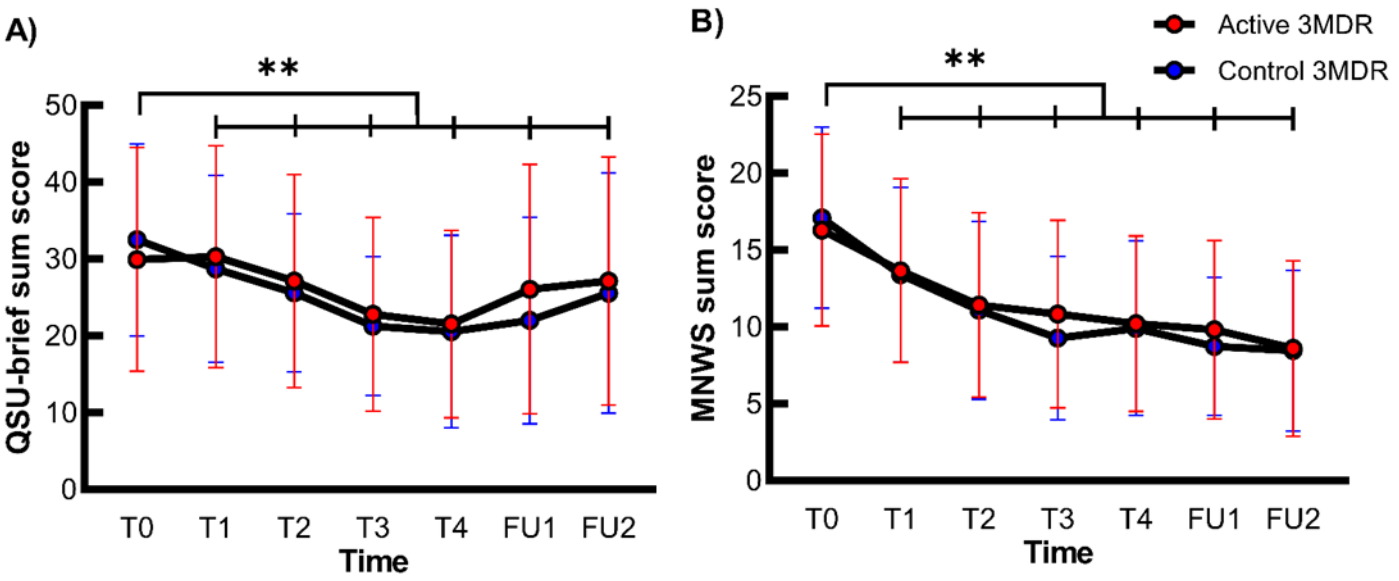

Figure S3. The effect of active 3MDR-SC on craving and withdrawal symptoms during and after treatment at follow-up. Shown is the mean (+/- SD) QSU-brief sum score ***(A)*** and MNWS sum score ***(B)*** at T0 up to T4 and at FU1 and FU2 in the active 3MDR-SC (red) and control 3MDR-SC (blue) group (n = 69 for the QSU-brief and n = 70 for the MNWS sum score). **, main effect of time of $p < .001$.

Note: In addition to missing data mentioned in figure S2 (see third note), missing data was also present for the QSU-brief sum score at T3 for a participant in control group (n = 1).

Table S8. Results of the rmANOVA on QSU-brief and MNWS sum score during T0-T4 and at FU1 and FU2.

Source	*SS*	*df*	*MS*	*F*	*p*	η_p^2
Between-subject effects on QSU-brief sum score						
Intercept	43933.485	1	43933.485	423.229	**<.001****	.863
Group	92.837	1	92.837	.894	.348	.013
Error	6954.963	67	103.805			
Within-subject effects on QSU-brief sum score						
Time * group	273.767	3.431	79.783	.569	.659	.008
Time	6067.324	3.431	1768.176	12.608	**< .001****	.158
Error	32242.850	229.904	140.245			
Polynomial within-subject contrasts on QSU-brief sum score						
Time: linear	2609.867	1	2609.867	12.534	**< .001****	.158
Error	13951.413	67	208.230			
Time: quadratic	2715.427	1	2715.427	28.875	**< .001****	.301
Error	6300.725	67	94.041			
Time: cubic	439.357	1	439.357	6.803	**.011***	.092
Error	4327.358	67	64.587			
Time: order 4	202.061	1	202.061	4.543	**.037***	.064
Error	2979.903	67	44.476			
Time: order 5	100.384	1	100.384	3.376	.071	.048

Error	1992.100	67	29.733			
Simple within-subject contrasts on QSU-brief sum score						
Time: T1 vs. T0	227.691	1	227.691	4.569	**.036***	.064
Error	3339.178	67	49.838			
Time: T2 vs. T0	1664.331	1	1664.331	14.343	**< .001****	.176
Error	7774.278	67	116.034			
Time: T3 vs. T0	5842.515	1	5842.515	52.077	**< .001****	.437
Error	7516.703	67	112.190			
Time: T4 vs. T0	7770.692	1	7770.692	49.222	**< .001****	.424
Error	10577.250	67	157.869			
Time: FU1 vs. T0	3853.488	1	3853.488	18.419	**< .001****	.216
Error	14017.063	67	209.210			
Time: FU2 vs. T0	1848.910	1	1848.910	6.071	**.016***	.083
Error	20404.424	67	304.544			
Between-subject effects on MNWS sum score						
Intercept	8797.069	1	8797.069	485.899	**<.001****	.877
Group	.548	1	.548	.030	.862	.000
Error	1231.123	68	18.105			
Within-subjects effects on MNWS sum score						
Time * group	38.128	3.953	9.646	.420	.792	.006
Time	3649.485	3.953	923.311	40.159	**< .001****	.371
Error	6179.595	268.777	22.992			
Polynomial within-subject contrasts on MNWS sum score						
Time: linear	3165.180	1	3165.180	90.815	**< .001****	.572
Error	2369.995	68	34.853			
Time: quadratic	408.742	1	408.742	23.188	**< .001****	.254
Error	1198.654	68	17.627			
Time: cubic	63.336	1	63.336	5.496	**.022***	.075
Error	783.633	68	11.524			
Time: order 4	2.604	1	2.604	.230	.633	.003
Error	771.029	68	11.339			
Time: order 5	.918	1	.918	.115	.735	.002
Error	542.341	68	7.976			
Simple within-subject contrasts on MNWS sum score						
Time: T1 vs. T0	729.863	1	729.863	33.141	**< .001****	.328
Error	1497.541	68	22.023			
Time: T2 vs. T0	1954.399	1	1954.399	74.864	**< .001****	.524
Error	1775.211	68	26.106			
Time: T3 vs. T0	3285.857	1	3285.857	114.877	**< .001****	.628
Error	1945.030	68	28.603			
Time: T3 vs. T0	3355.825	1	3355.825	102.127	**< .001****	.600
Error	2234.438	68	32.859			
Time: FU1 vs. T0	4081.004	1	4081.004	92.055	**< .001****	.575
Error	3014.606	68	44.332			
Time: FU2 vs. T0	4911.446	1	4911.446	109.783	**< .001****	.618
Error	3042.172	68	44.738			

Shown is the source, sum of squares (SS), degrees of freedom (df), mean square (MS), F-value (*F*), p-value (*p*), and partial eta squared (η_p^2) of within-subjects effects and contrasts. *, $p < 0.05$. **, $p < 0.001$.

Clinical symptoms

There was for BDI and STAI-state sum score no significant time (T0, T4, FU1 and FU2) * group (active and control) interaction effect. A significant large main effect of time was found, with simple contrasts

revealing a significant reduction of BDI and STAI-state sum score from T0 to T4, from T0 to FU1 and from T0 to FU2, independent of treatment group. See figure S4 and table S9 for all statistics.

There was a strong significant positive correlation between BDI and MNWS sum score (r_b = .411, p < .001), independent of time and treatment group. A strong significant positive correlation was also apparent between STAI-state and MNWS sum score (r_b = .481, p < .001).

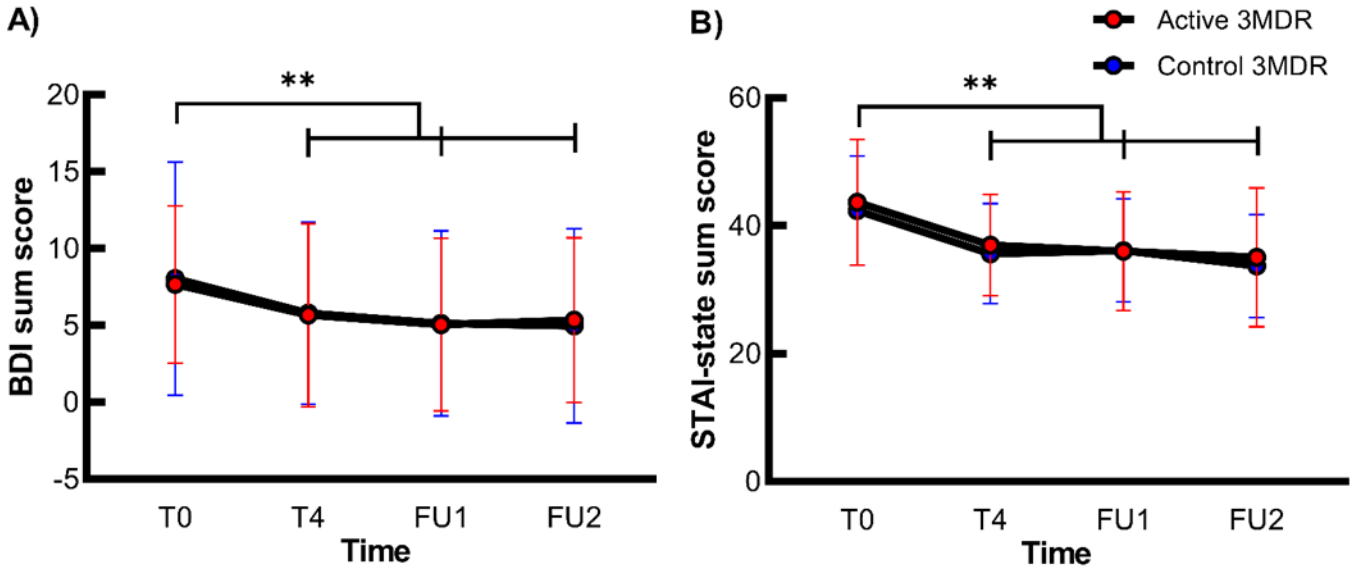

Figure S4. Depression symptoms and state-dependent anxiety before, directly following treatment and at follow-up. Shown is the mean (+/- SD) BDI sum score ***(A)*** and STAI-state sum score ***(B)*** at session T0, T4, FU1 and FU2 in the active 3MDR-SC (red) and control 3MDR-SC (blue) group (n = 71). **, main effect of time of p < .001.

Table S9. Results of the rmANOVA on BDI and STAI-state sum score at T0, T4, FU1 and FU2, directly following treatment and at follow-up.

Source	*SS*	*df*	*MS*	*F*	*p*	η_p^2
Between-subject effects on BDI sum score						
Intercept	2259.572	1	2259.572	94.173	**<.001****	.577
Group	2.639	1	2.639	.110	.741	.002
Error	1655.583	69	23.994			
Within-subjects effects on BDI sum score						
Time * group	17.132	2.878	5.953	.599	.610	.009
Time	337.963	2.878	117.428	11.814	**< .001****	.146
Error	1973.953	198.585	9.940			
Simple within-subjects contrasts on BDI sum score						
Time: T4 vs. T0	287.685	1	287.685	13.848	**< .001****	.167
Error	1433.414	69	20.774			
Time: FU1 vs. T0	483.044	1	483.044	26.444	**< .001****	.277
Error	1260.392	69	18.267			
Time: FU2 vs. T0	520.881	1	520.881	22.582	**< .001****	.247
Error	1591.598	69	23.067			
Between-subject effects on STAI-state sum score						
Intercept	951.130	1	951.130	298.348	**<.001****	.812

Group	1.903	1	1.903	.597	.442	.009
Error	219.971	69	3.188			
Within-subject effects on STAI-state sum score						
Time * group	39.095	2.772	14.106	.284	.821	.004
Time	3659.180	2.772	1320.280	26.592	**<.001****	.278
Error	9494.820	191.235	49.650			
Simple within-subjects contrasts on STAI-state sum score						
Time: T4 vs. T0	3840.713	1	3840.713	46.363	**< .001****	.402
Error	5716.019	69	82.841			
Time: FU1 vs. T0	4371.739	1	4371.739	48.188	**< .001****	.411
Error	6259.838	69	90.722			
Time: FU2 vs. T0	6028.666	1	6028.666	44.821	**< .001****	.394
Error	9280.884	69	134.506			

Shown is the source, sum of squares (SS), degrees of freedom (df), mean square (MS), F-value (*F*), p-value (*p*), and partial eta squared (η_p^2) of within-subjects effects and contrasts. *, $p < 0.05$. **, $p < 0.001$.

Physiological reactivity during 3MDR-SC

There was no significant three-way interaction between session (T1, T2 and T3) * treatment phase (baseline, recall and task for three smoking cues) * group. There was, however, a significant small interaction between session * group for HRV and SC, and pairwise comparisons for the groups separately revealed a significant main effect of session in the control group, with higher HRV and skin conductance at T1 as compared to the other sessions, while no significant main effect of session was present in the active 3MDR-SC group. Thus, lower HRV and skin conductance was found in the active as compared to the control 3MDR-SC group only at T1, independent of treatment phase. For all statistics, see figure S5 and table S10.

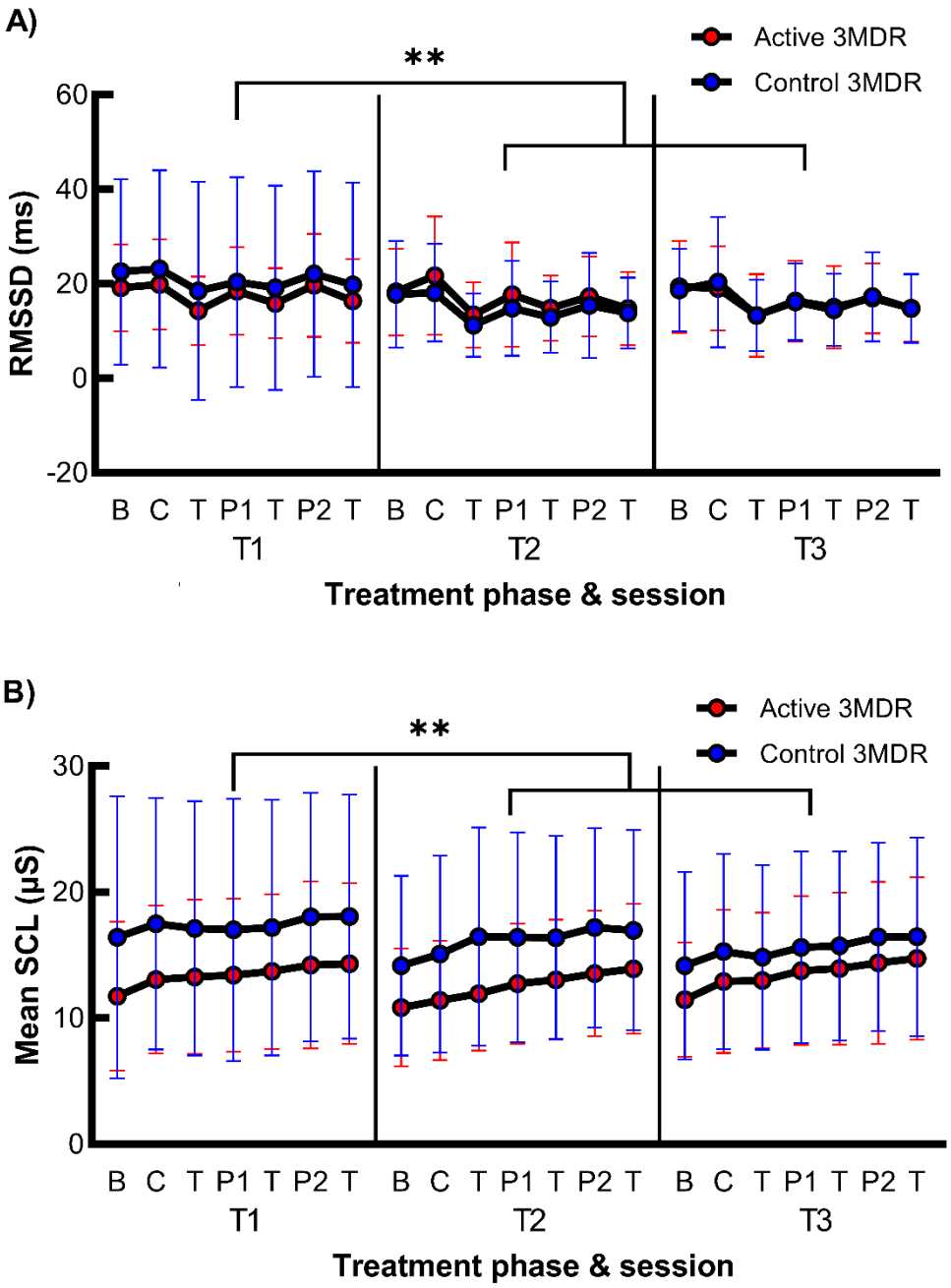

Figure S5. The effect of active 3MDR-SC on HRV and skin conductance reactivity during the three-day treatment. Shown is the mean (+/- SD) RMSSD ***(A)*** and mean SCL ***(B)*** at baseline (B), during recall of a puffed cigarette (C), first personalized picture (P1) or second personalized picture (P2) before the (non-)distractor task, and during each (non-)distractor task (T) in the active 3MDR-SC group (red) and control 3MDR-SC group (blue) at session T1, T2 and T3 (n = 79). **, session * condition interaction effect of $p < .001$. *B = baseline, C = puffed cigarette, T = (non-)distractor task, P1 = first personalized picture, P2 = second personalized picture.*

Note: Of the HRV data, 7.6% of the data points were missing (n = 125), and of the skin conductance data, 4.7% of the data points were missing (n = 77).

Table S10. Results of the linear mixed models on HRV and skin conductance reactivity at T1, T2 and T3.

Source	df_{num}	df_{den}	*F*	*p*	η^2
Fixed effects on HRV					
Session * phase * group	12	1395.330	.153	1.000	.001
Session * group	2	1405.032	7.309	**< .001****	.010
Phase * group	6	1395.417	.082	.998	< .001
Session * phase	12	1395.330	.225	.997	.002
Group	1	76.061	.191	.663	.003
Session	2	1405.032	15.854	**< .001****	.022
Phase	6	1395.417	12.705	**< .001****	.052
Intercept	1	76.061	365.749	**< .001****	
Fixed effects on HRV for the active 3MDR-SC group					
Session	2	728.758	2.798	.062	.008
Fixed effects on HRV for the control 3MDR-SC group					
Session	2	674.513	12.603	**< .001****	.036
Fixed effects on SC					
Session * phase * group	12	1442.985	.126	1.000	.001
Session * group	2	1444.438	9.096	**< .001****	.012
Phase * group	6	1443.005	.483	.821	.002
Session * phase	12	1442.985	.384	.970	.003
Group	1	75.882	4.858	**.031***	.060
Session	2	1444.438	13.429	**< .001****	.018
Phase	6	1443.005	16.260	**< .001****	.063
Intercept	1	75.882	389.020	**< .001****	
Fixed effects on skin conductance for the active 3MDR-SC group					
Session	2	749.822	2.540	.080	.007
Fixed effects on skin conductance for the control 3MDR-SC group					
Session	2	694.634	15.219	**< .001****	.042

Comparison	*M difference*	*SE*	*df*	*p*	*95% CI*
Pairwise comparisons on HRV for the active 3MDR-SC group					
T1-T2	1.148	.485	728.725	.055	-.017, 2.313
T1-T3	.566	.495	729.000	.759	-.622, 1.754
T2-T3	-.582	.505	728.541	.748	-1.793, .629
Pairwise comparisons on HRV for the control 3MDR-SC group					
T1-T2	5.247	1.116	676.861	**< .001****	2.568, 7.926
T1-T3	4.264	1.106	675.891	**< .001****	1.611, 6.918
T2-T3	-.983	1.117	670.760	1.000	-3.664, 1.699
Pairwise comparisons on skin conductance for the active 3MDR-SC group					
T1-T2	.523	.243	749.580	.095	-.060, 1.105
T1-T3	.114	.249	749.945	1.000	-.482, .711
T2-T3	-.409	.250	749.954	.307	-1.008, .191
Pairwise comparisons on skin conductance for the control 3MDR-SC group					
T1-T2	1.213	.353	694.939	**.002***	.365, 2.060
T1-T3	1.926	.353	694.939	**< .001****	1.079, 2.774
T2-T3	.714	.354	694.020	.133	-.136, 1.563

Shown is the source, degrees of freedom of the numerator (df_{num}) and denominator (df_{den}), F-value (*F*), p-value (*p*), and eta squared (η_p^2) of fixed effects, and the mean (M) difference, standard error (SE), degrees of freedom (df), p-value (*p*), and 95% confidence interval (CI) of pairwise comparisons. *, $p < 0.05$. **, $p < 0.001$.

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