Supplemental Materials

Methods

Baseline period

During the baseline period, both monkeys in a pair simultaneously completed both the spatial and object tasks five days/week (Monday–Friday) in separate chambers during the first (run-1) of the two daily behavioral test sessions. Immediately following run-1, vehicle was administered to both monkeys via the vascular access port, and 30 min later, they returned to the testing chambers and simultaneously completed the second test session (run-2).

Acute periods

During the first acute period, two monkeys received THC doses with a few differences from the ascending order. However, preliminary analyses revealed that the results from all seven pairs of monkeys were indistinguishable from the five pairs with ascending doses. All seven monkeys in the THC group received doses of 30, 60, 120, and 180 μg/kg; five animals also received 240 μg/kg. Each dose of THC/vehicle was administered for 3-5 days during a single week, with at least 23h between drug administrations and 71h, the approximate elimination half-life of THC (1), between each change in dose (see (2) for additional details).

During the first and second acute periods, and similar to the baseline period, both monkeys in a pair simultaneously completed both tasks during run-1. Immediately following run-1, THC or vehicle was administered to the monkeys via the vascular access port, and 30 min later, they returned to the testing chambers and simultaneously completed run-2. However, it should be noted that during the baseline phase (Week 0) there was a 12s delay, which was increased to 16s for the remainder of the study (Weeks 1-27).

Dose selection

Following the first acute period, monkeys assigned to the THC group received either 120 (*n*=3) or 240 (*n*=4) μg/kg of THC for the remainder of the six month study period. These doses were selected based on the results of the first acute period, which revealed that the dose-related behavioral effects of acute THC-induced intoxication differed across monkeys. For example, while administration of 30 μg/kg similarly affected latencies to initiate trials and completion rates (≥96%) in all seven THC-exposed monkeys on the object task, administration of 120 μg/kg increased the latencies to initiate trials by 146% and completion rates fell to <88% in only three of the seven monkeys. Similar effects were found in the other four monkeys only after administration of 240 μg/kg of THC; i.e., the latencies to initiate trials increased by 112% and task completion rates fell to <86%. Performance measures on the spatial task also differed in a similar dose-related manner between these same two subgroups. These data indicate that the dose of THC that was acutely intoxicating (i.e., affected responding to stimuli) differed across animals, which is consistent with the substantial inter-individual variability of cognitive effects of acute THC administration in adult rhesus monkeys (3) and humans (4), as well as psychological measures in humans (5, 6). Moreover, the doses of THC that impaired spatial working memory task performance in the adolescent monkeys are similar to the typical dose of THC that is self-administered by monkeys (7, 8), the typical amount of THC that is consumed by young adults (9, 10), and doses that acutely impair performance of cognitive tasks in humans (5, 11, 12). Collectively, these findings support the use of doses that are known to acutely impair performance on cognitive tasks.

Statistical analyses

To model and analyze the 27 weeks of data, a segmented linear model was implemented (Supplemental Figure 1). For each individual delay, the model can be described by the following parameters: b11 denotes the slope of the phase I segment of the THC-exposed animals; b12 the slope of segment for phase II; and b10 is the intercept of the phase I segment. The quantities b01, b02 and b00 denote the corresponding values for vehicle monkeys. For each group, the phase I and II segments are joined at a change point (Kt for the THC group and

Kv for the vehicle group). The parameter b3 is the coefficient for the effect of the baseline measure.

Here we summarize in some detail the approach used for the modeling. After computing the primary weekly variables, we first graphed the working memory accuracy rate averages over time as presented in Figures 2A, 2C, and 2E, as well as the individual monkey profiles over time and separated by treatment group. Visually it quickly became apparent that for the single-reinforcement object trials there was no apparent difference between groups and little, if any, difference for double-reinforcement object trials. However, it was also evident that the groups differed on the spatial task. Because the purpose of the study was to examine any group differences over time, we next employed the nonparametric local smoother, LOESS, (seen in Supplemental Figure 2A) to the data shown in Figure 3A to remove the local variability in each trajectory. Both the LOESS curve and the raw data indicated that for spatial trials a linear over time model is problematic and that a distinct curvature was present in the smoothed time plots with two visually apparent phases. We choose to model this as a segmented linear model with just one “break point”. This parsimonious model has readily interpretable parameters and includes the single line model as a sub-model. The fitted models are given in Figures 2 and 3, where the fitted values for accuracy are back-transformed values from the fitted logistic; a graph of the fitted model overlaid on the LOESS smooth of the raw data is shown in Supplemental Figures 2 and 3. These figures provide visual justification of the goodness-of-fit. In addition, this modeling allows us to see if a single line model provides a better fit in comparison to the segmented linear model by testing whether the slope before the breakpoint is the same as the slope afterwards. If the null hypothesis of equality cannot be rejected, then a single line is an adequate model and if one rejects the null hypothesis, then a single line is not a good fit. For spatial trials, the p-values for this test by delay and AUC for each treatment group were: $p < 0.001$ (vehicle) and $p < 0.001$ (THC) for 1s; $p < 0.001$ (vehicle) and $p < 0.001$ (THC) for 4s; $p < 0.001$ (vehicle) and $p = 0.002$ (THC) for 8s; $p < 0.001$ (vehicle) and $p = 0.215$ (THC) for 16s;

and $p < 0.001$ (vehicle) and $p = 0.012$ (THC) for AUC. Once we established the suitability of the segmented linear model for spatial trials, we kept this model for single-reinforcement and double-reinforcement object trials for comparative purposes.

MLE estimation was used to estimate the model parameters of the segmented linear models and the variances of the appropriate random effects. Results in the paper are based on hypothesis tests involving each of the noted parameters and analyzed within each delay separately.

In order to compare the performances between the two groups across delays, a larger model encompassing all four delays was fit, taking into account the correlations within each animal. In this model, the intercept, slopes and change point for each group were estimated concurrently for all delays. Baseline working memory accuracy rate was also adjusted as a covariate. Due to the complexity of this larger model, only between-delays comparisons are based on it. However, the parameter estimates for this larger model are quite comparable to those from the within-delay models.

The analysis comparing the first and second acute periods was done using a corrected database. Based on the weekly working memory accuracy rates during both acute periods, the delays when run-1 working memory accuracy rates were low for each monkey were eliminated in a step-down fashion (2). To determine if run-1 performance was low or at chance level on either task or reinforcement conditions, we started from the 16s delay and tested the null hypothesis that for this delay, week and monkey run-1 accuracy rate was at the chance performance level of 25% versus the alternative that run-1 accuracy rate was greater than 25%. An exact binomial test was applied to obtain the critical value for each number of completed trials. If the number of correct trials for run-1 was greater than the critical value, then the performance for that monkey in that week was considered to be above chance for the 16s delay (and thus for all shorter delays) and all data from both run-1 and run-2 of that monkey were included. If the number of correct trials for run-1 was less than the critical value, then the performance was considered to be low or at chance and measurements for both run-1 and run-2 at the 16s delay for that week were removed. If 16s delay data were excluded, we next stepped down to the 8s delay for that task to determine if the monkey's run-1 performance was above chance, and so on for each shorter delay. For example, if a monkey performed at chance on a task during a given week at both the 8s and 16s delays, but above chance at the 4s delay, all the data (i.e., both run-1 and run-2) from the 1s and 4s delays were included in the corrected data set, but none of the data from the 8s and 16s delays were included. After the elimination, the percent change in working memory accuracy rate from run-1 to run-2 of the remaining delays was computed through the following formula: percent change = [(working memory accuracy rate in run-2 minus working memory accuracy rate in run-1)/working memory accuracy rate in session 1] * 100%.

Modeling and analyses were done using SAS PROC NLMIXED for the main study and PROC GLIMMIX for the acute study.

Results

Spatial data

In the analysis of spatial trials performed to compare results across delays, no estimates could be made for the change point and second slope for the THC group at the 16s delay. Therefore, only one straight line was modeled for THC at the 16s delay in this combined analysis. Consequently, the difference in the change points between THC and vehicle at 16s delay cannot be estimated and compared to those of other delays.

Single-reinforcement object data

Results of single-reinforcement object trials were very similar to those of double-reinforcement trials. However, before the change points, the improvement rates of each group were generally not significantly different from 0, except for the vehicle group at 1s delay (slope was positive, $p < 0.001$) and 4s delay (slope was positive, $p = 0.002$) and the THC group at 4s delay (slope was positive, $p = 0.007$). After the change points, performances of both groups did not significantly change with time except for the THC group at 1s delay (slope was positive, $p = 0.040$) and 8s delay (slope was positive, $p = 0.003$). The THC group had no significant differences from the vehicle group in the phase I improvement rates and times to reach the second phase except for the 8s delay ($p = 0.039$ for a lower improvement rate in THC and $p < 0.001$ for a later change point in THC). There were no significant differences of accuracy rates at the change points between THC and vehicle groups. Analysis of AUC showed that the THC and vehicle groups had no significant differences in terms of slopes (phase I and II), change points, or AUC at the change point. The model including all 4 delays showed that the difference in the change points between THC and vehicle groups did not depend on delays except that this difference at the 1s delay was smaller than that at the 4s delay ($p = 0.028$). These results collectively imply that there were no substantial differences between the THC and vehicle groups after repeated exposure to THC on the single-reinforcement object trials.

Results for other variables of the spatial task

In addition to working memory accuracy rate, other measured variables included control accuracy rates, working memory and control completion rates, working memory and control reaction times, and initiation times. Control accuracy rate is the proportion of correct trials among the completed control trials for a given delay; completion rate is the proportion of completed trials among presented trials; and latency is the time difference between the appearance of the sample stimulus (initiation latency) or choice probe(s) (reaction latency) and the response.

Graphs of these variables gave no indication of the pattern seen in working memory accuracy rate. In order to have a general idea how these response variables changed after repeated THC exposure, summary tables (Supplemental Tables 1-6) at each delay for both groups are provided. In addition, to the four individual delays that are summarized, the weekly responses of a monkey were averaged across the four delays and denoted as “averaged delay”. In the tables, the mean and standard deviation (SD) of the response at baseline, every four weeks after baseline until week 27 and the overall week 0 to week 27 are computed. The t-statistic and p-value for the comparison between THC and vehicle for each group of weeks are provided. As described in the main text, because THC did not have any overall apparent long-term effects on the working memory accuracy rate in either double-reinforcement or single-reinforcement object trials, summaries are provided only for the spatial task.

The tables show that the data for each of these measures in the two THC and vehicle groups were quite similar over time. There were only a very few scattered significant differences among these variables between the THC and vehicle groups, with no apparent trends in the p-values.

References

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Supplemental Table 1. Summary of Control Trial Accuracy Rate Statistics for Spatial Trials											
Delay	Group	Summary	Week								
			0	1-4	5-8	9-12	13-16	17-20	21-24	25-27	0-27
1	THC	Mean	0.9536	0.9298	0.9407	0.9490	0.9574	0.9401	0.9780	0.9746	0.9521
		SD	0.0652	0.0759	0.0476	0.0486	0.0443	0.0356	0.0281	0.0475	0.0265
	Vehicle	Mean	0.9475	0.9427	0.9595	0.9499	0.9484	0.9759	0.9643	0.9206	0.9526
		SD	0.0587	0.0435	0.0450	0.0554	0.0468	0.0513	0.0610	0.1194	0.0323
	THC-Vehicle	T Stat	0.1842	-0.3899	-0.7615	-0.0318	0.3701	-1.5139	0.5393	1.1113	-0.0332
		p-value	**0.8569**	**0.7034**	**0.4610**	**0.9752**	**0.7178**	**0.1559**	**0.5996**	**0.2882**	**0.9740**
4	THC	Mean	0.9125	0.9133	0.8926	0.9035	0.9425	0.9065	0.8637	0.8817	0.9017
		SD	0.1175	0.0779	0.0669	0.0616	0.0679	0.1299	0.0928	0.1071	0.0495
	Vehicle	Mean	0.8548	0.8781	0.9166	0.9306	0.9051	0.9063	0.9101	0.8889	0.9039
		SD	0.1318	0.0817	0.0821	0.0589	0.0825	0.0778	0.1016	0.1293	0.0667
	THC-Vehicle	T Stat	0.8651	0.8230	-0.5987	-0.8414	0.9271	0.0052	-0.8925	-0.1126	-0.0708
		p-value	**0.4040**	**0.4266**	**0.5605**	**0.4166**	**0.3721**	**0.9959**	**0.3897**	**0.9122**	**0.9447**
8	THC	Mean	0.9250	0.9310	0.9084	0.9692	0.9274	0.9574	0.9464	0.9563	0.9412
		SD	0.0878	0.0657	0.0872	0.0385	0.0566	0.0338	0.0337	0.0450	0.0222
	Vehicle	Mean	0.8631	0.8437	0.9012	0.9268	0.8963	0.9175	0.8827	0.8810	0.8921
		SD	0.1544	0.1104	0.0727	0.0915	0.1284	0.0800	0.1789	0.1493	0.0911
	THC-Vehicle	T Stat	0.9221	1.7987	0.1691	1.1321	0.5861	1.2183	0.9255	1.2790	1.3860
		p-value	**0.3746**	**0.0973**	**0.8685**	**0.2797**	**0.5687**	**0.2465**	**0.3730**	**0.2251**	**0.1910**
16	THC	Mean	0.8921	0.9055	0.8708	0.9014	0.9161	0.9324	0.8667	0.9524	0.9043
		SD	0.1030	0.0556	0.1207	0.0846	0.1110	0.0484	0.1646	0.0615	0.0436
	Vehicle	Mean	0.8325	0.8385	0.9019	0.9273	0.9354	0.9104	0.8887	0.8016	0.8893
		SD	0.1101	0.1598	0.0876	0.0588	0.0513	0.0803	0.0841	0.2196	0.0700
	THC-Vehicle	T Stat	1.0454	1.0478	-0.5526	-0.6630	-0.4177	0.6214	-0.3153	1.7497	0.4811
		p-value	**0.3164**	**0.3154**	**0.5907**	**0.5198**	**0.6835**	**0.5460**	**0.7579**	**0.1057**	**0.6391**
averaged	THC	Mean	0.9208	0.9199	0.9031	0.9308	0.9359	0.9341	0.9137	0.9413	0.9248
		SD	0.0819	0.0516	0.0636	0.0496	0.0382	0.0363	0.0615	0.0469	0.0306
	Vehicle	Mean	0.8745	0.8758	0.9198	0.9336	0.9213	0.9275	0.9115	0.8790	0.9096
		SD	0.0942	0.0829	0.0657	0.0517	0.0654	0.0639	0.0775	0.1210	0.0598
	THC-Vehicle	T Stat	0.9820	1.1957	-0.4823	-0.1044	0.5080	0.2387	0.0597	1.2703	0.5985
		p-value	**0.3455**	**0.2549**	**0.6383**	**0.9185**	**0.6207**	**0.8153**	**0.9534**	**0.2281**	**0.5606**

Supplemental Table 2. Summary of Working Memory Trial Completion Rate Statistics for Spatial Trials											
Delay	**Group**	**Summary**	**Week**								
			0	**1-4**	**5-8**	**9-12**	**13-16**	**17-20**	**21-24**	**25-27**	**0-27**
1	**THC**	**Mean**	0.9960	0.9737	0.9696	0.9913	0.9714	0.9482	0.9702	0.9633	0.9708
		SD	0.0069	0.0314	0.0485	0.0133	0.0626	0.1133	0.0190	0.0635	0.0280
	Vehicle	**Mean**	0.9942	0.9614	0.9772	0.9370	0.9495	0.9882	0.9457	0.9296	0.9578
		SD	0.0103	0.0839	0.0377	0.1146	0.0565	0.0112	0.0629	0.1296	0.0346
	THC-Vehicle	**T Stat**	0.3814	0.3626	-0.3267	1.2459	0.6864	-0.9287	0.9896	0.6185	0.7743
		***p*-value**	**0.7096**	**0.7232**	**0.7495**	**0.2366**	**0.5055**	**0.3714**	**0.3419**	**0.5478**	**0.4538**
4	**THC**	**Mean**	0.9924	0.9487	0.9563	0.9787	0.9742	0.9417	0.9375	0.9415	0.9559
		SD	0.0102	0.0600	0.0550	0.0254	0.0485	0.0818	0.0588	0.0706	0.0270
	Vehicle	**Mean**	0.9888	0.9491	0.9665	0.9365	0.9364	0.9772	0.9420	0.9147	0.9487
		SD	0.0153	0.0875	0.0479	0.1014	0.0740	0.0316	0.0724	0.1357	0.0433
	THC-Vehicle	**T Stat**	0.5143	-0.0111	-0.3726	1.0696	1.1303	-1.0734	-0.1265	0.4635	0.3727
		***p*-value**	**0.6164**	**0.9913**	**0.7160**	**0.3058**	**0.2804**	**0.3042**	**0.9014**	**0.6513**	**0.7159**
8	**THC**	**Mean**	0.9964	0.9560	0.9429	0.9689	0.9616	0.9169	0.9501	0.9494	0.9511
		SD	0.0094	0.0440	0.0817	0.0385	0.0614	0.0990	0.0428	0.0782	0.0303
	Vehicle	**Mean**	0.9835	0.9400	0.9600	0.9353	0.9363	0.9651	0.9405	0.9077	0.9434
		SD	0.0186	0.0980	0.0590	0.1064	0.0867	0.0418	0.0700	0.1402	0.0559
	THC-Vehicle	**T Stat**	1.6392	0.3957	-0.4512	0.7847	0.6299	-1.1868	0.3119	0.6867	0.3192
		***p*-value**	**0.1271**	**0.6993**	**0.6599**	**0.4478**	**0.5406**	**0.2583**	**0.7605**	**0.5054**	**0.7550**
16	**THC**	**Mean**	0.9924	0.9438	0.9246	0.9637	0.9586	0.9038	0.9345	0.9196	0.9381
		SD	0.0144	0.0563	0.0911	0.0350	0.0644	0.0962	0.0419	0.0808	0.0383
	Vehicle	**Mean**	0.9683	0.9348	0.9565	0.9159	0.9124	0.9802	0.9092	0.8879	0.9310
		SD	0.0424	0.0929	0.0562	0.1290	0.1205	0.0230	0.1143	0.1559	0.0670
	THC-Vehicle	**T Stat**	1.4240	0.2176	-0.7889	0.9453	0.8950	-2.0443	0.5500	0.4783	0.2434
		***p*-value**	**0.1799**	**0.8314**	**0.4455**	**0.3632**	**0.3884**	**0.0635**	**0.5924**	**0.6410**	**0.8118**
averaged	**THC**	**Mean**	0.9943	0.9555	0.9483	0.9757	0.9664	0.9276	0.9481	0.9435	0.9540
		SD	0.0095	0.0465	0.0668	0.0266	0.0588	0.0963	0.0342	0.0714	0.0291
	Vehicle	**Mean**	0.9837	0.9463	0.9651	0.9312	0.9336	0.9777	0.9343	0.9100	0.9452
		SD	0.0205	0.0899	0.0496	0.1098	0.0838	0.0257	0.0766	0.1386	0.0492
	THC-Vehicle	**T Stat**	1.2394	0.2406	-0.5322	1.0416	0.8476	-1.3277	0.4344	0.5683	0.4052
		***p*-value**	**0.2389**	**0.8139**	**0.6043**	**0.3181**	**0.4132**	**0.2090**	**0.6717**	**0.5803**	**0.6925**

Supplemental Table 3. Summary of Control Trial Completion Rate Statistics for Spatial Trials

Delay	Group	Summary	Week 0	1-4	5-8	9-12	13-16	17-20	21-24	25-27	0-27
1	THC	Mean	1.0000	0.9813	0.9768	0.9920	0.9836	0.9557	0.9702	0.9841	0.9782
		SD	0.0000	0.0282	0.0390	0.0138	0.0433	0.1002	0.0291	0.0420	0.0241
	Vehicle	Mean	0.9929	0.9679	0.9509	0.9571	0.9464	0.9845	0.9405	0.8849	0.9513
		SD	0.0189	0.0850	0.0620	0.0693	0.0595	0.0201	0.1247	0.1846	0.0437
	THC-Vehicle	T Stat	1.0000	0.3955	0.9352	1.3044	1.3375	-0.7477	0.6151	1.3868	1.4266
		p-value	**0.3370**	**0.6994**	**0.3681**	**0.2166**	**0.2058**	**0.4691**	**0.5500**	**0.1907**	**0.1792**
4	THC	Mean	0.9911	0.9598	0.9839	0.9866	0.9676	0.9482	0.9286	0.9603	0.9632
		SD	0.0236	0.0427	0.0310	0.0354	0.0450	0.0879	0.0815	0.0504	0.0316
	Vehicle	Mean	0.9911	0.9518	0.9884	0.9479	0.9580	0.9821	0.9077	0.9206	0.9535
		SD	0.0236	0.0928	0.0218	0.0792	0.0564	0.0328	0.1153	0.1525	0.0389
	THC-Vehicle	T Stat	0.0000	0.2082	-0.3117	1.1792	0.3489	-0.9573	0.3905	0.6537	0.5165
		p-value	**1.0000**	**0.8385**	**0.7606**	**0.2612**	**0.7332**	**0.3573**	**0.7030**	**0.5256**	**0.6149**
8	THC	Mean	1.0000	0.9527	0.9563	0.9565	0.9732	0.9512	0.9524	0.9325	0.9560
		SD	0.0000	0.0277	0.0442	0.0650	0.0492	0.0637	0.0667	0.0750	0.0275
	Vehicle	Mean	0.9857	0.9455	0.9714	0.9268	0.9616	0.9696	0.9464	0.9206	0.9512
		SD	0.0378	0.1235	0.0534	0.1129	0.0526	0.0336	0.0679	0.1525	0.0411
	THC-Vehicle	T Stat	1.0000	0.1494	-0.5795	0.6045	0.4265	-0.6778	0.1655	0.1853	0.2548
		p-value	**0.3370**	**0.8838**	**0.5730**	**0.5568**	**0.6773**	**0.5107**	**0.8713**	**0.8561**	**0.8032**
16	THC	Mean	0.9929	0.9277	0.9571	0.9682	0.9554	0.9461	0.9673	0.9881	0.9587
		SD	0.0189	0.0540	0.0801	0.0393	0.0935	0.0822	0.0315	0.0315	0.0353
	Vehicle	Mean	0.9696	0.9402	0.9759	0.9321	0.9164	0.9836	0.9048	0.9048	0.9391
		SD	0.0577	0.1043	0.0266	0.1251	0.1054	0.0207	0.1295	0.1828	0.0517
	THC-Vehicle	T Stat	1.0120	-0.2815	-0.5879	0.7265	0.7322	-1.1704	1.2410	1.1889	0.8273
		p-value	**0.3315**	**0.7831**	**0.5675**	**0.4815**	**0.4781**	**0.2646**	**0.2383**	**0.2575**	**0.4242**
averaged	THC	Mean	0.9960	0.9554	0.9685	0.9758	0.9699	0.9503	0.9546	0.9663	0.9640
		SD	0.0069	0.0323	0.0451	0.0324	0.0560	0.0805	0.0444	0.0368	0.0275
	Vehicle	Mean	0.9848	0.9513	0.9717	0.9410	0.9456	0.9800	0.9249	0.9077	0.9488
		SD	0.0288	0.0993	0.0352	0.0939	0.0645	0.0224	0.0970	0.1675	0.0428
	THC-Vehicle	T Stat	0.9958	0.1018	-0.1445	0.9275	0.7534	-0.9399	0.7381	0.9031	0.7935
		p-value	**0.3390**	**0.9206**	**0.8875**	**0.3720**	**0.4657**	**0.3658**	**0.4746**	**0.3842**	**0.4429**

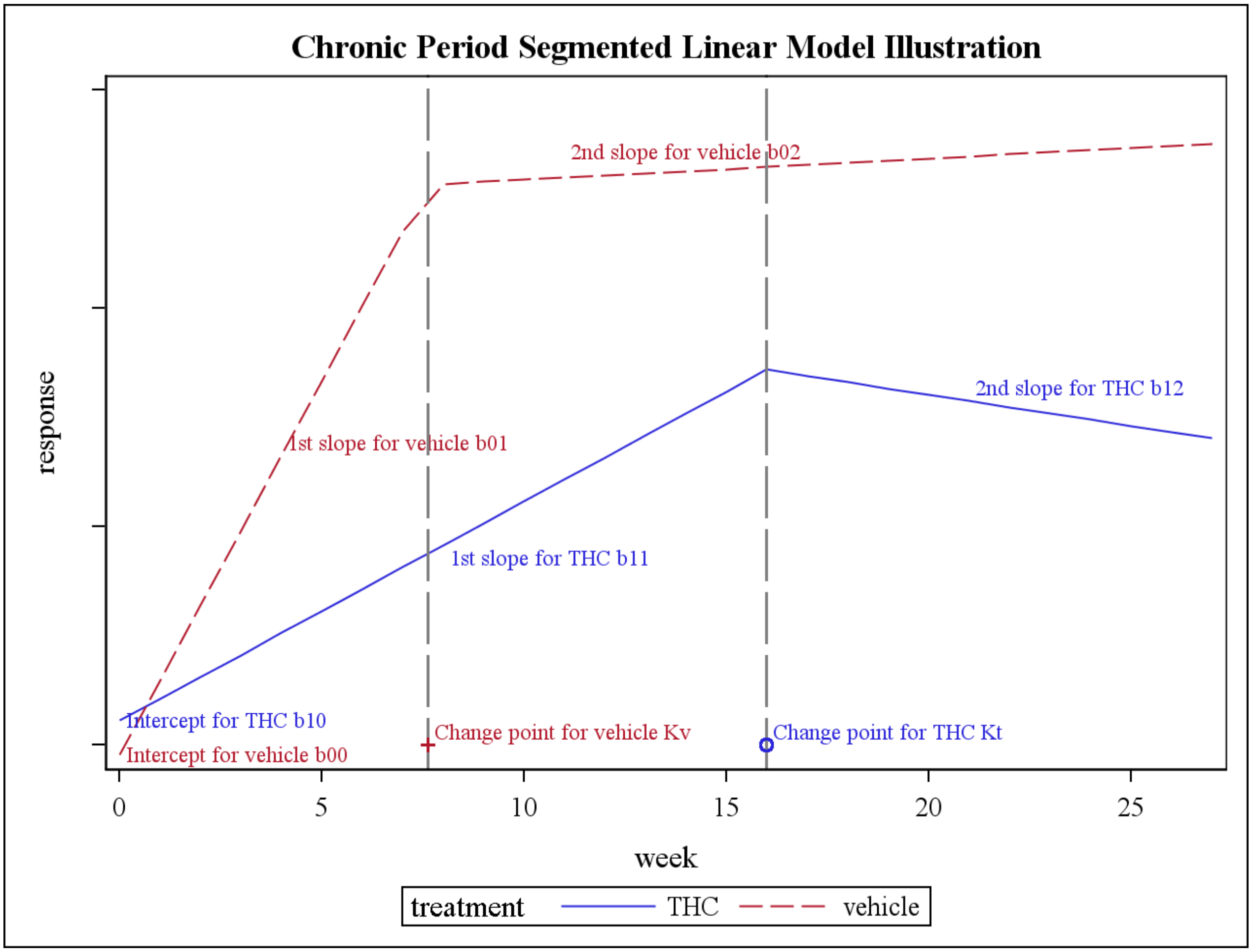
Supplemental Table 4. Summary of Working Memory Trial Reaction Time Statistics for Spatial Trials											
Delay	**Group**	**Summary**	**Week**								
			0	**1-4**	**5-8**	**9-12**	**13-16**	**17-20**	**21-24**	**25-27**	**0-27**
1	**THC**	**Mean**	902.8	882.6	729.1	610.7	693.8	1214.6	848.2	874.1	837.2
		SD	427.9	281.8	300.3	297.4	353.0	1162.7	430.3	666.4	208.8
	Vehicle	**Mean**	908.4	826.5	762.8	1021.3	675.6	781.6	807.4	993.6	835.3
		SD	600.1	449.0	456.0	860.0	446.2	563.5	705.5	1104.0	497.0
	THC-Vehicle	**T Stat**	-0.0202	0.2798	-0.1629	-1.1940	0.0848	0.8867	0.1306	-0.2451	0.0090
		***p*-value**	**0.9842**	**0.7844**	**0.8733**	**0.2556**	**0.9338**	**0.3927**	**0.8983**	**0.8105**	**0.9930**
4	**THC**	**Mean**	1829.1	1790.1	1616.5	1544.0	1343.9	1359.3	1615.8	1645.9	1565.9
		SD	1268.2	989.8	696.7	587.5	646.4	460.8	1063.3	1179.9	677.1
	Vehicle	**Mean**	1627.3	1487.3	1020.4	840.2	1074.1	851.4	1160.4	1239.5	1110.0
		SD	962.8	676.8	606.7	414.3	275.3	354.9	694.0	1021.2	434.8
	THC-Vehicle	**T Stat**	0.3353	0.6681	1.7072	2.5905	1.0158	2.3107	0.9489	0.6891	1.4989
		***p*-value**	**0.7432**	**0.5167**	**0.1135**	**0.0236**	**0.3298**	**0.0394**	**0.3614**	**0.5039**	**0.1597**
8	**THC**	**Mean**	1518.0	2059.9	1671.9	1552.5	1395.0	1584.9	1721.6	1533.8	1645.1
		SD	744.4	1230.9	729.5	444.4	390.7	831.0	846.4	1091.3	722.1
	Vehicle	**Mean**	1924.9	1937.5	1489.3	1164.5	1200.2	1079.1	1260.0	1582.5	1399.8
		SD	984.8	1074.3	1099.7	793.9	270.6	642.8	782.4	1580.7	713.9
	THC-Vehicle	**T Stat**	-0.8721	0.1981	0.3662	1.1284	1.0844	1.2740	1.0597	-0.0671	0.6391
		***p*-value**	**0.4002**	**0.8463**	**0.7206**	**0.2812**	**0.2995**	**0.2268**	**0.3102**	**0.9476**	**0.5348**
16	**THC**	**Mean**	1577.5	2632.2	2104.9	1866.6	1878.2	1992.4	2221.5	2090.9	2094.0
		SD	688.0	1633.5	977.6	541.7	801.0	646.3	1177.7	1763.5	908.2
	Vehicle	**Mean**	1834.2	2132.4	1937.9	1535.2	1619.9	1212.3	1763.3	1247.8	1656.5
		SD	863.0	1186.9	1630.4	914.7	673.2	752.3	1406.3	809.8	851.3
	THC-Vehicle	**T Stat**	-0.6154	0.6548	0.2325	0.8248	0.6532	2.0810	0.6609	1.1495	0.9300
		***p*-value**	**0.5498**	**0.5250**	**0.8201**	**0.4256**	**0.5259**	**0.0595**	**0.5212**	**0.2727**	**0.3707**
averaged	**THC**	**Mean**	1456.8	1841.2	1530.6	1393.5	1327.7	1537.8	1601.8	1536.2	1535.6
		SD	724.1	1005.7	621.8	387.9	494.1	498.8	790.4	1066.8	593.4
	Vehicle	**Mean**	1573.7	1595.9	1302.6	1140.3	1142.4	981.1	1247.8	1265.8	1250.4
		SD	758.8	828.6	928.0	689.2	368.6	536.2	825.4	1072.3	616.7
	THC-Vehicle	**T Stat**	-0.2948	0.4979	0.5401	0.8470	0.7952	2.0115	0.8195	0.4728	0.8815
		***p*-value**	**0.7732**	**0.6276**	**0.5990**	**0.4136**	**0.4420**	**0.0673**	**0.4285**	**0.6448**	**0.3954**

Supplemental Table 5. Summary of Control Trial Reaction Time Statistics for Spatial Trials											
Delay	**Group**	**Summary**	**Week**								
			0	**1-4**	**5-8**	**9-12**	**13-16**	**17-20**	**21-24**	**25-27**	**0-27**
1	**THC**	**Mean**	522.6	708.2	567.3	428.2	632.3	759.7	552.3	476.8	590.9
		SD	149.8	230.0	331.7	120.1	326.3	622.7	344.4	138.2	179.1
	Vehicle	**Mean**	505.2	859.5	427.3	876.9	558.3	449.7	652.9	604.8	629.2
		SD	128.2	999.5	83.1	856.6	306.1	219.0	428.5	758.5	280.4
	THC-Vehicle	**T Stat**	0.2332	-0.3904	1.0832	-1.3725	0.4373	1.2426	-0.4845	-0.4393	-0.3049
		***p*-value**	**0.8195**	**0.7031**	**0.3000**	**0.1950**	**0.6696**	**0.2378**	**0.6367**	**0.6683**	**0.7657**
4	**THC**	**Mean**	1451.1	1393.4	1642.5	1183.2	972.5	1249.8	1281.2	1929.1	1361.8
		SD	640.6	510.7	929.6	419.3	341.8	413.6	505.8	1460.8	338.9
	Vehicle	**Mean**	1309.9	1207.6	787.5	1362.9	1035.1	842.4	794.0	1838.8	1105.2
		SD	707.8	1101.8	461.2	1224.4	332.9	387.5	228.6	2116.1	365.1
	THC-Vehicle	**T Stat**	0.3913	0.4047	2.1797	-0.3673	-0.3471	1.9017	2.3221	0.0929	1.3627
		***p*-value**	**0.7025**	**0.6928**	**0.0499**	**0.7198**	**0.7345**	**0.0815**	**0.0386**	**0.9275**	**0.1980**
8	**THC**	**Mean**	1285.5	1741.3	1788.6	1229.1	1465.1	1832.2	1213.5	2351.8	1622.2
		SD	689.1	955.1	1217.4	435.8	616.8	799.6	549.7	951.9	455.8
	Vehicle	**Mean**	1602.1	1569.1	1354.1	1497.4	1590.5	1130.1	2423.3	1258.5	1558.4
		SD	1071.0	1018.1	679.4	1011.4	450.0	657.5	1279.8	838.8	636.1
	THC-Vehicle	**T Stat**	-0.6577	0.3264	0.8247	-0.6446	-0.4346	1.7944	-2.2980	2.2800	0.2155
		***p*-value**	**0.5231**	**0.7498**	**0.4257**	**0.5313**	**0.6716**	**0.0980**	**0.0403**	**0.0417**	**0.8330**
16	**THC**	**Mean**	1370.4	1820.2	1635.4	1261.8	1295.2	1591.5	2262.7	1278.6	1595.5
		SD	739.3	891.2	1003.3	461.5	369.8	766.7	1688.7	973.2	582.8
	Vehicle	**Mean**	1435.9	1363.9	1314.1	1386.6	1185.2	1035.6	1850.1	1870.2	1399.7
		SD	781.0	612.4	815.0	1161.2	494.9	589.6	1028.2	1579.8	544.8
	THC-Vehicle	**T Stat**	-0.1612	1.1164	0.6576	-0.2641	0.4710	1.5206	0.5521	-0.8436	0.6493
		***p*-value**	**0.8746**	**0.2861**	**0.5232**	**0.7962**	**0.6461**	**0.1543**	**0.5910**	**0.4154**	**0.5284**
averaged	**THC**	**Mean**	1157.4	1415.8	1408.4	1025.6	1091.3	1358.3	1327.4	1509.1	1292.6
		SD	494.2	492.4	851.4	272.0	211.6	375.3	430.4	684.5	299.9
	Vehicle	**Mean**	1213.3	1250.0	970.8	1280.9	1092.3	864.5	1430.1	1399.2	1177.3
		SD	535.9	821.5	404.5	875.0	223.9	367.4	673.9	1162.8	400.4
	THC-Vehicle	**T Stat**	-0.2028	0.4579	1.2285	-0.7373	-0.0087	2.4880	-0.3397	0.2154	0.6094
		***p*-value**	**0.8427**	**0.6552**	**0.2428**	**0.4751**	**0.9932**	**0.0285**	**0.7400**	**0.8331**	**0.5536**

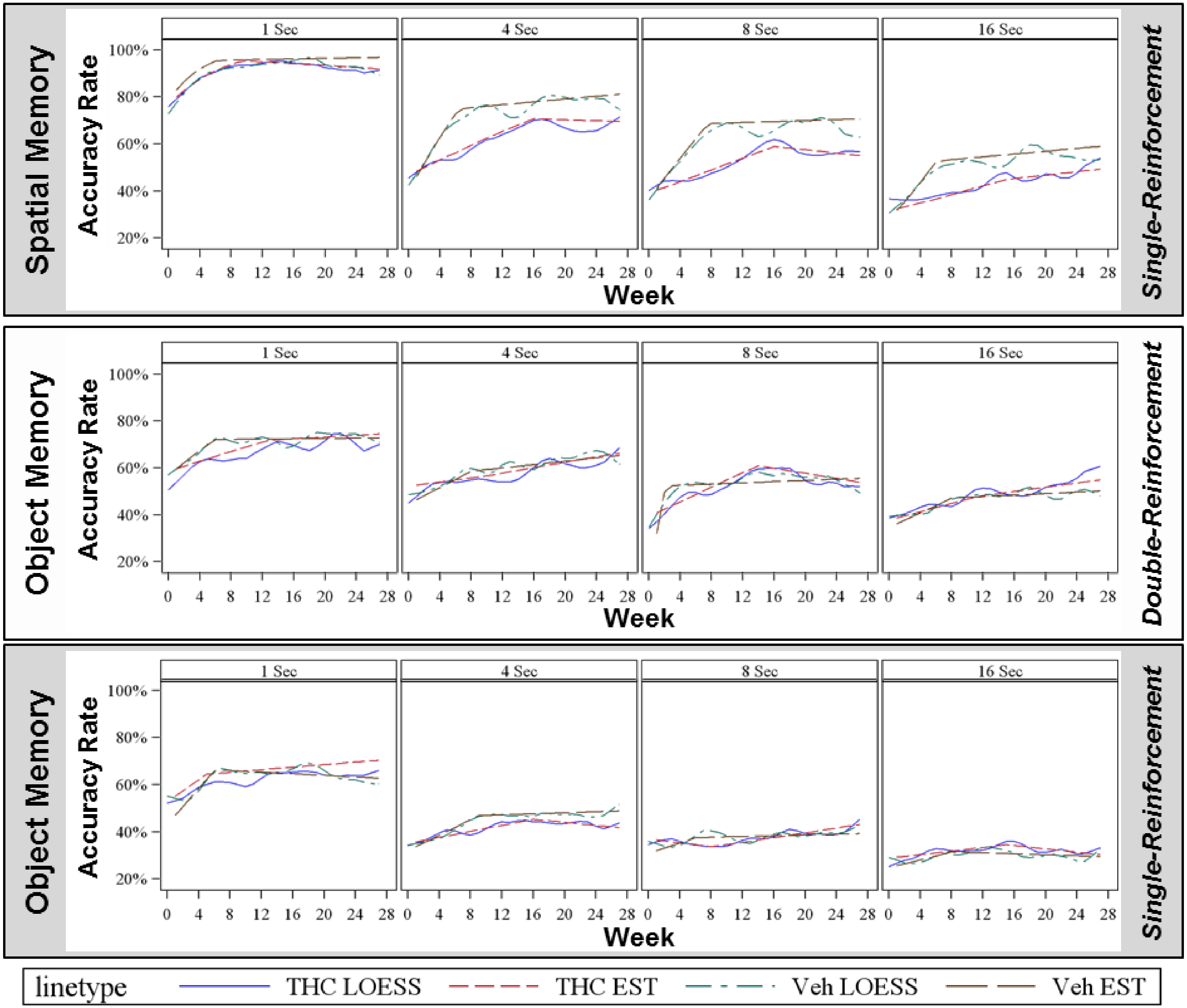
Supplemental Table 6. Summary of Initiation Time Statistics for Spatial Trials

Delay	Group	Summary	Week								
			0	1-4	5-8	9-12	13-16	17-20	21-24	25-27	0-27
1	THC	Mean	216.8	280.3	268.6	249.5	251.5	291.7	287.7	299.5	272.6
		SD	61.9	66.1	69.1	43.2	68.2	113.2	77.6	148.0	42.4
	Vehicle	Mean	269.3	287.4	288.7	293.0	283.2	223.8	303.0	320.5	283.8
		SD	123.7	169.6	114.6	128.2	93.6	38.9	125.4	191.3	67.2
	THC-Vehicle	T Stat	-1.0033	-0.1028	-0.3964	-0.8497	-0.7227	1.4987	-0.2732	-0.2305	-0.3733
		p-value	**0.3355**	**0.9199**	**0.6987**	**0.4121**	**0.4837**	**0.1598**	**0.7894**	**0.8216**	**0.7155**
4	THC	Mean	210.4	289.4	269.5	249.0	246.2	272.8	294.3	305.8	271.9
		SD	56.7	78.1	70.3	39.2	65.8	59.5	82.8	154.8	46.7
	Vehicle	Mean	269.6	297.4	293.2	264.3	291.2	225.2	303.3	343.6	285.7
		SD	120.1	189.7	131.0	78.2	93.6	35.3	133.7	277.1	71.1
	THC-Vehicle	T Stat	-1.1777	-0.1032	-0.4219	-0.4611	-1.0409	1.8174	-0.1507	-0.3157	-0.4293
		p-value	**0.2617**	**0.9195**	**0.6805**	**0.6530**	**0.3185**	**0.0942**	**0.8827**	**0.7576**	**0.6753**
8	THC	Mean	205.0	279.1	274.6	251.1	248.4	260.4	301.2	298.0	269.9
		SD	59.3	72.9	60.5	35.2	65.3	42.0	90.8	155.7	46.0
	Vehicle	Mean	259.7	286.7	278.5	275.7	286.0	219.8	279.1	352.0	279.2
		SD	114.3	156.9	112.1	97.6	99.3	33.4	101.4	280.2	67.1
	THC-Vehicle	T Stat	-1.1241	-0.1153	-0.0824	-0.6274	-0.8366	2.0009	0.4300	-0.4456	-0.3027
		p-value	**0.2830**	**0.9101**	**0.9357**	**0.5421**	**0.4192**	**0.0685**	**0.6748**	**0.6638**	**0.7673**
16	THC	Mean	211.7	275.0	271.7	252.7	229.5	293.4	282.0	310.8	270.0
		SD	59.6	71.4	85.3	27.7	41.9	116.5	67.1	146.0	41.7
	Vehicle	Mean	261.0	286.0	279.3	292.8	286.1	213.5	284.4	297.0	275.7
		SD	123.7	175.6	128.9	133.9	104.2	30.1	126.1	167.7	68.6
	THC-Vehicle	T Stat	-0.9493	-0.1532	-0.1296	-0.7765	-1.3339	1.7579	-0.0455	0.1638	-0.1873
		p-value	**0.3612**	**0.8808**	**0.8990**	**0.4525**	**0.2070**	**0.1042**	**0.9645**	**0.8726**	**0.8546**
averaged	THC	Mean	211.0	281.0	271.1	250.6	243.9	279.6	291.3	303.5	271.1
		SD	59.0	70.8	70.6	35.8	59.2	80.9	78.6	150.6	43.7
	Vehicle	Mean	264.9	289.4	284.9	281.4	286.6	220.6	292.4	328.3	281.1
		SD	120.0	172.7	121.0	107.8	97.3	33.3	120.5	228.5	68.1
	THC-Vehicle	T Stat	-1.0661	-0.1190	-0.2611	-0.7184	-0.9921	1.7830	-0.0208	-0.2397	-0.3270
		p-value	**0.3074**	**0.9072**	**0.7985**	**0.4862**	**0.3407**	**0.0999**	**0.9838**	**0.8146**	**0.7493**

Supplemental Figure 1. ***Illustration of Segmented Linear Model.*** In this model, b11 denotes the slope of the first phase segment of the THC group and b12 the slope of segment for the second phase. The quantities b01 and b02 denote the corresponding values for the vehicle group. The two segments are joined at a change point (Kt for the THC group and Kv for the vehicle group). MLE estimation is used to estimate all four model parameters for each group. See supplemental text for details.



Supplemental Figure 2. ***Goodness-of-Fit for Segmented Model*** - smoothed versus model estimated by delay.



Supplemental Figure 3. ***Goodness-of-Fit for Segmented Model*** - smoothed versus model estimated by AUC.