Chapter 25
Interaction

1   General Purpose

The medical concept of interaction is synonymous to the terms heterogeneity and synergism. Interaction must be distinguished from confounding. In a trial with interaction effects the parallel groups have similar characteristics. However, there are subsets of patients that have an unusually high or low response. The figure below gives an example of a study in which males seem to respond better to the treatment 1 than females. With confounding things are different. For whatever reason the randomization has failed, the parallel groups have asymmetric characteristics. E.g., in a placebo-controlled trial of two parallel-groups asymmetry of age may be a confounder. The control group is significantly older than the treatment group, and this can easily explain the treatment difference as demonstrated in the previous chapter. This chapter uses simply t-tests for assessing interactions.

treatment modality
0 - control medicine
1 - new medicine

2   Schematic Overview of Type of Data File

Outcome	Exposure 1	Exposure 2
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3   Primary Scientific Question

Can t-tests adequately demonstrate interaction between the effect on the outcome of two exposure variables.

4   Data Example of Interaction

A parallel-group study of verapamil versus metoprolol for the treatment of parox-
ysmal atrial tachycardias is given below. The numbers of episodes of paroxysmal
atrial tachycardias per patient are the outcome variable.

VERAPAMIL		METOPROLOL		
MALES	52	28		
	48	35		
	43	34		
	50	32		
	43	34		
	44	27		
	46	31		
	46	27		
	43	29		
	49	25		
		464		302 766
FEMALES	38	43		
	42	34		
	42	33		
	35	42		
	33	41		
	38	37		
	39	37		
	34	40		
	33	36		
	34	35		
		368		378 746
	832	680		

Overall metoprolol seems to perform better. However, this is only true only for
one subgroup (males). SD = standard deviation, SE = standard error.

	Males	Females
Mean $_{verapamil}$ (SD)	46.4 (3.23866)	36.8 (3.489667)
Mean $_{metoprolol}$ (SD)	30.2 (3.48966)-	37.8 (3.489667)-
Difference means (SE)	16.2 (1.50554)	−1.0 (1.5606)
Difference between males and females	17.2 ($SE_1^2 + SE_1^2 = 2.166$)	

$$\text{t-value} = 17.2/2.166 = 8.\dots$$
$$p < 0.0001$$

We conclude, that there is a significant difference between the males and
females, and, thus, a significant interaction between gender and treat-efficacy.

df	One-Tail = .4 Two-Tail = .8	.25 .5	.1 .2	.05 .1	.025 .05	.01 .02	.005 .01	.0025 .005	.001 .002	.0005 .001
1	0.325	1.000	3.078	6.314	12.706	31.821	63.657	127.32	318.31	636.62
2	0.289	0.816	1.886	2.920	4.303	6.965	9.925	14.089	22.327	31.598
3	0.277	0.765	1.638	2.353	3.182	4.541	5.841	7.453	10.214	12.924
4	0.271	0.741	1.533	2.132	2.776	3.747	4.604	5.598	7.173	8.610
5	0.267	0.727	1.476	2.015	2.571	3.365	4.032	4.773	5.893	6.869
6	0.265	0.718	1.440	1.943	2.447	3.143	3.707	4.317	5.208	5.959
7	0.263	0.711	1.415	1.895	2.365	2.998	3.499	4.029	4.785	5.408
8	0.262	0.706	1.397	1.860	2.306	2.896	3.355	3.833	4.501	5.041
9	0.261	0.703	1.383	1.833	2.262	2.821	3.250	3.690	4.297	4.781
10	0.260	0.700	1.372	1.812	2.228	2.764	3.169	3.581	4.144	4.587
11	0.260	0.697	1.363	1.796	2.201	2.718	3.106	3.497	4.025	4.437
12	0.259	0.695	1.356	1.782	2.179	2.681	3.055	3.428	3.930	4.318
13	0.259	0.694	1.350	1.771	2.160	2.650	3.012	3.372	3.852	4.221
14	0.258	0.692	1.345	1.761	2.145	2.624	2.977	3.326	3.787	4.140
15	0.258	0.691	1.341	1.753	2.131	2.602	2.947	3.286	3.733	4.073
16	0.258	0.690	1.337	1.746	2.120	2.583	2.921	3.252	3.686	4.015
17	0.257	0.689	1.333	1.740	2.110	2.567	2.898	3.222	3.646	3.965
18	0.257	0.688	1.330	1.734	2.101	2.552	2.878	3.197	3.610	3.922
19	0.257	0.688	1.328	1.729	2.093	2.539	2.861	3.174	3.579	3.883
20	0.257	0.687	1.325	1.725	2.086	2.528	2.845	3.153	3.552	3.850
21	0.257	0.686	1.323	1.721	2.080	2.518	2.831	3.135	3.527	3.819
22	0.256	0.686	1.321	1.717	2.074	2.508	2.819	3.119	3.505	3.792
23	0.256	0.685	1.319	1.714	2.069	2.500	2.807	3.104	3.485	3.767
24	0.256	0.685	1.318	1.711	2.064	2.492	2.797	3.091	3.467	3.745
25	0.256	0.684	1.316	1.708	2.060	2.485	2.787	3.078	3.450	3.725
26	0.256	0.684	1.315	1.706	2.056	2.479	2.779	3.067	3.435	3.707
27	0.256	0.684	1.314	1.703	2.052	2.473	2.771	3.057	3.421	3.690
28	0.256	0.683	1.313	1.701	2.048	2.467	2.763	3.047	3.408	3.674
29	0.256	0.683	1.311	1.699	2.045	2.462	2.756	3.038	3.396	3.659
30	0.256	0.683	1.310	1.697	2.042	2.457	2.750	3.030	3.385	3.646
40	0.255	0.681	1.303	1.684	2.021	2.423	2.704	2.971	3.307	3.551
60	0.254	0.679	1.296	1.671	2.000	2.390	2.660	2.915	3.232	3.460
120	0.254	0.677	1.289	1.658	1.980	2.358	2.617	2.860	3.160	3.373
∞	0.253	0.674	1.282	1.645	1.960	2.326	2.576	2.807	3.090	3.291

The t-table has a left-end column giving degrees of freedom (≈ sample sizes), and two top rows with p-values (areas under the curve = p - values), one-tail meaning that only one end of the curve, two-tail meaning that both ends are assessed simulataneously. The t-table is, furthermore, full of t-values, that, with ∞ degrees of freedom, are equal to z-values (Chap. 36). The t-values are to be understood as mean results of studies, but not expressed in mmol/l, kilograms, but in so-called SEM-units (Standard error of the mean units), that are obtained by dividing your mean result by its own standard error. With many degrees of freedom (large samples) the curve will be a little bit narrower, and more in agreement with nature.

With 40–2 = 38 degrees of freedom (close to 40), and a t-value = 17.2/
2.166 = 8. . .. and thus larger than 3.551, the two-tail p -value is < 0.001.

5   Conclusion

T-tests can readily be applied for assessing interactions between the effects on the
outcome of two exposure variables. Interaction can also be assessed with analysis of
variance and regression modeling. These two methods are the methods of choice in
case you expect more than a single interaction in your data. They should be carried
out on a computer.

6   Note

More background, theoretical and mathematical information of interaction assess-
ments is given in Statistics applied to clinical studies 5th edition, Chap. 30, Springer
Heidelberg Germany, 2012, from the same authors.