

Digit Symbol Substitution Test Reveals Preservation of Cognitive Reserve After Phaxan™ but not After Propofol Anesthesia

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Introduction:

Phaxan™ (phax) is an aqueous solution of alphaxalone. A recent study comparing the properties of phax and propofol used the scores from repeated performance of the Digit Symbol Substitution Test (DSST) to compare recovery after anesthesia. A literature search revealed that DSST performance increases stepwise with repeat testing paradigms like that used in the phax study, and this stepwise increase from one test score to the next indicates "Cognitive Reserve" in the test subjects¹. Data from repeat DSST were analysed to investigate cognitive reserve after anesthesia with phax and propofol.

Methods:

The study (ACTRN12611000343909) was randomised, double blind, comparing propofol and phax using a Bayesian algorithm to determine dose equivalence for effects on the bispectral index (BIS). 24 male volunteers ASA grade 1 gave written informed consent (n=12 per group; propofol, phax). DSST was measured every 15 minutes for one hour before and 35, 50, 65 and 80 minutes after anesthesia with phax or propofol. The numbers of correct answers at each of the 8 testing times were standardised for each subject as % of the fourth measurement for that individual (last of the pre anesthetic readings). DSST measurements published for normal individuals of the same age (Zihl et al¹) were similarly treated for comparison. Values so calculated for each group (phax, propofol and Zihl et al¹) were subjected to linear regression for measurements 1-4 and 5-8. Thus improvement of DSST scores in normal subjects¹ could be compared with data before (measurements 1-4) and after (measurements 5-8) equipotent doses of phax and propofol.

Results:

Eleven subjects in each group were anesthetised to BIS value ≤ 50: propofol 2.43 (3.00-1.87); phax 0.5 (0.55-0.47); median, IQ mg/kg [figure 1]. The time to achieve BIS < 50 [mean (95% CI) was 36 (22-45) seconds for propofol and 36 (28-44) seconds in phax-treated subjects; n = 11 each. A cohort of 9 phax-treated subjects and 8 propofol-treated subjects received doses of drug that were within the IQ range [figure 1]. These doses caused the same depth and duration of anesthesia as assessed by the BIS [figure 2], the lowest average BIS reached being 30-31 for both propofol and phax subjects and mean time to BIS recovery to 90 being 21 minutes for both agents. Recovery of pre anesthetic performance in the DSST occurred 35 minutes after drug injection for both phax and propofol. More detailed analysis of the repeated measurements of DSST and comparison with previously published values¹ are shown in figure 3.

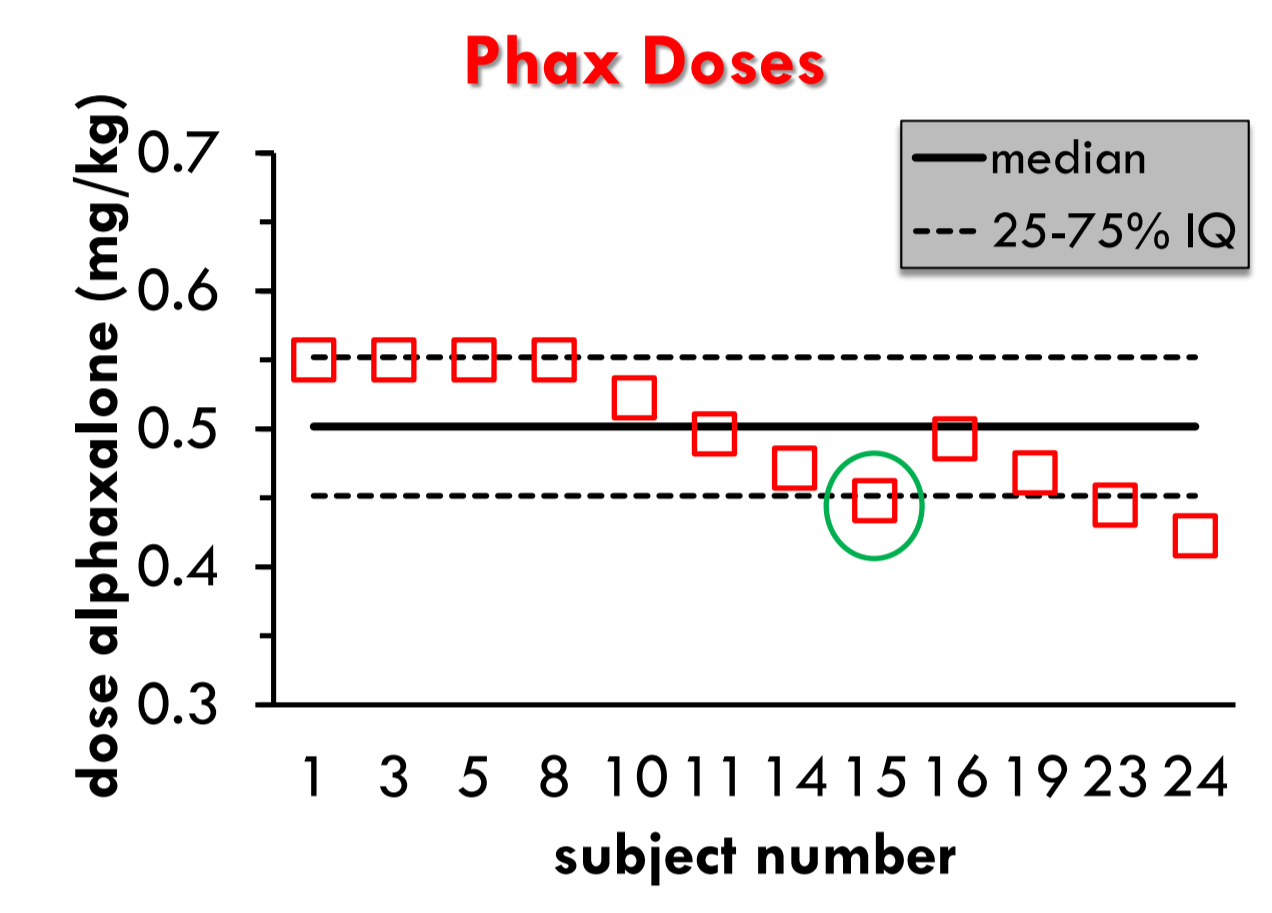
There were significant improvements in DSST scores for subjects in the phax and propofol groups prior to anesthesia equal with published data for normal subjects¹ [figure 3]. Phax treated subjects continued to improve their DSST scores after anesthesia (measurements 5-8) at the same rate as those published for normal subjects¹ whereas propofol treated subjects did not change their performance significantly even 80 minutes after drug injection.

Conclusions:

Phax causes fast onset short duration anesthesia equivalent to propofol. Using DSST as a measure of recovery from sedation, phax and propofol treated subjects recovered their pre anesthetic performance equally by 35 minutes after drug injection. However, under the repeat testing paradigm used for DSST, there is normally significant improvement in performance from test 5 through 8¹. This normal progression occurred with phax but not after propofol anesthesia. These results suggest that cognitive reserve as defined by Zihl et al¹ is preserved after phax anesthesia but it is compromised for at least 80 minutes after propofol. The relevance and longer term implications of these findings warrant further study.

Reference:

1.Zihl J, et al 2014; Cognitive Reserve in Young and Old Healthy Subjects: Differences and Similarities in a Testing-the-Limits Paradigm with DSST. PLoS ONE 9(1): e84590. * figure 1 DSST results from 140 subjects' 10 consecutive tests in Zihl et al. was redrawn for the central panel of figure 3.



Summary of doses within the median and IQ range of doses that led to BIS < 50

phax		propofol
0.52	median	2.85
0.49	n	8
0.55	IQ	3.00

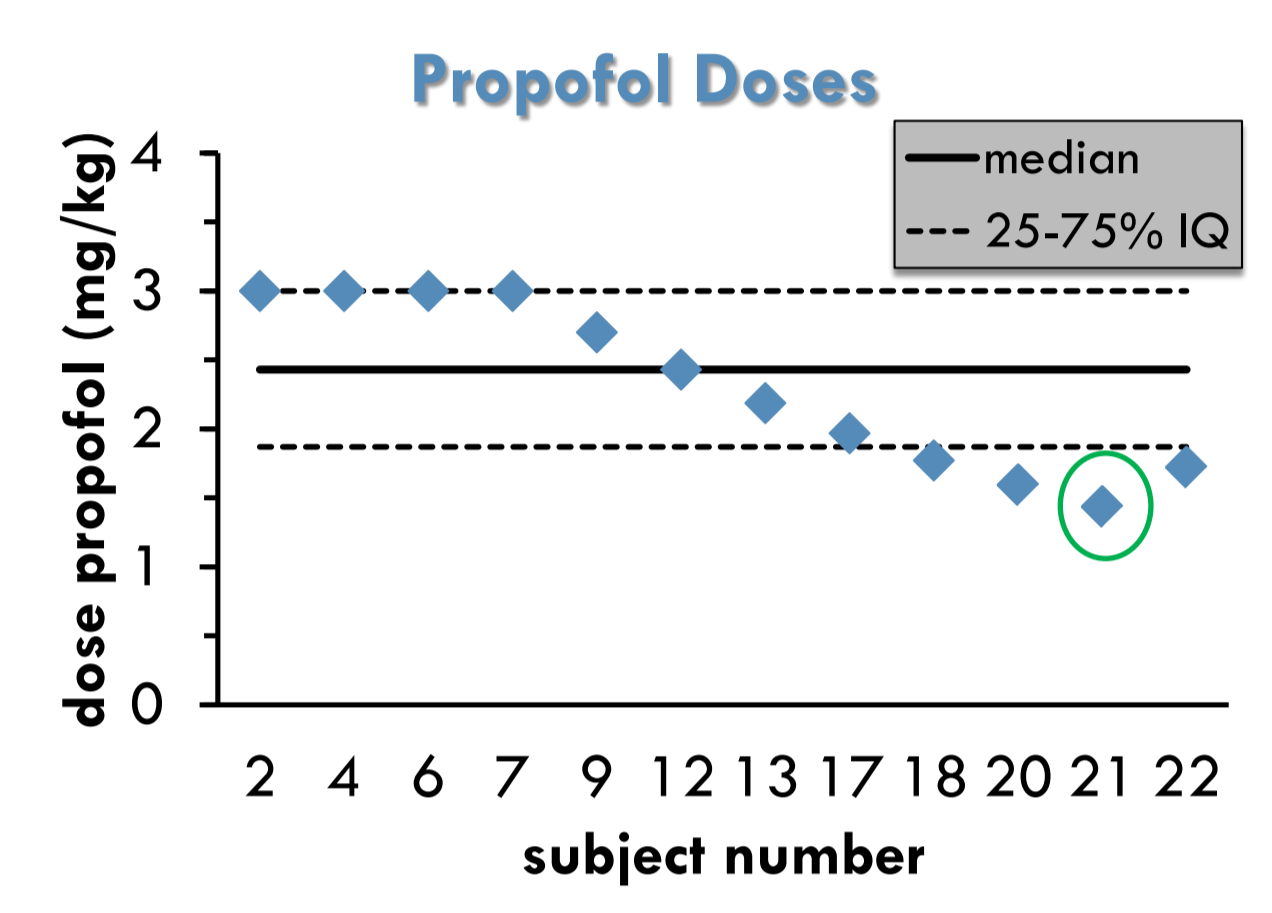
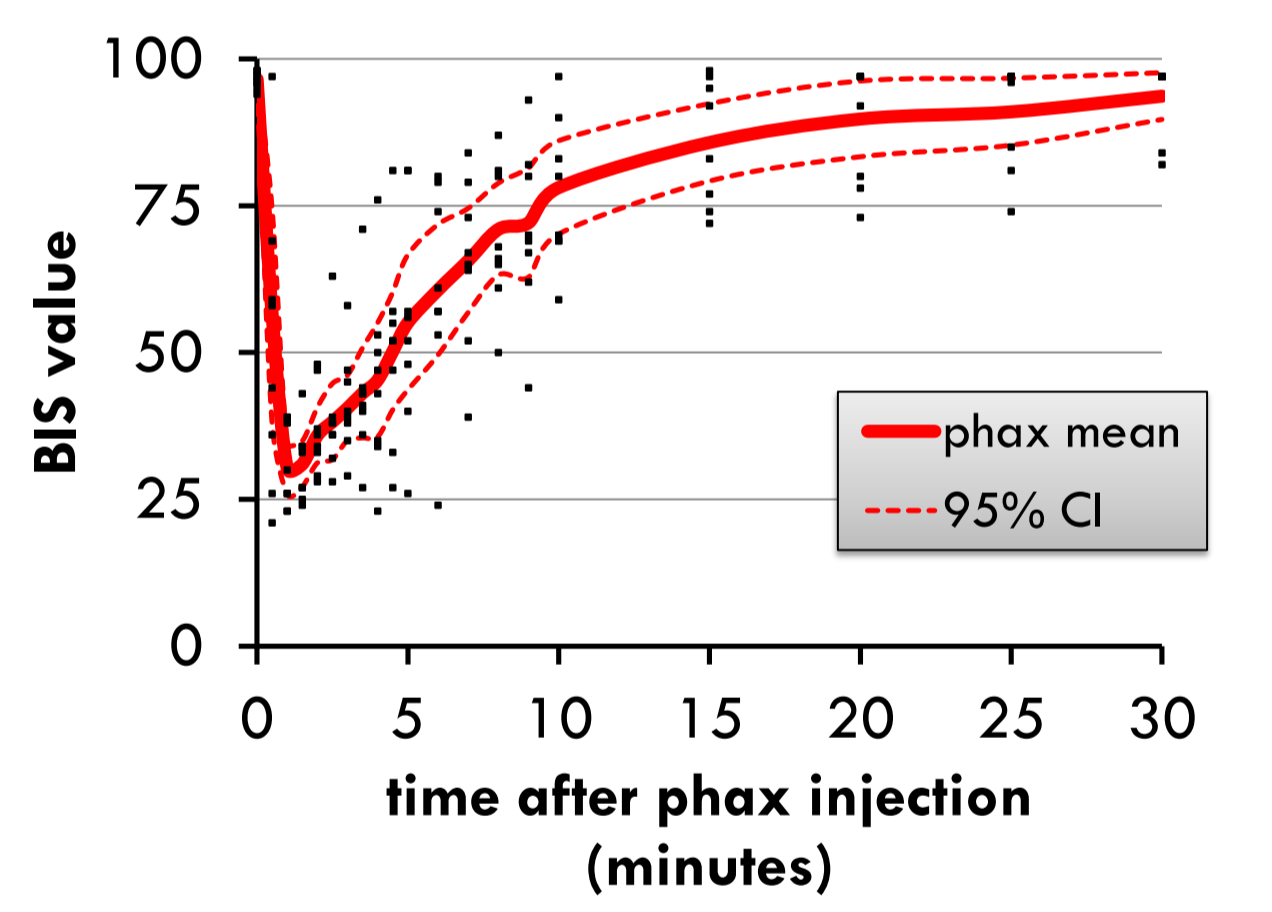


Figure 1: The graphs show the dose of drug given to each subject (Y axis) v the subject trial number, one graph for propofol subjects and one for phax-treated subjects. All subjects reached a BIS<50 except subject 15 (phax) and subject 21 (propofol) shown by a green circle around the datum point. These graphs show the effect of the Bayesian design - a progressive 10% dose reduction until one subject did not reach a BIS<50 (subjects 15 and 21). Subjects 16 and 22 had 20% increase in dose and thereafter subjects attained BIS<50 so subsequent subjects had a 10% dose reduction. The doses of drug that caused BIS<50 were combined for each group (N=11 each for phax and propofol) to calculate median and interquartile range shown by horizontal solid and dashed lines on the graphs. The subjects that received doses within that interquartile range (9 phax and 8 propofol subjects) were used for comparison of the two drugs' effects on the time response relationships of BIS and DSST. The table shows the median and IQ range for the doses of those subjects used in the BIS and DSST comparisons.



Time to recover BIS = 90 (minutes)

phax		propofol
21.00	mean	21.00
10.10	sd	9.20
9	n	8
p = 0.9999 unpaired t test		

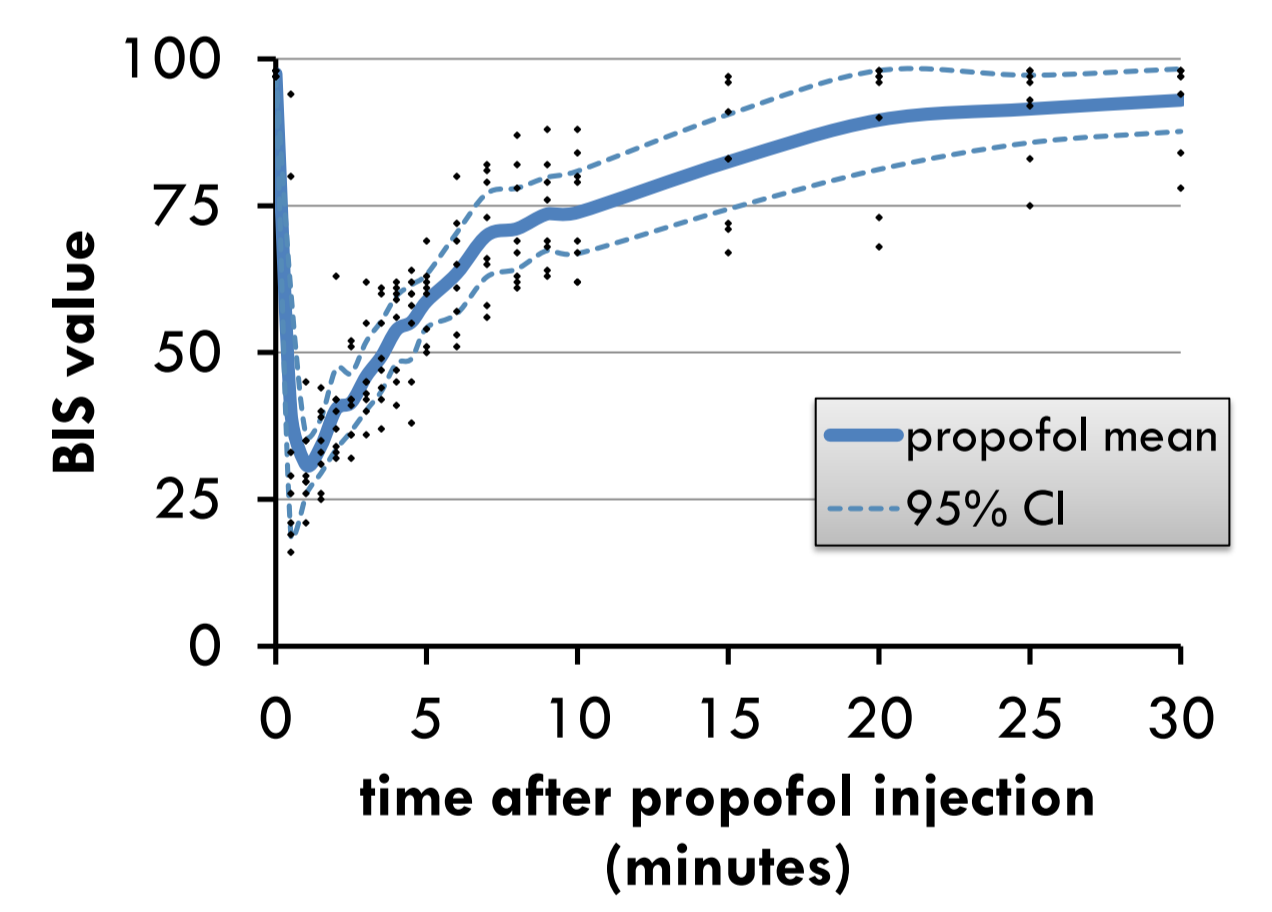


Figure 2: The graphs show the BIS measurements for the nine subjects that received phax 0.52 (0.49-0.55) [median (25/75 IQ)mg/kg] and the eight subjects that received propofol 2.85 (2.37-3) [median (25/75 IQ)mg/kg]. Both anesthetics caused the same speed of onset and offset and depth of anesthesia. Points show individual data, solid line the mean, and dotted lines 95% confidence limits.

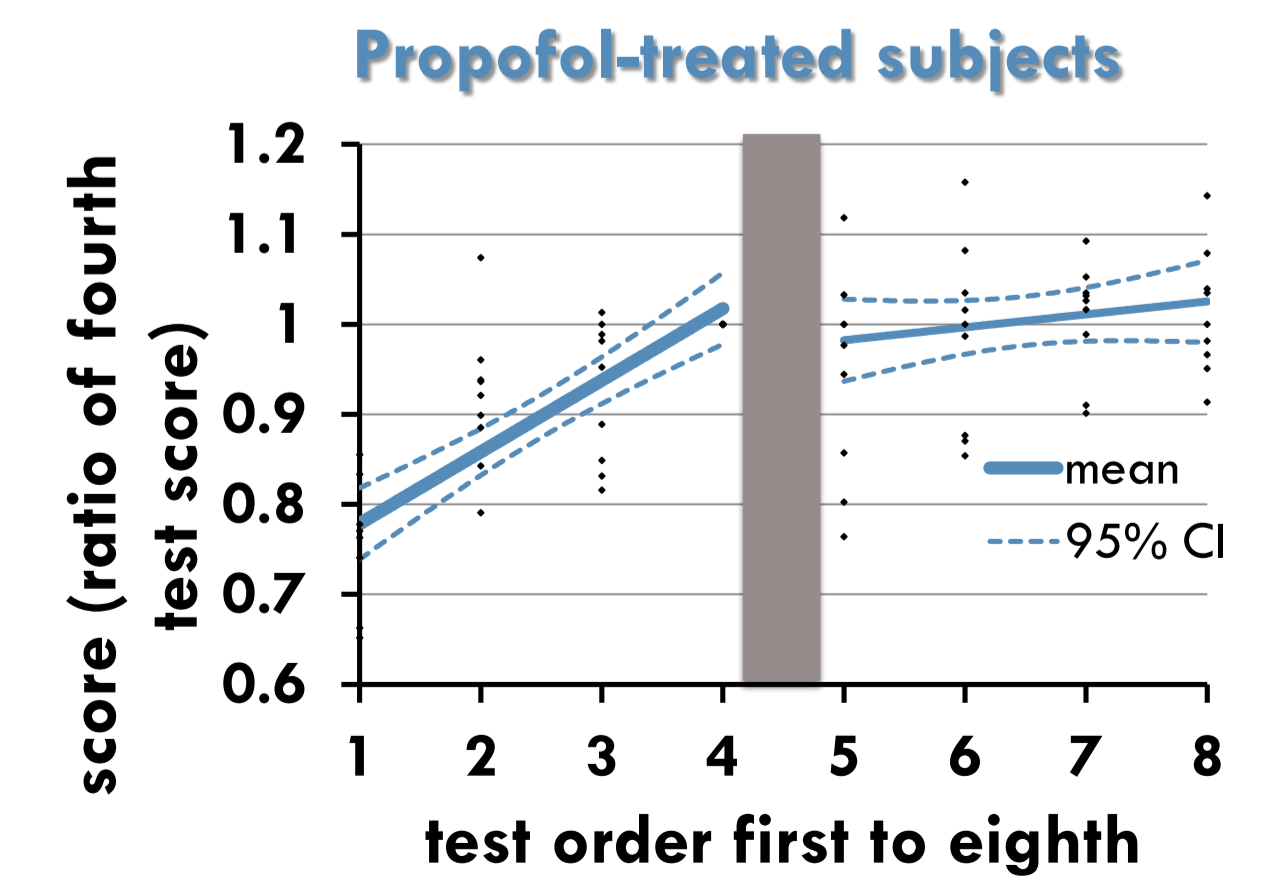
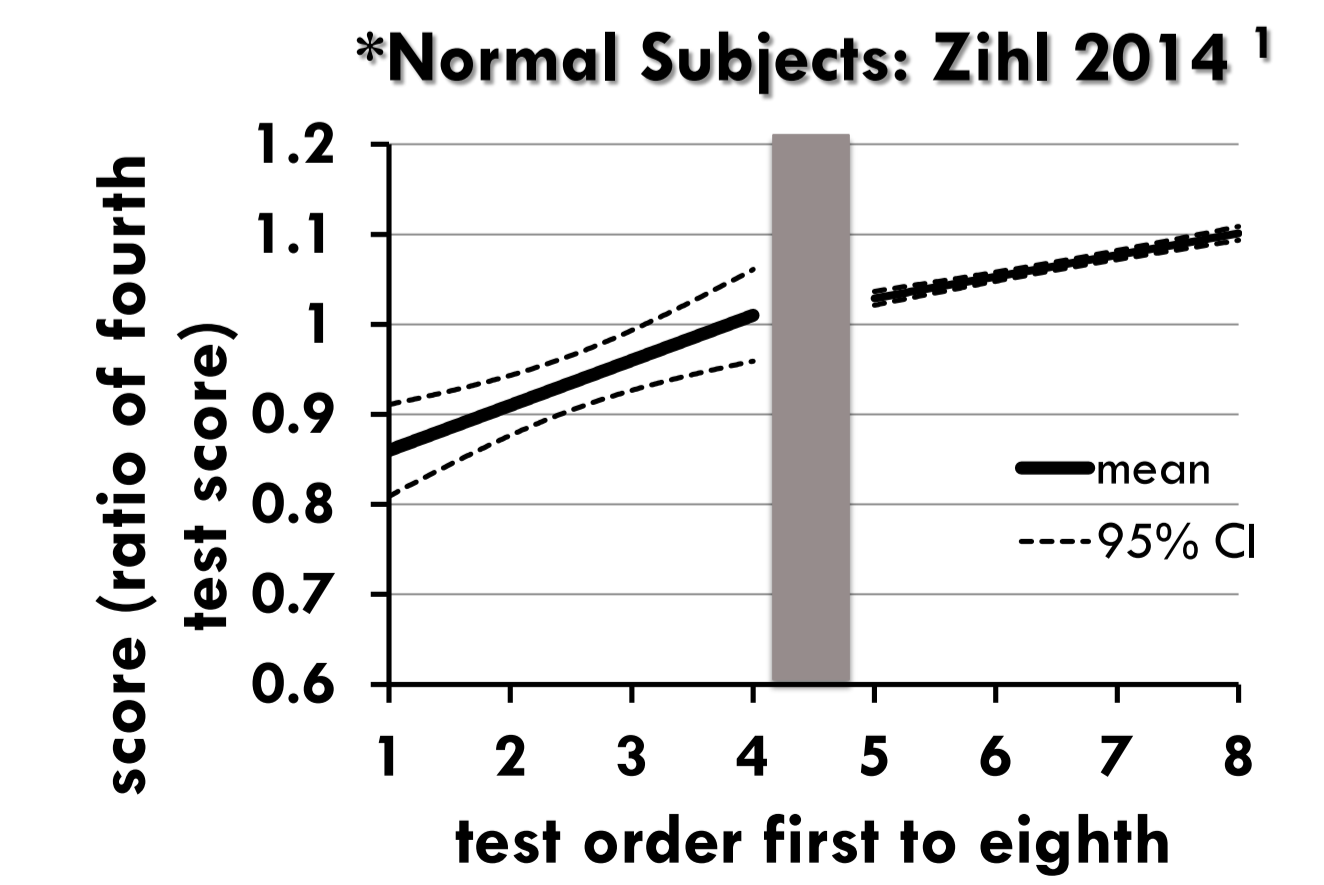
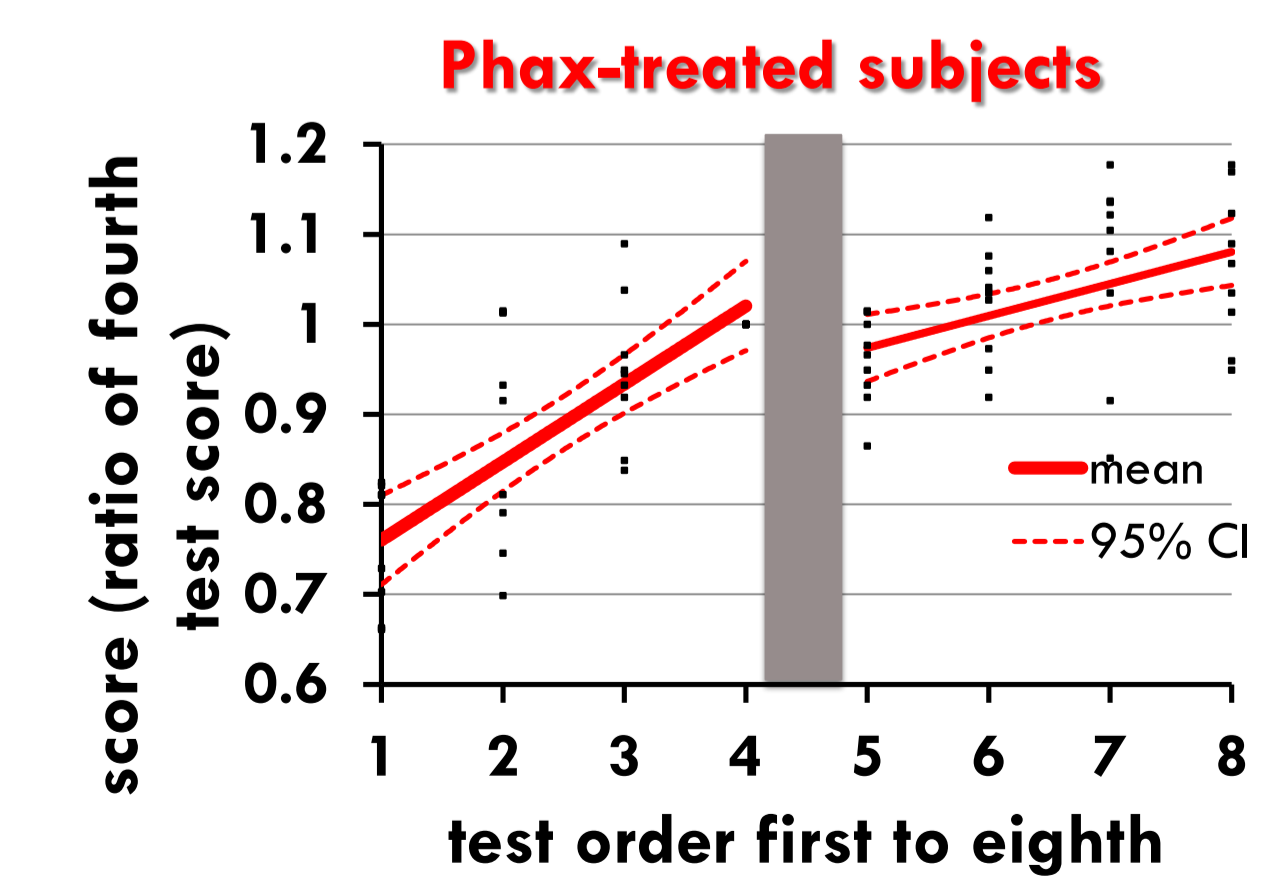


Figure 3: Linear regressions of DSST results (GraphPad Prism 6):
tests 1-4 (pre-anesthetic): all slopes significantly different from zero :
 Zihl (normal subjects) y = 0.0491x + 0.8154; R² = 0.9451; p=0.01
 propofol treated subjects y = 0.08x + 0.68; R² = 0.87; p=0.005
 phax treated subjects y = 0.09x + 0.67; R² = 0.94; p=0.005
tests 5-8 (post-anesthetic): only normal (Zihl subjects¹) and phax subjects have slopes significantly greater than zero :
 Zihl (normal subjects) y = 0.03x + 0.88; R² = 0.98; p=0.01
 propofol treated subjects y = 0.01x + 0.91; R² = 0.94; **NS**
 phax treated subjects y = 0.04x + 0.8; R² = 0.88; p=0.005

Recovery to pre anesthetic DSST performance levels occurred fully and equally after phax and propofol at test 5. Normal cognitive reserve, as measured by a continuing improvement in DSST score only occurred after phax anesthesia and NOT after propofol anesthesia, extending to 80 minutes post drug injection. Cognitive recovery is better after anesthesia with phax than after anesthesia with propofol.