

THE RELATION BETWEEN PLACEBO EFFECT AND SEROTONIN TRANSPORTER GENETIC POLYMORPHISM : A DOUBLE-BLIND CLINICAL TRIAL IN HEALTHY ADULTS

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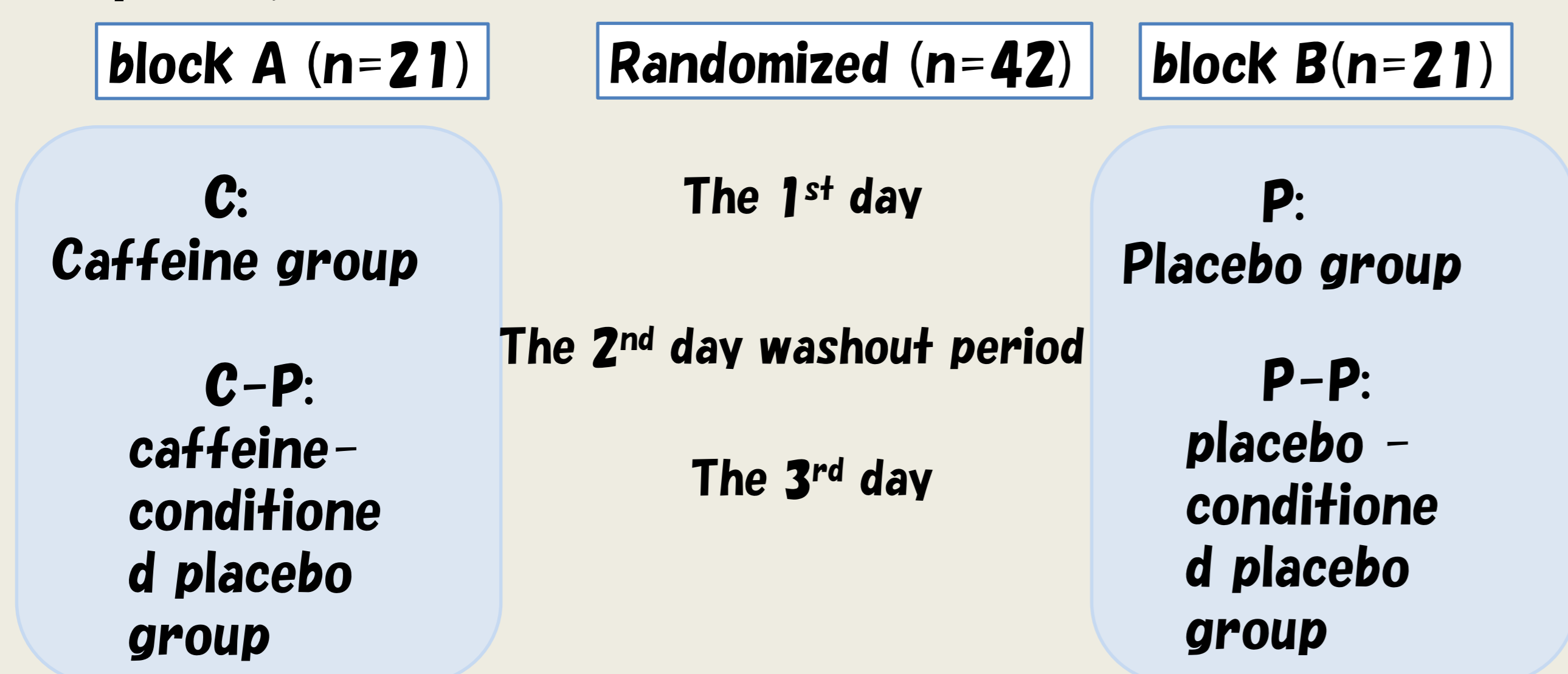
Objective

Clinical benefit of drugs for patients is not only through pharmacological mechanisms, but also through non-pharmacological action (placebo effect). The placebo effect may involve expectation based on previous experience (conditionality) (Finniss et al. 2010). In terms of the placebo effect, individuals can be grouped into two categories: responders and non-responders. There are several reports that the placebo effect was involved in brain activity and gene polymorphisms of chemical mediator (Hall et al. 2015). To study the hypothesis, we conducted a clinical trial using caffeine in order to examine whether responder or non-responder to placebo is associated with blood flow changes in the prefrontal area of the brain and particular polymorphisms of the serotonin transporter-linked polymorphic region (5-HTTLPR).

Methods

Study design

The study was designed to compare the effects of 200mg dosage of placebo (lactose) and caffeine. Participants were block-randomized (block size of two) to randomized single studies. The block A participants took active drug (caffeine group) on the first day, and placebo on the third day (caffeine-conditioned placebo group), while the block B participants took placebo (placebo group) on the first and third days (placebo-conditioned placebo group). The second day was a washout period.



The preparation of test drugs

We prepared one capsule contained 100 mg lactose and caffeine.

Evaluation items

Subjective indicators:

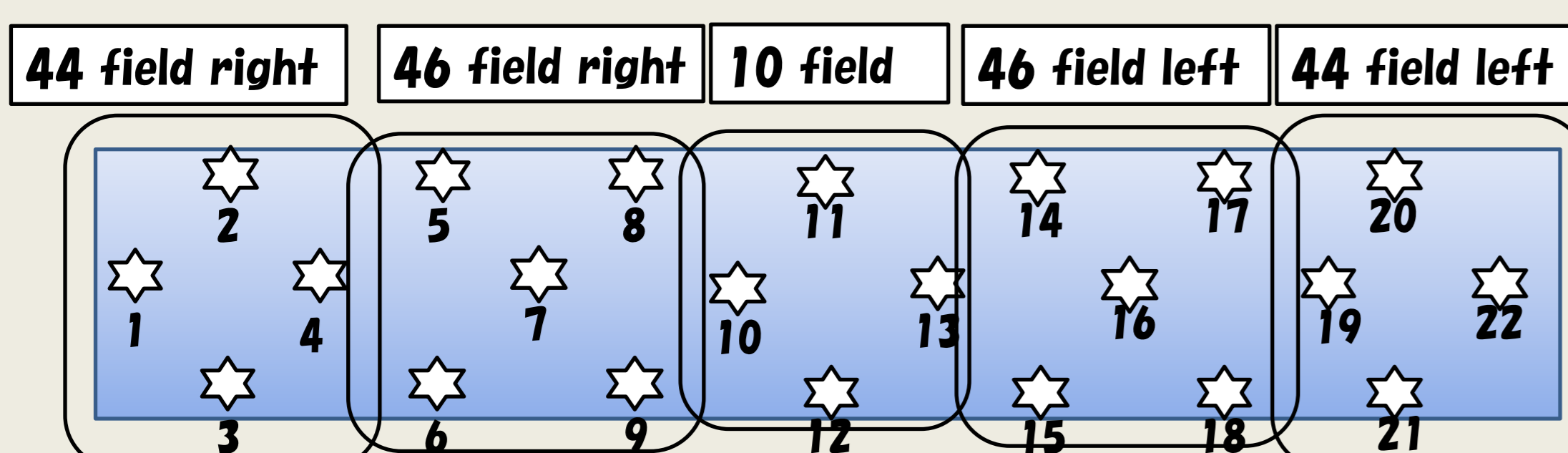
Self-reported feelings of drowsiness on established scales (Stanford Sleepiness Scale). Feeling of drowsiness - VAS (Visual analogue scale).

Objective indicator:

Activity in the prefrontal area of the brain was measured in terms of blood flow using near-infrared spectroscopy (NIRS). Polymorphisms of 5-HTT were evaluated by PCR methods. This study was approved by the Ethics Committee of our University.

NIRS measurement

NIRS noninvasively measures relative changes in the concentrations and blood flow is increased in the corresponding area.

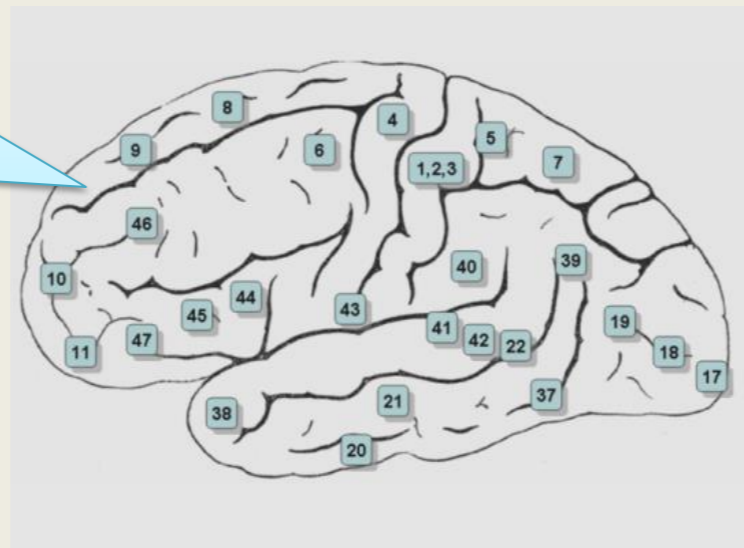


Scheme. Schematic illustration of the NIRS set-up

NIRS was used to measure blood volume at 22 points marked with stars. The 22 points are located in the following fields of Brodmann's brain map.

- 1~4 stars : 44 field (right)
- 5~9 stars : 46 field (right)
- 10~13 stars : 10 field
- 14~18 stars : 44 field (left)
- 19~22 stars : 46 field (left)

46: Prefrontal cortex
It controls a working memory and attention concentration and judgment



Serotonin transporter genotype

The S/S and S/L homo- and hetero-genotypes were identified.

Results & Discussion

Genotyping

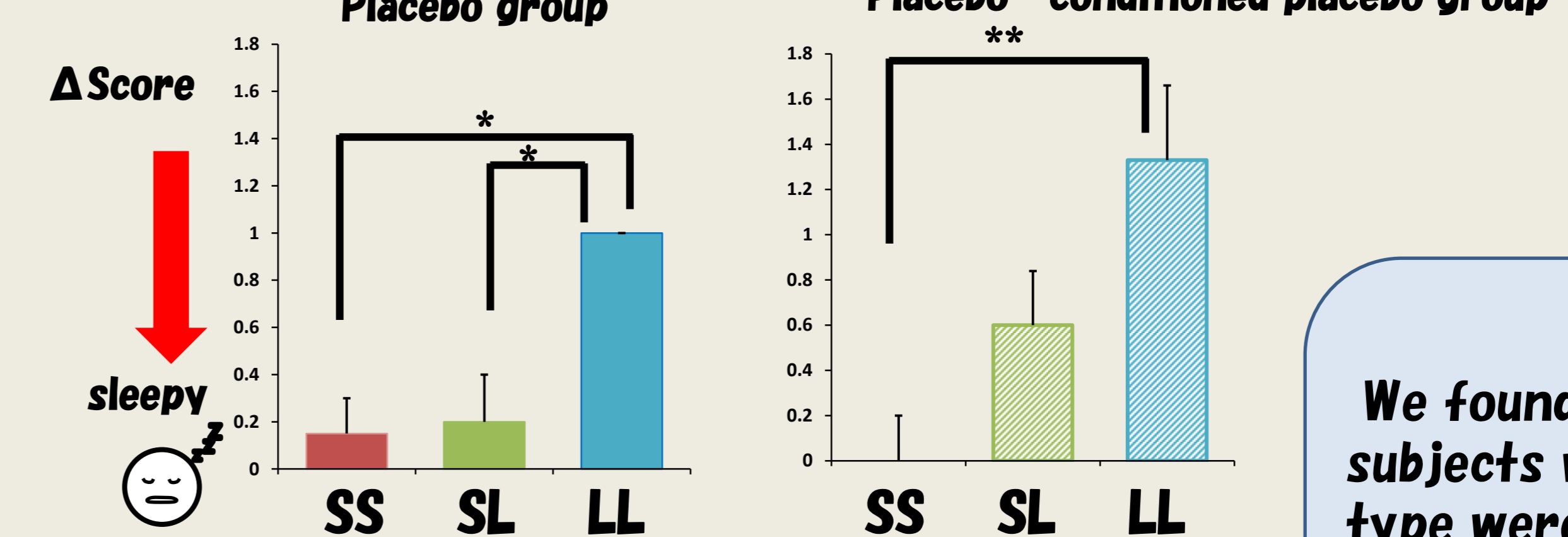
SS type: 52.4 % (n=22)

SL type: 40.5 % (n=17)

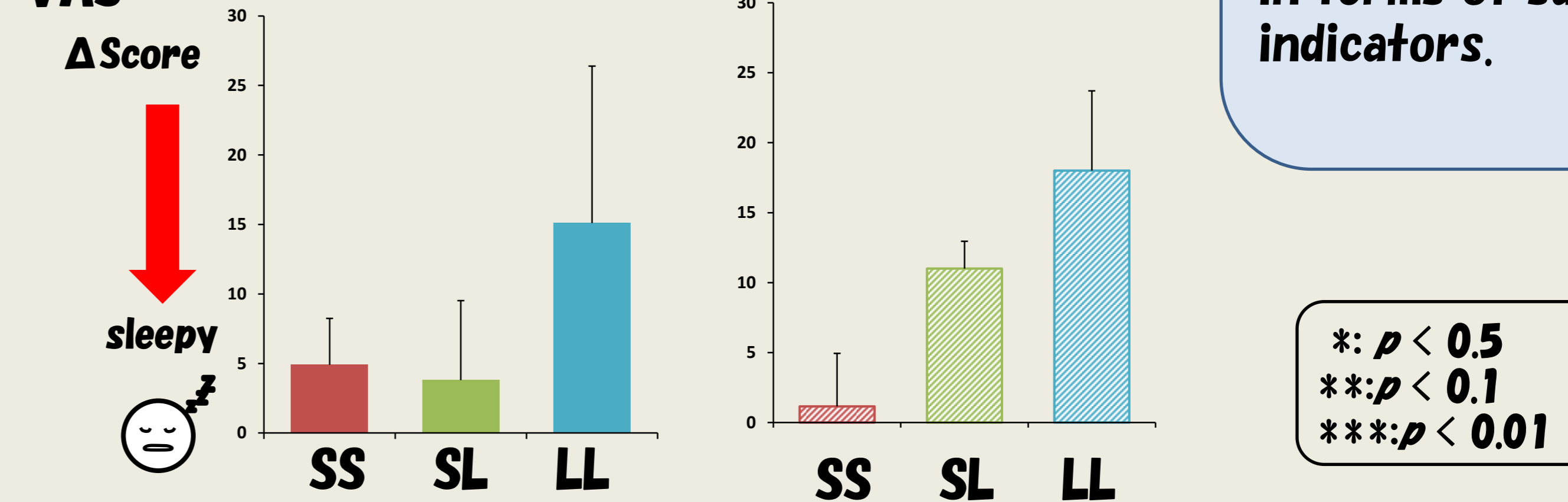
LL type: 7.10 % (n= 3)

The frequency of the L/L genotype in Japanese people is 3.2%, whereas it is 32.2% in Americans. As for S/S type, the frequency is 61.1% in Japanese people, but 18.8% in Americans (Chiao and Blizinsky 2010). There may be an ethnic difference in placebo reaction.

SSS

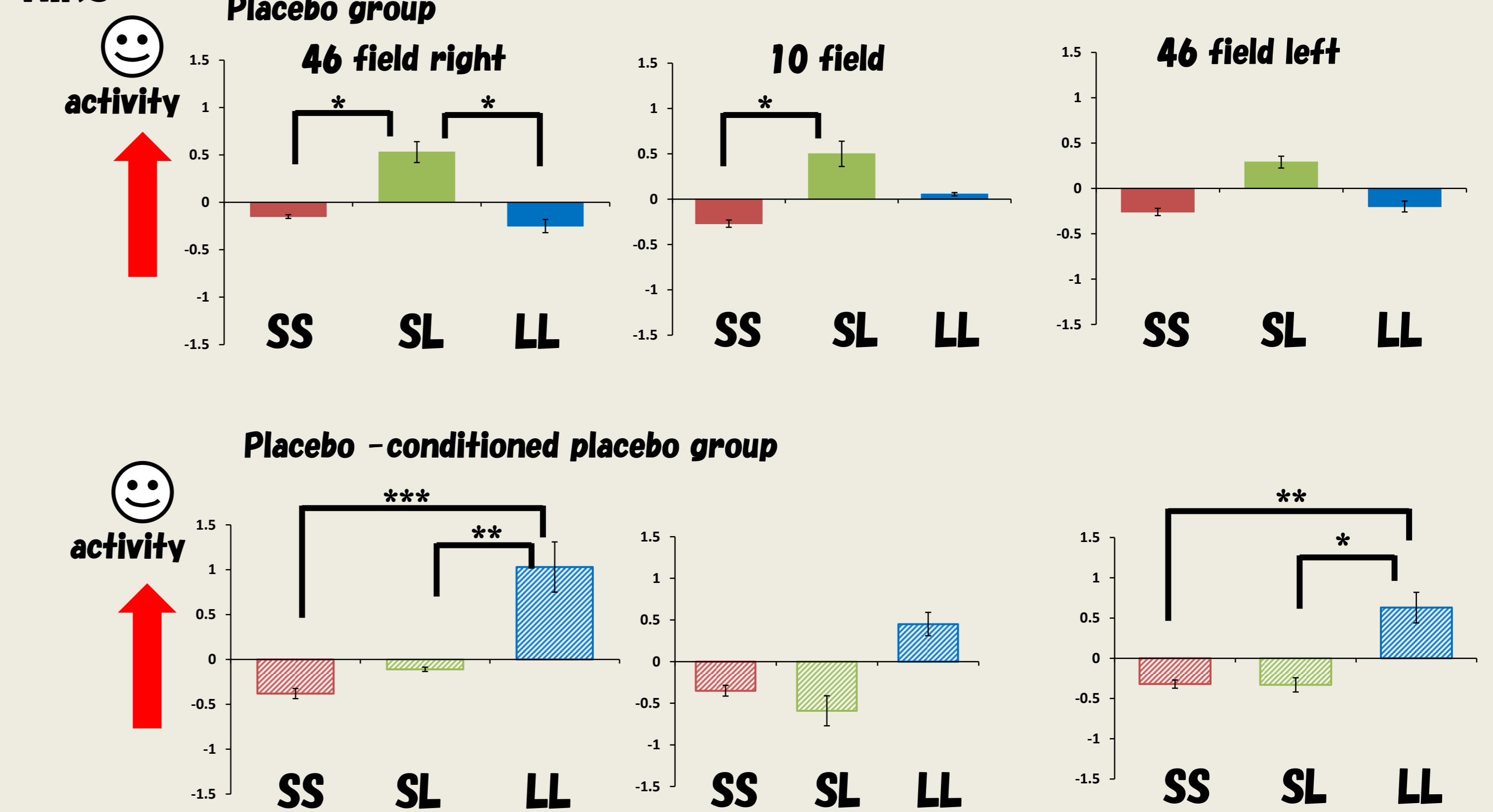


VAS



We found that subjects with the L/L type were susceptible to the placebo effect in terms of subjective indicators.

NIRS



NIRS measurement of L/L type in the placebo conditionality group on the third day also showed increased blood flow in the 46 field area of the brain prefrontal region as compared with S/S and S/L type.

Conclusion

Our results indicate that subjects with L/L genotype showed a significantly greater placebo response in terms of both self-reported feeling of drowsiness and blood flow in the prefrontal area of the brain associated with working memory (46 area). And the L/L genotype of 5-HTTLPR, which is rare in Japanese (3.2%) but common in Americans (32.2%) may be associated with a greater placebo effect.

Acknowledgements

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