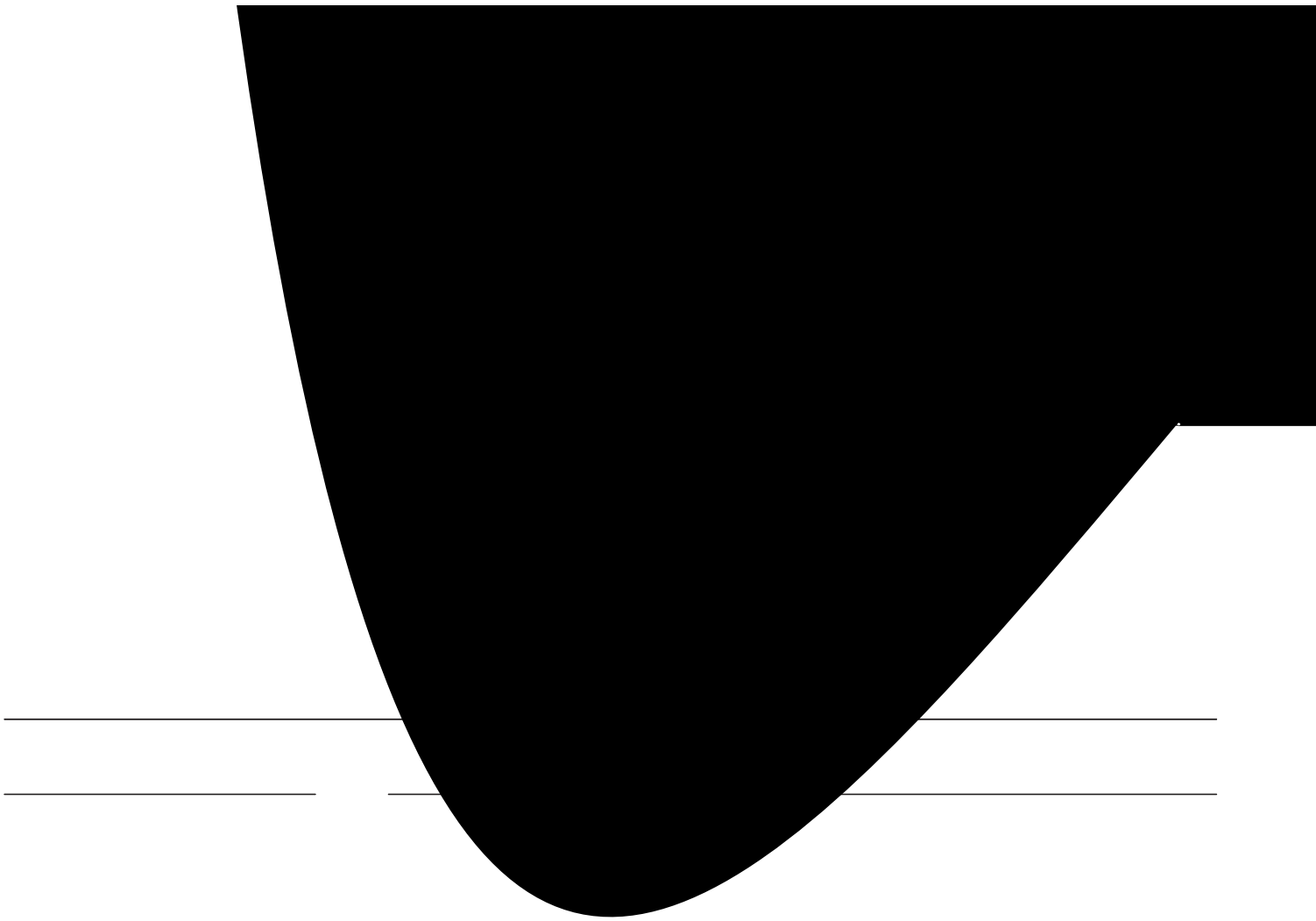

One key determinant of individual differences may lie in genetic variation of the serotonin transporter (5-HTT), a monoamine transporter protein that returns serotonin (5-HT) from the synaptic cleft to the presynaptic neuron. 5-HTT is thought to play a key role in nociceptive processing, as evidenced by 5-HTT knockout rodent studies and human

et al., 2015), citalopram administration should produce stronger reductions in pain-related brain activity and NPS responses in l/l homozygotes. Finally, stronger brain responses to painful shock—an index of individual differences in hypersensitivity—should predict the magnitude of beneficial citalopram effects on pain. These last two points constitute two effects important for personalized medicine: (a) an interaction between genotype and treatment on pain-related brain responses, and (b) prediction from pain-related brain responses to individual differences in citalopram effects on pain within and across genetic groups, respectively.

2. Materials and methods

2.1. Participants

Fifty-six healthy males, recruited from a pool of 901 university students genotyped for 5-HTTLPR (see below), participated in this study as paid volunteers. Two participants finished the first scanning session, but skipped the second session. Four participants were excluded due to excessive head movement. Thus the final data analyses were performed on 50 participants balanced for 5-HTTLPR genotype: 25 male s/s homozygotes (18–23 years, 19.5 ± 1.7 years) and 25 male l/l homozygotes

100-Hz train of 0.5 ms electrical pulses with a duration of 3 s. The current intensity for ‘non-painful’ and ‘painful’ shocks was determined on an individual basis. Shocks, starting from 0.2 mA, were applied to participants and were repeated, raising 0.2 mA each time. The current inten-

perception, we identified a significant Genotype × Treatment interaction on NPS responses ($F(1,47) = 6.92$ $p = 0.012$, Fig. 3A). Post hoc analyses confirmed that citalopram significantly decreased NPS responses in l/l ($F(1,23) = 6.57$, $p = 0.018$, Fig. 3) but not in s/s homozygotes ($F(1,23) = 1.95$, $p = 0.18$). These results suggested that the Genotype × Treatment interaction was also manifested at the level of

reports. If so, the measurement of baseline pain-related brain responses can be useful in predicting treatment efficacy and guiding treatment decisions. More importantly, we were interested in whether such prediction was moderated by the 5-HTTLPR genotype, which may also be a critical factor. Brain sensitivity to painful stimulation, genotype, and their interaction, were entered as regressors for the regression analyses of the treatment efficacy.

These analyses showed that the relationship between cerebellum/AI sensitivity to painful shocks under placebo and the treatment efficacy was significantly moderated by 5-HTTLPR genotype (right AI: β = 0.47, p = 0.001; left cerebellum: β = 0.55, p = 0.002), suggesting that the interaction between 5-HTTLPR genotype and cerebellum/AI activity was a good predictor for the citalopram treatment efficacy. Post-hoc analyses further revealed that, in l/l homozygotes, citalopram treatment decreased pain reports to a greater degree in those who showed stronger cerebellum/AI activity to painful shocks under placebo (right AI: β = 0.54, p = 0.006, Fig. 4A; left cerebellum: β = 0.44, p = 0.027; Fig. 4B). In contrast, citalopram treatment decreased pain reports to a greater degree in those who showed weaker cerebellum/AI activity to painful shocks under placebo in s/s homozygotes (right AI: β = −0.43, p = 0.031, Fig. 4A; left cerebellum: β = −0.47, p = 0.017; Fig. 4B).

We further found that the relationship between NPS responses to

citalopram effects on pain reports. Stronger cerebellum/AI activity to painful shocks (without treatment) predicted greater citalopram-induced pain-report reduction in l/l homozygotes. However, for s/s homozygotes, citalopram treatment decreased pain reports to a greater degree in those who showed weaker cerebellum/AI activity to painful shocks. These genetic modulation effects were paralleled with significant Genotype × Treatment interactions on the NPS — a pattern of activity across multiple brain regions associated with physical pain perception. These results indicate that one's genetic makeup interacts with baseline neural responses to pain to influence the effect of citalopram on pain perception. The current finding has important implications for patient stratification and increasing efficacy of pain treatment.

The current

indicate a lack of 5-HTTLPR and citalopram influences on affective states