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A stratified precision medicine trial targeting α_{2A}-adrenergic receptor agonism as a treatment for the cognitive biotype of depression

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Cognitive impairments are a major contributor to psychosocial dysfunction in major depressive disorder, yet mechanistically selective treatments targeting these impairments are lacking. Here, in line with a precision medicine approach, we evaluated guanfacine immediate release (GIR), an α_{2A} receptor agonist, as a novel treatment aimed at enhancing cognitive control circuit function and behavioral performance in a neurobiologically defined subtype of depression, the cognitive biotype NCT04181736. This biotype was prospectively identified based on impairments in both cognitive control circuitry and associated behavioral performance. Seventeen participants with major depressive disorder meeting these prospective criteria completed 6–8 weeks of GIR treatment (target dose of 2 mg per night), consistent with our preregistered per-protocol analysis plan. GIR significantly increased activation and connectivity within the cognitive control circuit. The clinical response (defined as a ≥50% reduction on the 17-item Hamilton Depression Rating Scale (HDRS)) was achieved by 76.5%, of patients, exceeding conventional antidepressant response rates, and 84.6% also achieved remission (HDRS score of ≤7). GIR also led to significant improvements in cognitive control performance, global life satisfaction and quality of life. Here we demonstrate both clinical efficacy and circuit target engagement of GIR as a mechanistically selective treatment for the cognitive biotype of depression.

Cognitive impairment is a core feature of major depressive disorder (MDD), often persisting even after symptom remission and contributing to poor functional outcomes, heightened risk of suicide and treatment resistance. As many as one-third of individuals with MDD do not achieve full recovery despite multiple antidepressant trials[1,2], and for these patients, the burden is profound, including chronic disability, poor quality of life and elevated suicidality[3]. Even among treatment responders, residual cognitive dysfunction remains common and can be severely debilitating[4–8].

In this study, we focus on cognitive impairment in MDD, which is marked by dysfunction in neural circuits underlying cognitive control. This impairment is a key contributor to nonresponse to conventional antidepressants[9,10], as well as to poor functional and social outcomes and elevated suicide risk[11,12]. Our prior research identified a distinct subgroup of MDD, termed the 'cognitive biotype+'[12], present in approximately 27% of patients. This biotype is defined by significantly reduced task-evoked activation and functional connectivity within the cognitive control circuit, particularly in the dorsolateral prefrontal cortex

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(dLPFC) and dorsal anterior cingulate cortex (dACC), alongside measurable impairments on tasks assessing cognitive control. Importantly, individuals with this biotype show poor response to standard antidepressant treatments and report poor quality of life[12]. We propose that this subgroup requires mechanistically targeted treatments that specifically address underlying circuit dysfunction.

The standard drug development pipeline in psychiatry has produced only one FDA-approved therapy specifically addressing cognitive deficits in depression: vortioxetine[13]. However, the precise mechanism by which this multimodal drug enhances cognitive function remains unclear. Vortioxetine inhibits the serotonin reuptake transporter and directly modulates multiple serotonin receptors, acting as a partial agonist at 5-HT1B receptors, a full agonist at 5-HT1A receptors and an antagonist at 5-HT3, 5-HT1D and 5-HT7 receptors. It also indirectly modulates several other neurotransmitter systems, including dopaminergic, noradrenergic, histaminergic, cholinergic, GABAergic and glutamatergic systems[14]. Multitarget drugs such as vortioxetine are typically tested within conventional drug development frameworks that rely on heterogeneous patient samples and broad clinical outcome measures. This approach has largely failed to produce treatments that are effective for specific subgroups of patients with depression.

A promising advance in targeting cognitive impairment in depression comes from a randomized, double-blind trial of sodium benzoate, a D-amino acid oxidase inhibitor, in late-life depression[15]. In this trial, benzoate—unlike sertraline or placebo—significantly improved cognitive function, measured using a composite based on the Weschler Adult Intelligence and Memory Scales. Notably, benzoate did not produce a specific effect on clinician-rated depressive symptoms[15]. These findings underscore the potential of directly targeting cognitive domains using treatments with selective neurobiological mechanisms relevant to cognition.

In the BIomarker Guided (BIG) Study for Depression, we implemented a stratified precision medicine approach to target the cognitive control brain circuit underlying the cognitive biotype+ subgroup of adult depression. This biotype was prospectively defined by impairments in cognitive control circuit function and behavior. We evaluated guanfacine immediate release (GIR), a mechanistically selective drug, aligned with this circuit target[16]. In keeping with this precision medicine approach, the primary outcome was activation of the cognitive control circuit, assessed by functional magnetic resonance imaging (fMRI) and directly linked to GIR's mechanism of action. GIR is an alpha 2A (α_{2A}) receptor agonist that meets all key criteria for inclusion in the BIG stratified precision medicine study[16]. GIR is FDA-approved for hypertension and is also used off-label for other disorders. It was selected based on its established safety profile, neurobiological selectivity, preclinical efficacy and demonstrated translational relevance from animal models to humans. Selective α_{2A} receptor expression in prefrontal cortical regions—critical to the cognitive control circuit—has been confirmed using radioligand binding studies[17]. Preclinical research has shown that GIR enhances activation and synaptic plasticity in these prefrontal regions[17,18], with effects that translate across species[16]. GIR has also demonstrated antidepressant-like effects in preclinical work[19]. In humans, neuroimaging studies show that GIR increases dLPFC activation both in healthy subjects[20,21] and in clinical populations characterized by impaired cognitive control[22–24]. While we considered the extended-release formulation (GXR), FDA-approved for treating attention deficit hyperactivation disorder (ADHD) in youth, we opted against it owing to its limited study in adult cognitive impairment and lack of neuroimaging data to support its effects in this context.

We tested the hypothesis that GIR would enhance cognitive control circuit function and improve corresponding cognitive behavioral performance in the cognitive biotype+ subgroup of depression. We further hypothesized that GIR would reduce depression symptom severity and suicidality and improve quality of life. The primary outcome measure was the change in cognitive control circuit activation and connectivity—specifically, task-evoked activation in the right and left dLPFC and dACC—from pre- to post-treatment. Secondary outcomes included change in depressive symptoms, cognitive control performance, functional capacity, global life satisfaction and suicidality. We tested the association between the primary mechanistic circuit outcome and secondary clinical and behavioral outcomes.

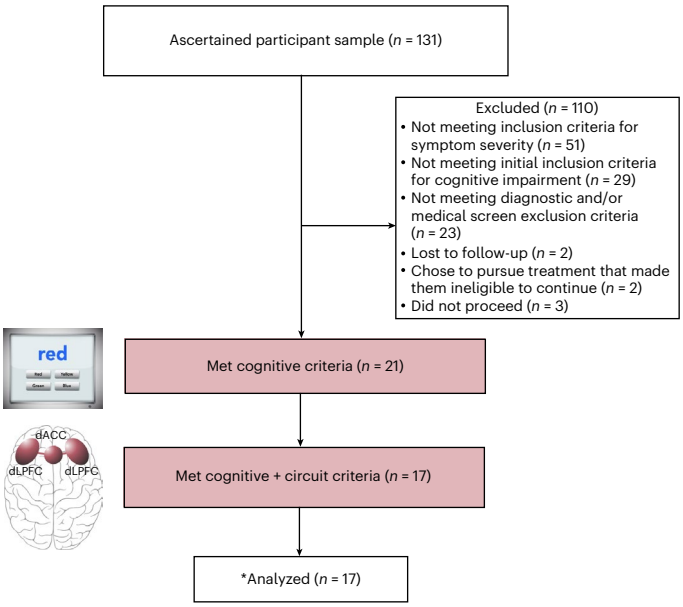

Fig. 1 | The cognitive biotype+ subgroup of depression met prospective symptom criteria for depressive symptom severity, poor performance on behavioral tests of cognitive control and poor function on the fMRI assessed cognitive control circuit of the brain. Specifically, this biotype is defined by the following thresholds at the pretreatment baseline: depressive symptom severity, HDRS-17 score ≥14[12]; behavioral performance deficits, scores ≤−0.5 s.d. below the normative mean on behavioral performance on one or more cognitive control tasks (maze, digit span and/or verbal interference (equivalent to the Stroop, cognitive test icon[47]); and cognitive control circuit dysfunction, activation ≤−0.5 s.d. below the normative mean for dLPFC regions defining the cognitive control circuit, measured by fMRI during a GoNoGo task (brain icon). The asterisk indicates four participants did not meet mechanistic imaging criteria and were excluded from per-protocol analyses.

Results

The cognitive biotype+ subgroup was prospectively defined by moderate-to-severe depressive symptoms (17-item Hamilton Rating Scale for Depression (HDRS-17) median 15, range 14–27; Supplementary Table 1), along with impairments in cognitive control circuit function and behavioral performance, each more than 0.5 s.d. below the healthy reference mean. Seventeen participants meeting these biotype criteria completed 6–8 weeks of treatment with GIR (Fig. 1). GIR led to significant improvements across all primary and secondary outcomes, including neural circuit function, cognitive performance, clinical symptoms and overall quality of life.

Depressive symptom outcomes

Following 8 weeks of treatment with GIR, 76.5% of participants (13 out of 17) achieved a clinical response defined as a ≥50% reduction in HDRS-17 score from baseline. Of the total cognitive biotype+ sample, 67.4% achieved remission from symptoms, defined by a HDRS-17 score of ≤7. Among those who responded to treatment, 84.6% (11 out of 13) met the criteria for remission (Fig. 2a).

These high rates of response and remission were reflected in a significant reduction in HDRS-17 depressive symptom scores, with large effect sizes observed both from pre- to post-treatment

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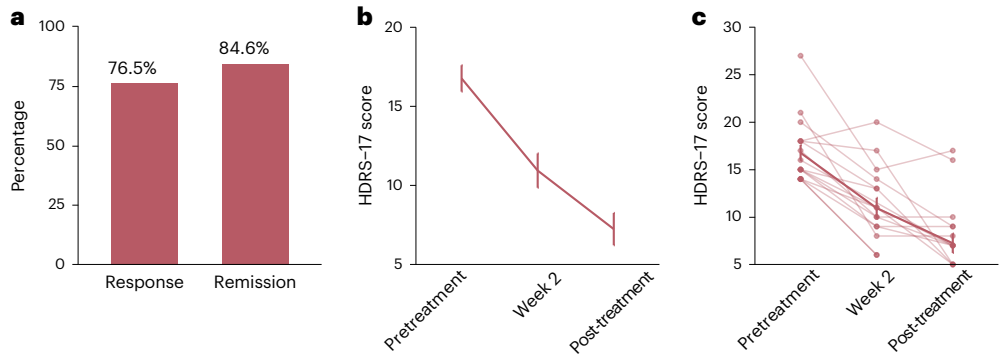

Fig. 2 | Treatment with GIR significantly improved depressive symptom severity. a, Within the cognitive biotype+ subgroup, 76.5% of participants achieved a clinical response defined by a ≥50% reduction in the HDRS-17 scores following 8 weeks of treatment with GIR. Among those who responded, 84.6% of participants achieved remission defined as a HDRS-17 score ≤7. Remission among all biotype participants was 64.7%. **b**, These high rates of response and remission were reflected in a significant reduction in HDRS-17 depressive symptom scores as early as 2 weeks post-treatment ($t(15) = 5.878$, $P = 3.041 \times 10^{-5}$, $d = 1.470$, 95% CI 0.937–2.002) and a further reduction in symptoms after treatment completion at 8 weeks ($t(16) = 12.996$, $P = 6.424 \times 10^{-10}$, $d = 3.152$, 95% CI 2.757–3.547). **c**, GIR-related reductions in HDRS-17 scores are shown for individual patients, indicated by individual data points and connected by faint lines with a bolded line for the sample mean. Data are presented as mean values ± s.e.m. Analyses in **b** and **c** were conducted using general linear models with two-sided alpha values, $n = 17$ participants. Only one measure was used to assess symptom outcome, and no correction for multiple comparisons across secondary outcome measures in other domains was applied. Replicates are not applicable as we are not reporting on laboratory tests. There was no control group.

($t(16) = 12.996$, $P = 3.04 \times 10^{-5}$, Cohen's $d = 3.152$, 95% confidence interval (CI) 2.757–3.547) and as early as week 2 ($t(15) = 5.878$, $P = 6.424 \times 10^{-10}$, $d = 1.470$, 95% CI 0.937–2.002) (Fig. 2b,c).

Cognitive control circuit outcomes

After 8 weeks of treatment with GIR, a general linear model with repeated measures revealed a significant main effect of treatment on activity and connectivity within regions defining the cognitive control circuit ($F(1,16) = 6.621$, $P = 0.020$) (Fig. 3). Planned contrasts revealed that GIR significantly increased circuit function, showing a medium effect size for dACC activation ($t(16) = 2.334$, $P = 0.033$, $d = 0.566$, 95% CI 0.021–1.112; Fig. 3a) and for connectivity between the dACC and left dLPFC ($t(16) = 2.753$, $P = 0.014$, $d = 0.668$, 95% CI 0.001–1.337; Fig. 3c).

The individual plots show that the effect of GIR on cognitive control circuit function was present for most participants (Figs. 3b,d). The effect of GIR on the cognitive control circuit remained significant when including GIR dosage and number of fMRI motion impacted by motion as covariates.

Specificity of cognitive control circuit outcomes

On exploratory analyses, we evaluated the specificity of the effect of GIR on the cognitive control circuit. We evaluated the pre- and post-GIR function of five additional circuits for which we have previously established standard scores relative to a healthy reference benchmark—default mode, salience and frontoparietal attention circuits derived from fMRI under task-free conditions and negative and positive affect elicited by emotion tasks[25,26]. At the pretreatment baseline, the cognitive biotype+ subgroup had a score below −0.5 s.d. from the normative mean for the task-free attention circuit. However, exploratory general linear models with time (pre–post treatment) as a within-subjects factor showed that GIR had no significant effect. No other circuit showed significant changes from pre- to post-treatment.

Cognitive behavioral performance outcomes

After 8 weeks of treatment with GIR, a general linear model with repeated measures demonstrated a significant interaction between treatment and behavioral performance outcomes, indicating that the measures changed differentially with GIR ($F(5,80) = 2.980$, $P = 0.016$).

This interaction was also reflected in a significant main effect of GIR treatment on behavioral performance outcomes ($F(1,16) = 19.362$, $P = 3.916 \times 10^{-4}$) (Fig. 4). Planned contrasts revealed that GIR significantly enhanced cognitive performance, showing large effect sizes for the ability to selectively inhibit irrelevant information and to selectively inhibit responses. This was reflected in improved performance on the verbal interference task ($t(16) = 3.355$, $P = 0.004$, $d = 0.814$, 95% CI 0.564–1.063; Fig. 4a) and reaction time on the GoNoGo task ($t(16) = 2.894$, $P = 0.013$, $d = 0.773$, 95% CI 0.047–1.500; Fig. 4c). These improvements were largely consistent effects across individual participants for both tasks (Fig. 4b,d). Details of results for all cognitive behavioral measures are provided in Supplementary Table 2. The significant effects were retained when covarying for GIR dosage.

Psychosocial outcomes

After 8 weeks of treatment with GIR, we observed an improvement in global satisfaction with life, showing a large effect size ($t(16) = 3.633$, $P = 0.002$, $d = 0.881$, 95% CI 0.032–1.438; Fig. 5a,b).

We also observed a significant interaction between treatment and specific quality of life domains assessed by the World Health Organization Quality of Life–Brief (WHOQOL–BREF) ($F(3,48) = 4.484$, $P = 0.007$). This interaction was also reflected in a main effect of treatment on quality of life ($F(1,16) = 11.913$, $P = 0.003$). GIR significantly enhanced quality of life, with moderate-to-large effect sizes across domains of physical health ($t(16) = 3.159$, $P = 0.006$, $d = 0.766$, 95% CI 0.319–1.214; Supplementary Fig. 1a), psychological function ($t(16) = 3.628$, $P = 0.002$, $d = 0.880$, 95% CI 0.288–1.472; Supplementary Fig. 1b) and social relationships ($t(16) = 2.445$, $P = 0.026$, $d = 0.593$, 95% CI 0.250–0.936; Supplementary Fig. 1c). The environmental domain was not significantly different (Supplementary Table 2).

GIR-related effects for satisfaction with life and quality of life remained significant when covarying for GIR dosage.

Suicidality outcomes

We did not observe a significant effect of GIR on suicidality outcomes in the cognitive biotype+ subgroup (Supplementary Table 2). This null finding may, in part, reflect the study's exclusion of participants with active suicidality.

Association of cognitive control circuit function with depressive symptoms, cognitive performance and psychosocial outcomes

Using repeated measures correlation analysis, we found significant associations between pre and post GIR improvements in cognitive

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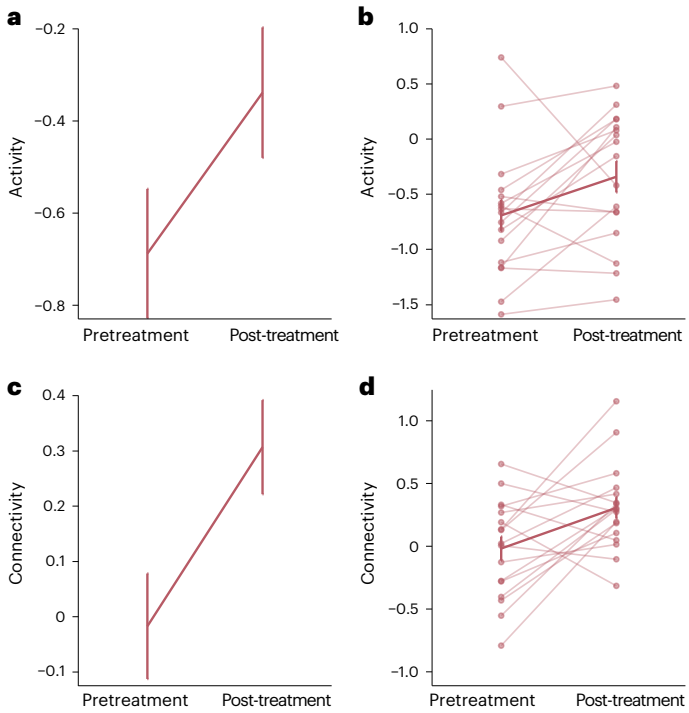

Fig. 3 | Treatment with GIR significantly improved cognitive control circuit function from pretreatment baseline to the 8-week post-treatment follow-up. **a**, Treatment with GIR significantly improved cognitive control circuit function as evidenced by increased dACC activity from pretreatment baseline to the 8-week post-treatment follow-up, with a medium effect size ($t(16) = 2.334$, $P = 0.033$, $d = 0.566$, 95% CI 0.021–1.112). **b**, GIR-related improvements in cognitive control circuit dACC activity are shown for individual patients, indicated by individual data points and connected by faint lines with a bolded line for the sample mean. **c**, Treatment with GIR significantly improved cognitive control circuit function, as further evidenced by increased connectivity of the dACC with the left dLPFC, with a medium effect size ($t(16) = 2.753$, $P = 0.014$, $d = 0.668$, 95% CI 0.001–1.337). **d**, GIR-related improvements in cognitive control circuit dACC–left dLPFC connectivity are shown for individual patients, indicated by individual data points and connected by faint lines with a bolded line for the sample mean. Data are presented as mean values ± s.e.m. Analyses were conducted using general linear models with two-sided alpha values, $n = 17$ participants. The primary circuit outcome measures were modeled as a repeated measures factor to account for correlations among the measures and control for multiple comparisons by estimating effect within a unified model framework, and no correction for multiple comparisons across secondary outcome measures was applied. Replicates are not applicable as we are not reporting on laboratory tests. There was no control group.

control circuit function and HDRS-17 assessed depressive symptoms specific to activity in the dACC ($r_{rm} = -0.593$, $P = 0.009$; Fig. 6) as well as connectivity of the dACC with the dLPFC ($r_{rm} = -0.518$, $P = 0.028$).

GIR-related improvement in cognitive control dACC activity was also associated with improvement in cognitive performance, specifically GoNoGo reaction time ($r_{rm} = 0.566$, $P = 0.028$), and improvement in dACC-connectivity was associated with better psychosocial function, assessed by the WHOQOL–BREF psychological health domain ($r_{rm} = 0.480$, $P = 0.044$).

Discussion

The BIG Study for Depression aimed to evaluate a stratified precision medicine approach by targeting the cognitive biotype of depression—prospectively defined by impairments in both cognitive control circuit function and cognitive performance—using the selective α_{2A} agonist GIR. After 8 weeks of GIR treatment, patients with the cognitive biotype showed improved activation and connectivity of the cognitive control circuit measured by fMRI as the primary outcome, supporting evidence of target engagement. Behaviorally, GIR treatment led to improved performance on GoNoGo and Stroop tasks, both of which assess the ability to inhibit irrelevant information. GIR also significantly reduced depressive symptom severity and enhanced psychosocial function. These improvements showed moderate to large effect sizes. After 8 weeks of GIR treatment, 64.7% of patients achieved remission from their depression and 76.5% showed a clinical response. Among responders, 86.4.7% achieved remission. These rates double the typical 33% remission seen with standard antidepressants[27,28] and exceed previously reported response and remission rates for the cognitive biotype of depression when treated with standard antidepressants[12].

Within the cognitive control circuit, GIR treatment increased task-evoked activation in the dACC and strengthened connectivity between the dACC and left dLPFC. These effects align with foundational evidence demonstrating guanfacine's consistent procognitive impact across rodents, monkeys and humans, supporting a mechanism that translates across species[16,17]. Guanfacine enhances prefrontal function by mimicking the beneficial effects of norepinephrine at

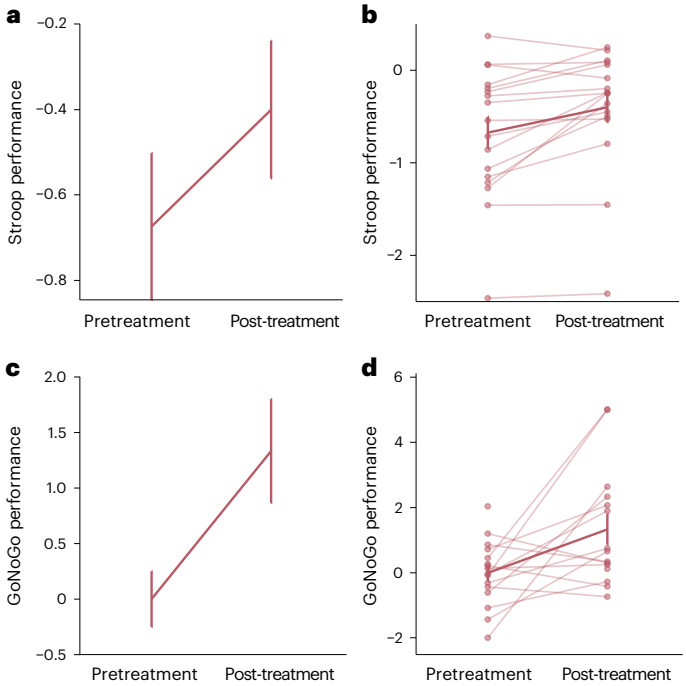

Fig. 4 | Treatment with GIR significantly improved performance on WebNeuro behavioral tests assessing cognitive control. **a**, Treatment with GIR significantly improved behavioral performance on the WebNeuro test of verbal interference, assessing constructs equivalent to the Stroop test, from pretreatment baseline to the 8-week post-treatment follow-up, showing a large effect size ($t(16) = 3.355$, $P = 0.004$, $d = 0.814$, 95% CI 0.564–1.063). **b**, GIR-related improvements on verbal interference performance are shown for individual patients, indicated by individual data points and connected by faint lines with a bolded line for the sample mean. **c**, Treatment with GIR significantly improved behavioral performance for reaction time on the WebNeuro GoNoGo test, from pretreatment baseline to the 8-week post-treatment follow-up, showing a large effect size ($t(16) = 2.894$, $P = 0.013$, $d = 0.773$, 95% CI 0.047–1.500). **d**, GIR-related improvements on GoNoGo performance are shown for individual patients, indicated by individual data points and connected by faint lines with a bolded line for the sample mean. Data are presented as mean values ± s.e.m. Analyses were conducted using general linear models with two-sided alpha values, $n = 17$ participants. The behavioral measures were modelled as a repeated measures factor to account for correlations among the measures and control for multiple comparisons by estimating effect within a unified model framework, and no correction for multiple comparisons across secondary outcome measures in other domains was applied. Replicates are not applicable as we are not reporting on laboratory tests. There was no control group.

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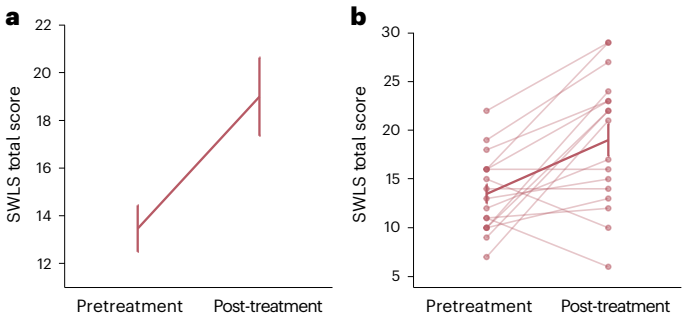

Fig. 5 | Treatment with GIR significantly improved global satisfaction with life assessed by the SWLS. a, Treatment with GIR significantly improved satisfaction with life from pretreatment baseline to the 8-week post-treatment follow-up, showing a large effect size ($t(16) = 3.633$, $P = 0.002$, $d = 0.881$, 95% CI 0.032–1.438). **b**, GIR-related improvements on satisfaction with life are shown for individual patients, indicated by individual data points and connected by faint lines with a bolded line for the sample mean. Data are presented as mean values ± s.e.m. Analyses were conducted using general linear models with two-sided alpha values, $n = 17$ participants. No correction for multiple comparisons across secondary outcome measures in other domains was applied. Replicates are not applicable as we are not reporting on laboratory test. There was no control group.

postsynaptic α_{2A} receptors on dLPFC spines, strengthening connectivity through inhibition of the cAMP–PKA–K^+ signaling pathway[16]. This mechanism may help preserve dLPFC function and circuit connectivity, counteracting the disruptive effects of chronic stress commonly seen in MDD[16]. Although our trial was not explicitly designed to test causal mechanisms, the findings provide strong indications that GIR improves outcomes via a specific dorsal prefrontal cognitive control circuit mechanism. GIR treatment led to targeted improvements in both activity and connectivity within dorsal prefrontal regions of this circuit. To assess the specificity, we explored the impact of GIR on five additional neural circuits quantified using the Stanford EtCere imaging protocol implemented in this trial. GIR had no measurable effect on these other circuits, including the task-free default mode, salience and frontoparietal attention networks, as well as the negative and positive affect circuits evoked by emotion-eliciting tasks.

Behaviorally, GIR significantly improved performance on the GoNoGo and Stroop tasks—both of which assess inhibition related aspects of cognitive control—with large effect sizes. These findings provide converging evidence for the mechanistically selective effects of GIR in the cognitive biotype+ subgroup of MDD. GIR-related increases in dACC activity (elicited by the GoNoGo task) were specifically correlated with improvements in behavioral performance on that task. These measures may serve as behavioral readouts of cognitive control circuit engagement. Supporting this, among participants recruited using our prospective cognitive control biotype strategy, 81% (17/21) of those with verified cognitive control circuit dysfunction also showed impairments on WebNeuro tests of cognitive control. Behavioral readouts may have utility for screening patients and monitoring treatment outcomes. However, in broader clinical populations, these tests may reflect dysfunction across a range of neural substrates, not all of which are relevant to GIR's mechanism of action. In contrast, neural circuit markers offer a more direct window into the specific brain mechanisms targeted by treatment, enabling a more precise match between patient and intervention.

Clinically, the high rate of response and remission in the cognitive biotype+ subgroup supports the utility of a precision medicine approach to tailoring treatment with mechanisms of action that address underlying circuit dysfunctions. The findings provide new evidence to suggest that GIR acts as an antidepressant in humans. These findings build on the foundational work demonstrating the antidepressant properties of GIR's mechanism of action in rodent studies[16,19]. Consistent with the study's design, the high response and remission rates are probably due to two key factors: the use of GIR, a treatment mechanistically designed to enhance outcomes for patients with impairments in prefrontal cognitive control circuitry, and the prospective recruitment of patients specifically identified as having this impairment. Put simply, we matched a targeted treatment, GIR, to a defined cognitive biotype and anticipated improved remission because GIR enhances the function of the very prefrontal circuitry that is impaired in this biotype.

GIR also led to significant improvements in quality of life and satisfaction with life, supporting the view that alleviating cognitive impairment in MDD is necessary for alleviating the burden due to impaired psychosocial function[5,12]. Furthermore, GIR-related improvements in depression severity were correlated with improvements in both cognitive control circuit function and in cognitive performance, showing moderate effect sizes. Enhanced quality of life was also associated with GIR-related improvements in cognitive behavior. These converging findings suggest that selective α_{2A} agonism is a mechanism by which functioning of the dLPFC-anchored cognitive control circuit is normalized, enabling improvements in cognitive performance together with improved depression and the enhanced ability to function in daily life.

These promising results must be considered in the context of study limitations. Although the sample was prospectively selected using stringent criteria, it was relatively small. A larger sample size is needed to evaluate the generalizability of the findings and specific associations between changes in cognitive control circuit measures and clinical behavioral measures. The BIG Study for Depression was an open-label trial. Future randomized controlled trials are needed to verify whether the observed effects on circuit function, behavioral readouts and symptoms are specific to the drug and to the cognitive biotype of depression. Including participants who do not meet criteria for the cognitive biotype (that is, a cognitive biotype subgroup) would allow direct evaluation of the biotype-specific effects of GIR, consistent with its proposed mechanism of action. With additional assessment points, such trials could also establish the causal chain through which

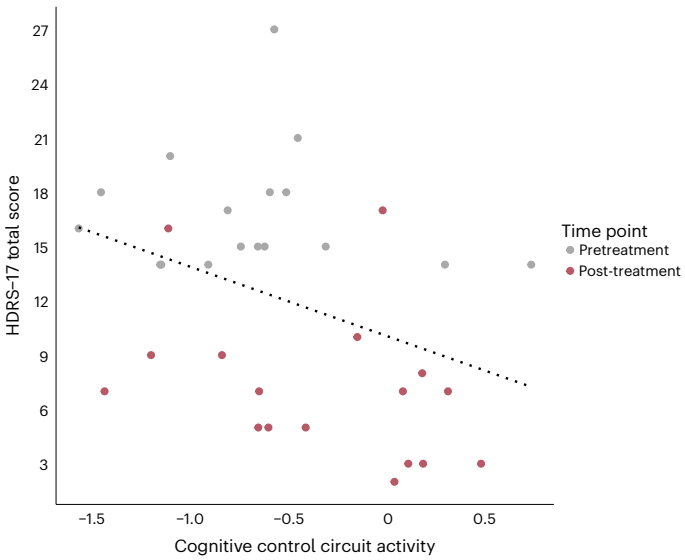

Fig. 6 | Significant association between improvements in cognitive control circuit dorsal anterior cingulate activity and reduction in depressive symptoms assessed by the HDRS-17 for the change in pretreatment baseline to the 8-week post-treatment follow-up. Improvement in circuit activity is shown on the *x* axis, and reduction in HDRS-17 assessed symptom severity is shown on the *y* axis. The analysis was conducted using a repeated measures correlation with two-sided alpha values, $n = 17$ participants, and no correction for correlations with other circuit scores. Replicates are not applicable as we are not reporting on laboratory tests. There was no control group.

GIR engages cognitive control circuitry, enhances cognitive behavior and reduces depressive symptoms. These studies would help determine whether early target engagement of the circuit is necessary and sufficient for a sustained therapeutic response, and whether changes in cognitive control circuit function predict longer-term remission. Although both circuit and behavioral measures used in this study have robust test–retest reliability over 8 weeks (refs. 29,30) and practice effects are minimized through the use of parallel test versions, future studies could more precisely determine how much natural variation in repeated measurement contributes to the effects of GIR on the cognitive biotype. It will also be important to examine the effects of GIR on other circuits, biotypes and indications. For instance, in an fMRI study of healthy subjects, GIR modulated the control of emotional processing via prefrontal–amygdala connectivity[20], a mechanism relevant to the negative affect circuit and to negative processing biases in depression[31]. GIR's protection from the effects of chronic stress has also implicated reductions in inflammation by deactivating microglia[16]. Since low-grade inflammation has been observed in as many as one-third of patients with depression[32], particularly those with cognitive deficits[33], future studies could consider incorporating laboratory-based markers. ADHD and its comorbidity with depression could be a promising area for expanding investigation of the effectiveness of GIR in adults, given the use of extended-release guanfacine to treat cognition-related aspects of ADHD in children and adolescents.

In conclusion, within the cognitive+ biotype, defined prospectively by impairments in both cognitive control circuitry and behavioral performance, GIR's α_{2A} receptor agonism demonstrates preliminary efficacy in enhancing circuit function, improving cognitive performance and achieving high rates of symptom remission along with improved quality of life. These findings highlight the potential of biomarker-stratified precision medicine approaches in depression, particularly when using repurposed medications with established safety profiles. They also open the door for further investigation of selective α_{2A} compounds in the cognitive biotype+ subgroup of depression. More broadly, the results advance the identification of biotypes tailored to mechanistically informed therapeutics in psychiatry, aligned with Research Domain Criteria constructs, and offer a path to address unmet needs in patients who remain underserved by current treatment options.

Methods

Overview of the stratified precision medicine design

The BIG Study for Depression is a single-site, open-label, biomarker-stratified precision medicine trial investigating circuit, behavioral and clinical endpoints in participants with the cognitive biotype of MDD treated with the selective α_{2A} receptor agonist GIR. The study was registered on ClinicalTrials.gov (NCT04181736) and conducted at Stanford School of Medicine, with enrollment from 14 September 2022 to 27 October 2023. All participants gave written informed consent after the procedures had been fully explained in accordance with Helsinki guidelines, under Stanford IRB (no. 49147) (see Supplementary Fig. 2 for details).

We analyzed data for 17 participants who met all per-protocol criteria, including eligibility for the cognitive biotype+ subgroup of MDD, and completed at least 6 weeks of GIR treatment.

Of these 17 participants, 16 (94.1%) completed the full 8 weeks of treatment. We evaluated the effect of GIR on primary fMRI circuit endpoints and secondary outcomes, including cognitive control performance, symptoms, life satisfaction, quality of life and suicidality endpoints.

Cognitive biotype+ definition

The cognitive biotype+ subgroup was defined prospectively as required by our stratified precision medicine design. Prospective biotype stratification criteria encompassed clinical, behavioral and circuit measures (Fig. 1). Clinically, all participants in this subgroup met criteria for moderate or greater depression severity, indicated by a HDRS-17 score of ≥14. Behaviorally, cognitive biotype+ participants showed reduced performance on cognitive control tests at a threshold of ≤−0.5 s.d. below the healthy reference mean. Cognitive control circuit function was assessed using fMRI. Using personalized circuits scores, we verified that cognitive biotype+ participants had reduced dLPFC activation, at a threshold of ≤−0.5 s.d. below the healthy reference mean. Procedures used to evaluate these criteria are described in 'Study and cognitive biotype+ elgibility'.

Our goal for circuit and behavioral criteria was to assign individual participants to a biotype based on their relative extremes of performance and circuit function without assuming a specific statistical threshold and without undersampling the biotype. We selected a cutoff of ≤−0.5 s.d. from the normative mean, a commonly used threshold in cognitive neuroscience and clinical neuropsychology, to indicate meaningful impairment[34]. We decided against a more extreme threshold, such as 2 s.d. below the reference mean, as this would only capture approximately 2.5% of participants and we would risk undersampling the biotype.

Study and cognitive biotype+ eligibility

A pool of 131 participants was recruited directly from the community on the basis of initial inclusion criteria: age between 18 and 69 years, completed the HDRS-17 (ref. 35), fluent in English, medication naive to GIR, able to undergo a brain MRI and attend all study visits and provide written informed consent. Further screening was undertaken in a series of steps to assess for general study inclusion and exclusion and for biotype-specific criteria, detailed in Supplementary Fig. 2.

Participants completed a structured psychiatric interview with clinical coordinators using the MINI-Plus[36], in which the inclusion diagnosis of current, past or recurrent nonpsychotic MDD was assessed according to DSM-5-TR criteria. Exclusion diagnoses of bipolar disorder, psychosis, obsessive compulsive disorder, post-traumatic stress disorder, ADHD, substance use disorders and/or suicidal ideation representing imminent risk were also assessed.

At the first step for assessing biotype criteria, we evaluated symptom criteria based on the HDRS-17 (ref. 35) severity threshold of ≥14, and 80 participants met this criterion threshold (Fig. 1).

Next, we evaluated criteria based on behavioral tests of cognitive control and scheduled participants for a medical screen for GIR eligibility at the Stanford Clinical Translational Unit. Of the 80 who met symptom criteria, 51 met behavioral criteria for the cognitive biotype+ based on performance ≤−0.5 s.d. below the healthy mean. Of these, 23 participants were not medically eligible because they met at least one of the exclusion criteria for GIR contraindications: syncope, sudden cardiac death in a first-degree relative and/or use of a strong cytochrome P450 3A4 inhibitor, blood pressure readings indicating hypotension (systolic ≤90 and/or diastolic ≤60 mmHg) and/or bradycardia (≤55 beats per min) on two of three separate measurements at least 5 min apart, electrocardiogram abnormality, laboratory test indicators of liver or kidney abnormalities, or positive urine test for drugs that clinical personnel judge unsafe for GIR in the context of other screening information. Thus, 28 participants who met behavioral criteria were also medically eligible.

At the next step, the pretreatment baseline functional MRI scan was assessed for participants' circuit eligibility for the cognitive biotype+ subgroup while they were medication-free. Cognitive biotype+ circuit eligibility was confirmed for 24 of these participants. Seventeen completed at least 6 weeks of GIR treatment and were included in per-protocol analysis. The remaining seven did not proceed, were discontinued due to commencing an ineligible medication or side effects or were lost to follow-up, as outlined in Fig. 1.

Per-protocol cognitive biotype+ sample characteristics

The resulting sample of 17 per-protocol participants meeting all cognitive biotype+ and treatment completion criteria had a mean age of

31.4 years (s.d. 11.1 years) with an equivalent number of females (47%) and males (53%). Within the sample, 29.4% were Caucasian, 41.2% Asian, 11.8% African American, 5.9% multiracial and the remaining 11.8% reported 'other' race. Baseline HDRS-17 assessed depression severity was 15 (range 14–27). MINI-Plus identified comorbid anxiety was present in 23.8% of the sample. The majority of participants (64.7%) had been treated for depression previously, and the median number of prior treatment failures was 2 (range 0–7). The median final dose of GIR was 2 mg nightly (range 0.25–2 mg) (see Supplementary Table 1 for further details).

GIR treatment

We chose GIR for this study because of its selectivity for α_{2A} receptor agonism, concentrated in the prefrontal circuits regions of interest for the cognitive biotype of depression. GIR enhances prefrontal function by mimicking the beneficial effects of norepinephrine at postsynaptic α_{2A} receptors on dLPFC spines, strengthening connectivity through inhibition of the cAMP–PKA–K^+ signaling pathway[16]. Foundational evidence demonstrates that this mechanism translates across species with consistent effects across rodents, monkeys and humans[16,17]. In rodent work, GIR is more effective at protecting cognition from stress exposure than clonidine[37], suggesting that guanfacine's selective benefits are not primarily due to reducing norepinephrine release, as clonidine is more potent than guanfacine in this regard. The selectivity of GIR for α_{2A} receptor agonism is 10× higher than for α2B receptors[38]. Steady-state levels are typically attained within 4 days, and the average elimination half-life is approximately 17 h (range 10–30 h; FDA package insert[39]). Clinical studies have established the safety profile of GIR in humans, and there is no evidence for tachyphylaxis with GIR in trials of up to 8 weeks[40–42]. The most common adverse events include drowsiness, dry mouth, headache and dizziness.

Before commencing GIR, participants who had been taking psychotropic medications underwent a carefully monitored down-titration and subsequent washout period of five half-lives, overseen by the participant's primary mental health provider. In one case, due to clinical considerations, a participant continued on escitalopram 20 mg, an exception approved by the study team.

GIR was dosed once nightly to minimize the potential sedative effects. GIR was commenced at a dose of 0.5 mg and up-titrated every 3 days by 0.5 mg to a goal dose of 2 mg by the second week. The total treatment period was 8 weeks, and participants met protocol criteria by completing at least 6 weeks of treatment. Owing to the open-label design, clinical personnel were not blinded to treatment status. However, all analyses were undertaken with personnel blind to the participants' response status.

Adverse events

We assessed adverse events weekly at virtual or in-person visits with a trained, experienced coordinator or a study clinician. Consistent with prior reports, the most commonly reported adverse events were mild and included dry mouth (64%) and daytime fatigue (43%) (Supplementary Table 3). Two participants withdrew due to side effects. One participant was withdrawn from the study due to worsening of suicidal ideation, which was assessed to be related to discontinuation of the participant's prior antidepressant.

Study assessments and assessment sessions

The flow of study assessments is outlined in Supplementary Fig. 3.

Three key sessions were conducted:

(1) Screening: initial prospective screening for cognitive biotype+ criteria using the HDRS-17 and WebNeuro cognitive control tests. Participants were provided with access to WebNeuro for completing on their own laptop.
(2) Pretreatment baseline: an fMRI session to assess the cognitive control circuit, re-assessment with HDRS-17 and WebNeuro cognitive tests to establish the pretreatment baseline, and additional secondary measures of symptoms and function.
(3) Post-treatment: repeat of primary and secondary measures after 8 weeks of treatment with GIR.

The primary and secondary measures assessed in each of these sessions are detailed in the following assessment subsections.

Primary cognitive control circuit measures. Primary outcomes were derived from fMRI during a GoNoGo task using the validated Stanford EtCere Image Processing System implemented in a containerized environment to ensure reproducibility[25,26].

For acquisition, fMRI scans were acquired at the Stanford Center for Cognitive Neurobiological Imaging using a GE 3T UHP scanner (GE Healthcare) with a Nova Medical 32-channel head coil. Head motion was restricted with foam pads, and participant alertness was monitored using an eye-tracking system. The FIRMM system was also used to record head motion for postacquisition quality control.

Functional runs used the following established protocol: repetition time (TR) of 2 s, echo time (TE) of 30 ms, flip angle of 54°, field of view (FOV) of 220.8 × 220.8 mm, 92 × 92 matrix, 60 slices, 2.4 mm thickness, calibration volumes 2. A total of 180 contiguous slices, each 1 mm thick, covered the whole brain with an in-plane resolution of 1 mm × 1 mm. A T1-weighted sagittal plan scan was also acquired for anatomical registration of functional images using a 3D spoiled gradient echo sequence: TR of 8.3 ms, TE of 3.2 ms, flip angle of 11 degrees, TI of 500 ms, NEX of 1 and ASSSET of 1.5; frequency direction: S/I; matrix of 256 × 256, 180 contiguous slices, 1 mm isotropic voxels.

During scanning, participants completed the GoNoGo task[26,31], incorporated within the Stanford EtCere Imaging Processing System's acquisition module. This task includes 180 Go trials (the word 'press' in green), to which participants respond as quickly as possible, and 60 NoGo trials (the word 'press' in red), for which participants are required to withhold responses. Stimuli are presented in a pseudorandom order, with stimulus duration 500 ms and an interstimulus interval of 750 ms[43].

For preprocessing, the Stanford EtCere Image Processing System implements motion correction, high-pass filtering (128 s), registration to Montreal Neurological Institute space using operations based on the Functional Magnetic Resonance Imaging of the Brain Software Library[44], and predefined quality control thresholds: less than 25% of time points censored for frame-wise displacement and a temporal signal-to-noise ratio of at least 50.

The Stanford EtCere Image Processing System uses dLPFC and dACC regions of interest to define the cognitive control circuit. These regions have been verified using Neurosynth[45] and meet previously established quality control and psychometric criteria[25,26].

Quantification of activity and connectivity was performed using the quantification module of the Stanford EtCere Image Processing System, validated in prior work[25]. Task-evoked activation was quantified using a generalized linear model analysis in which the 'NoGo' and 'Go' stimuli were convolved with a canonical hemodynamic response. Activation was quantified as beta estimates, and task-related connectivity was quantified using a psychophysiological interaction method. Connectivity from dACC to left and right dLPFC, and from left and right dLPFC to ACC were averaged across these two directions of connectivity for each pair of regions.

Each of the activation and functional connectivity measures were expressed in s.d. units relative to the mean and standard deviation of our healthy reference dataset. This standardized referencing method enabled the derivation of personalized circuit scores for each individual participant using our prior established method[25,26]. Personalized circuit scores provided a standardized method for determining which

patients met cognitive biotype+ criteria (≤−0.5 s.d. below the healthy reference). They were also used to quantify circuit change from baseline to post-treatment.

Cognitive behavioral performance. Behavioral performance on these tests was assessed using a standardized, computerized test battery, WebNeuro[30], which has established norms across nine decades of the healthy lifespan[30,46,47], test–retest reliability over an 8-week retest period relevant to this study, construct validity with respect to traditional neuropsychological batteries and brain measures[30,48], and utility in distinguishing cognitive impairments in psychiatric groups[49–52]. Cross-cultural consistency has also been established[53].

Cognitive behavioral performance criteria for the cognitive biotype+ subgroup were verified as part of our prospective stratification procedure during participant screening. Stratification criteria for the cognitive biotype+ subgroup were established using cutoffs on behavioral tests of cognitive control, including maze, GoNoGo, digit span and verbal interference. The cutoff for performance was ≤−0.5 s.d. below the normative mean on one or more of these cognitive control tests. These tests were selected to assess complementary aspects of cognitive control that implicate dorsal prefrontal brain regions. We drew on a cognitive neuroscience-based framework for cognitive control, emphasizing goal-directed action selection and response inhibition[54], along with classical cognitive theory, which includes working memory and interference suppression[55,56].

The same cognitive behavioral tests were re-administered at the pretreatment baseline scan and the post-treatment session. Parallel forms of the tests were used to minimize practice effects. Thus, we selected the maze test to assess goal selection, GoNoGo to assess response inhibition, digit span to assess working memory and a verbal interference (analogous to the Stroop) to assess suppression of interfering information. At baseline and post-treatment, we also included a switching of attention test (analogous to Trails B) to assess processing speed which is implicated in some classical theories of cognitive control[55,56].

Performance on each test was represented by a composite score that was the average of constituent test scores (maze: trials completed, completion time, path learning time, total errors and overrun errors; digit span: maximum recall span, correct trials; verbal interference: total errors, reaction time; switching of attention: completion time, average connection time, errors), winsorized at 5 s.d. GoNoGo reaction time data was obtained from in-scanner sessions. Each score was referenced to the healthy reference mean and expressed in s.d.

Symptom assessments. *Depression symptom severity*. HDRS-17–rated depression symptom severity was a secondary outcome. The HDRS-17 scores range from 0 (no depression) to 52 (severe depression) and a threshold of HDRS-17 ≥14 was applied for the cognitive biotype+ subgroup as outlined in the study eligibility section above.

The HDRS-17 was re-administered at the pretreatment baseline scan and the post-treatment session. We assessed continuous change in severity as well as categorical outcomes for response (≥50% improvement from baseline on the HDRS-17) and remission (≤7 on the HDRS-17).

Psychosocial assessments. Global life satisfaction and quality of life were assessed at baseline and post-treatment. We used the satisfaction with life scale (SWLS), a 5-item participant-rated state using a 7-item Likert scale[57,58], with scores ranging from 5 to 35.[59]

We also used the WHOQOL–BREF scale, a 26-item scale evaluating quality of life in the domains of physical health, psychological function, social relationships and environment[60]. Scores for each domain range from 0 to 100.

Suicidality. Suicidality was assessed at baseline and post-treatment using the observer-rated 5-item ideation subscale of the Columbia–Suicide Severity Rating Scale[61]. Scores range from 0 (absent) to 5 (high).

Outcome measures after 8 weeks of treatment with GIR

To assess the effect of GIR, we evaluated the change from baseline to post-treatment in our primary mechanistic endpoint—cognitive control circuit function—and in secondary endpoints, including cognitive behavioral performance, depressive symptom severity (response and remission), psychosocial function and suicidality.

Statistical analysis

Statistical analyses were conducted in R studio version 2022.12.0+353. For our primary cognitive control circuit measure, we used a general linear model that included a within-subjects effect for treatment (pre- versus post-treatment) and circuit function, with five repeated measures for each region of activity and connectivity defining the cognitive control circuit: left and right dLPFC activity, dACC activity, dACC–left dLPFC connectivity, and dACC–right dLPFC connectivity. We tested for the interaction between treatment and circuit measure and the main effect of treatment. Planned paired *t*-test contrasts tested for the effect of GIR on the change in each circuit measure. We reran the general linear model to evaluate whether covariates, including GIR dosage and scanner head motion, contributed to significant effects of GIR.

For secondary measures, general linear models were also undertaken with treatment as a within-subjects factor. For measures of depression symptom severity, global satisfaction with life and suicidality, these models included a within-subjects effect for treatment (pre- versus post-treatment). For cognitive behavioral performance, we modeled the within-subjects effect of treatment and included a within-subjects repeated measures factor for the six measures of cognitive control. Similarly, for WHOQOL, we modeled a within-subjects repeated measure for the four quality of life domains. Planned paired *t*-test contrasts tested for the effect of GIR on change in each set of secondary measures in each model. We reran these models to evaluate whether the covariate of GIR dosage contributed to significant effects of GIR.

Given each analysis was prespecified to address study hypotheses, we set a two-sided alpha level of 0.05 for each analysis within each modality for primary and secondary endpoints. We did not adjust this alpha level since each measure was included to test a specific hypothesis about the effect of GIR on circuit, behavioral and clinical function. This approach aligns with the use of multiple endpoints in other areas of precision medicine, for example, the inclusion of both cognitive and functional endpoints in Alzheimer's disease trials[62]. To aid interpretation of clinical meaningfulness, we reported effect sizes for each measure. Change from baseline to post-treatment effect sizes were computed as Cohen's *d* for paired *t*-tests. For the primary circuit outcome and secondary outcomes that showed a significant effect of GIR, we assessed their associations using repeated measures correlations. These correlations were prespecified and conceptually linked, aimed at evaluating the relationship between the primary mechanistic outcome and key clinical and behavioral measures.

On exploratory analyses, we assessed the specificity of dysfunction in the cognitive biotype+ subgroup at baseline as well as the specificity of GIR-related change by examining five other circuits implicated in depression and quantified using our Stanford EtCere Image Processing System: default mode, frontoparietal attention, salience and positive and negative affect circuits[25,26].

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available after approval of a proposal with investigator support.

Code availability

Code for all analyses following the extraction of the imaging features of interest is available via GitHub at https://github.com/jennajubeir/big_cog_biotype.

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Author contributions

L.M.H. undertook conceptualization, formal analysis, writing of the original draft as well as review and editing, visualization and clinical oversight. J.J. performed formal analysis, writing of the original draft as well as review and editing and visualization. R.H. undertook investigation, writing (review and editing) and clinical oversight. L.T. performed formal analysis and writing (review and editing). L.B. performed data curation and writing (review and editing), data acquisition and management. X.Z. performed formal analysis, writing (review and editing) and visualization. T.L. performed data quality oversight and review. B.J. performed statistical oversight and review. R.O.H. performed conceptualization, resources, writing (review and editing). A.F.S. performed conceptualization, resources, writing (review and editing). L.M.W. performed conceptualization, investigation, project administration, formal analysis, writing of the original draft as well as review and editing, supervision, resources and funding acquisition.

Competing interests

L.M.W. declares US patent applications 10/034,645 and 15/820,338: Systems and methods for detecting complex networks in MRI image data. A.F.S. has consulted for Compass, Axsome, ANeuroTech, NeuraWell, Signant, Otsuka, Sage, Douglas, Alto, Magnus, Skyland Trail and Parexel. He has equity in Corcept, Alto Neuroscience, Magnus, Delport, Insight Analytics, Madrigal, Seattle Genetics, Titan and Xhale. L.T. is employed by Ceribell Inc. The other authors declare no competing interests.

Additional information

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	REDCap
Data analysis	The 'Stanford Et Cere Image Processing System' in C++, R Studio version 2024.12.0+467

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available after approval of a proposal with investigator support.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	In this study, sex and gender have the same numbers: 8 (F), 7 (M)
Reporting on race, ethnicity, or other socially relevant groupings	Race: 7 (Asian), 2 (Black or African American), 5 (Caucasian), 1 (Multiracial), 2 (Other)
Population characteristics	Patients with major depressive disorder who meet criteria for the cognitive biotype+ subgroup, age: mean=31.4, SD=11.1.
Recruitment	Patients were recruited from Facebook advertisements and provided written informed consent after the procedures had been fully explained.
Ethics oversight	The study received Institutional Review Board (IRB) approval from Stanford University (# 49147) and is registered on ClinicalTrials.gov, NCT04181736.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☐ Life sciences ☒ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	This study employed a stratified precision medicine approach to evaluate the efficacy of guanfacine immediate release (GIR), a selective alpha 2A receptor agonist, in improving cognitive control circuit function, behavioral performance, and clinical outcomes in participants who fall within the cognitive biotype+ subgroup of major depressive disorder (MDD).
Research sample	The study sample consisted of 17 participants (8 females, 7 males) with a mean age of 31.4 years (SD = 11.1). Participants were identified based on pre-specified criteria for the cognitive biotype+ subgroup of MDD, including moderate-to-severe depressive symptoms (Hamilton Depression Rating Scale score ≥ 14), impaired cognitive control performance (≤ -0.5 SD below the normative mean on tests of cognitive control), and reduced functional activation within the cognitive control circuit on functional MRI. The racial composition of the sample was diverse, comprising 7 Asian, 2 Black or African American, 5 Caucasian, 1 Multiracial, and 2 categorized as "Other."
Sampling strategy	Participants were recruited through targeted advertisements on Facebook, focusing on individuals who reported symptoms of depression. Eligibility was determined based on a combination of data from self-report, clinical interviews, medical evaluations, and biomarker assessments.
Data collection	Functional magnetic resonance imaging (fMRI), cognitive tests, and questionnaires. No one was present besides the participant and the researcher. No one was blinded to the experimental condition or study hypothesis.
Timing	Data collection occurred across three time points: pre-treatment baseline, early treatment (2 weeks after initiating GIR treatment), and post-treatment (6–8 weeks after treatment initiation). Each participant underwent a baseline assessment within one week prior to starting treatment, with weekly monitoring and assessments conducted throughout the treatment period. First enrollment was September 14, 2022, and final enrollment was October 27, 2023.
Data exclusions	Participants were excluded from the analysis if they failed to meet the cognitive biotype+ subgroup criteria during stratification. Additionally, participants who did not complete at least six weeks of GIR treatment or were withdrawn due to adverse events were excluded.
Non-participation	A total of 150 individuals were screened for eligibility. Of these, 28 participants were enrolled in the study after meeting initial inclusion criteria, and 17 participants completed at least six weeks of guanfacine treatment and were included in the final analysis.
Randomization	There was no randomization, since all participants underwent the same treatment.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	ClinicalTrials.gov, NCT04181736
Study protocol	Available upon request
Data collection	Functional magnetic resonance imaging (fMRI), cognitive tests, and questionnaires. No one was present besides the participant and the researcher. No one was blinded to the experimental condition or study hypothesis.
Outcomes	The primary outcome measure was change in activation and connectivity of the cognitive control circuit as defined by cognitive control task-evoked activation in the right and left dLPFC and dACC from pre-treatment baseline to post-treatment. Secondary outcomes included change in depressive symptoms, cognitive control performance, functional capacity, global life satisfaction, and suicidality within the cognitive biotype.

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*

Magnetic resonance imaging

Experimental design

Design type	Structural and functional
Design specifications	Task-evoked activation was quantified using a generalized linear model analysis in which the order of 'NoGo' and 'Go' stimuli were recorded as task events and convolved with a canonical hemodynamic response. Activation in dLPFC and dACC were quantified as beta estimates and expressed in standard deviation units relative to the mean and standard deviation of a healthy reference dataset, which provided a standard benchmark for interpreting a score for each individual patient.
Behavioral performance measures	Composite scores were obtained by averaging performance on each individual test score: trials completed, completion time, path learning time, total errors, and overrun errors from the Maze, maximum recall span and correct trials from Digit Span, total errors and reaction time for Verbal Interference, and completion time, average connection time, and errors in the Switching of Attention Test. Because GoNoGo data was obtained from in-scanner data, only reaction times were assessed.

Acquisition

Imaging type(s): Structural and functional

Field strength: 3T

Sequence & imaging parameters: Task fMRI: TR=2s, TE=30ms, flip angle=54°, FOV=220.8x220.8mm, 92x92 matrix, 60 slices, 2.4mm thickness, calibration volumes=2.
T1-weighted anatomical: TR=8.3ms; TE=3.2ms; flip angle=11 degrees; TI=500ms, NEX=1 and ASSSET=1.5; frequency direction: S/I; matrix=256 x 256, 180 contiguous slices, 1mm isotropic voxels, slice orientation = sagittal.

Area of acquisition: ROI

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software: Stanford EtCere Image Processing pipeline

Normalization: FMRIB nonlinear and linear registration tool

Normalization template: Montreal Neurological Institute

Noise and artifact removal: Six realignment parameters as regressors of no interest. A high-pass filter with a cutoff period of 128s was applied.

Volume censoring: None

Statistical modeling & inference

Model type and settings: General linear models including a within subjects' effect for treatment and planned paired t-test contrasts

Effect(s) tested: Main effects of circuit, cognitive behavioral performance, and quality of life; Interactions of treatment*circuit, treatment*cognitive behavioral performance, and treatment*quality of life.

Specify type of analysis: ☐ Whole brain ☒ ROI-based ☐ Both

Anatomical location(s): Previously published regions of interest based on meta-analysis.

Statistic type for inference (See Eklund et al. 2016): General linear models including a within subjects' effect for treatment and planned paired t-test contrasts

Correction: None

Models & analysis

n/a	Involved in the study
☐	☒ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity: GoNoGo task-related connectivity between dLPFC and dACC was quantified using a psychophysiological interaction (PPI) method. PPI was used to seed connectivity from dACC to left and right dLPFC, and from left and right dLPFC to ACC, and we then averaged the two directions of connectivity for each pair of regions.