NCT4414930: Pharmacologic augmentation of targeted cognitive training in schizophrenia
Study Protocol

October 11, 2019

SPECIFIC AIMS: Pharmacologic Augmentation of Targeted Cognitive Training in Schizophrenia

This application responds to RFA-MH-18-705 by conducting efficient pilot testing of a novel intervention strategy for chronic psychotic disorders - **P**harmacologic **A**ugmentation of **C**ognitive **T**herapy (PACT) - via an experimental medicine approach. Antipsychotics are the major therapeutic tool for chronic psychotic disorders, including schizophrenia, but do not significantly alter their course or real-life impact. Specific cognitive therapies achieve modest symptom reduction and improved function and cognition in psychosis patients, including "bottom-up" sensory-based targeted cognitive training (TCT). While benefits of TCT are evident at the group level, almost half of all patients demonstrate little or no cognitive gains after 30-40 hours (h) of TCT. For patients and clinicians, the costs and logistical complexities associated with these time- and resource-intensive interventions can be prohibitive. Consistent with the scope of this RFA, we propose and will test a novel "augmentation strategy" for using medications to specifically enhance the benefits of TCT in schizophrenia.

Suppressing active psychosis with antipsychotics benefits cognitive interventions for schizophrenia, but it is possible that drugs with pro-cognitive effects will specifically, and perhaps synergistically, augment the clinical benefits of cognitive therapies. A "proof of concept" for this approach is found in the use of the pro-extinction drugs to selectively enhance the impact of cognitive therapy for anxiety disorders. In this "proof of concept", a learning-based therapy is paired with a medication that enhances a brain mechanism (extinction) that is both 1) critical to that form of learning, and 2) known to be deficient in some anxiety disorders. In this application, we will use the pro-attention drug, amphetamine, to enhance a brain mechanism (attention) that is both 1) critical to learning in TCT, and 2) known to be deficient in schizophrenia. We hypothesize that amphetamine will augment TCT learning and hence the clinical gains from TCT in schizophrenia patients, and that this PACT approach will be particularly effective in biomarker-defined subgroups of patients. A successful PACT will produce neurocognitive and clinical gains from TCT that are more robust, more rapidly achieved, more durable and/or impact a greater proportion of patients, compared to TCT alone.

Preliminary support for this hypothesis and the proposed experimental design comes from both our laboratory- and clinic-based studies. Our laboratory-based studies tested dose and time-course effects of amphetamine on TCT learning in antipsychotic-medicated schizophrenia patients (MH59803). Amphetamine (2.5 < 5 > 10 mg) significantly enhanced learning in an auditory discrimination task (Posit Science "Sound Sweeps") -- a key component of the TCT suite of exercises with established efficacy in schizophrenia patients. This enhanced learning was 1) not drug state-dependent, 2) retained for at least 1 week, 3) most robust among patients with the greatest baseline attentional deficits, and 4) associated with gains in auditory discrimination. Our data supported the acute, sub-acute and long-term safety of repeated amphetamine exposure in these antipsychotic-medicated patients. However, while amphetamine-enhanced learning during a 1-h Sound Sweeps test provides a valuable assay of "target engagement", we have no evidence that it predicts greater, faster or more lasting clinical, neurocognitive or functional gains with a full course of amphetamine+TCT.

Our clinic-based studies yielded key findings related to Sound Sweeps performance and predictors of therapeutic sensitivity to a full course of TCT in a "real world" psychiatric treatment facility. First, baseline levels of early auditory information processing (EAIP) significantly predicted learning during 1-h of Sound Sweeps. Second, schizophrenia patients exhibited significant clinical, neurocognitive and functional gains after 30-h of TCT, and gains in EAIP during the first hour of Sound Sweeps strongly predicted neurocognitive gains after a full course of TCT. In total, these findings with amphetamine, Sound Sweeps, auditory discrimination, EAIP and TCT provide a strong empirical and conceptual framework for a mechanistically-based hypothesis to be tested via the proposed randomized, placebo-controlled 30-h pilot trial of (amphetamine+TCT) vs. (placebo+TCT). We propose that: 1) amphetamine will enhance and/or accelerate the clinical, neurocognitive and functional gains after 30-h of TCT in schizophrenia patients, and 2) this "PACT" effect will be predicted by gains in learning and EAIP after 1-h of Sound Sweeps training. Via 3 Aims, this application provides **efficient pilot testing** of this PACT strategy in antipsychotic-medicated schizophrenia patients, using **clear Go/No-Go criteria** to inform a future, fully-powered "Confirmatory Efficacy trial":

Aim 1 – Confirm **target engagement**: In **two, 1-hour tests**, determine if amphetamine increases Sound Sweeps learning in a cohort of impaired schizophrenia patients (n=54).

Aim 2 – Efficiently test **clinical, neurocognitive and functional impact**, and their relationship to target engagement: In a **30-session, 10-week course of TCT**, determine if amphetamine augments the magnitude, rate and/or durability of TCT-induced gains, and whether these gains are associated with target engagement.

Aim 3 – Biomarkers of AMPH-induced gains: Determine whether higher basal levels of EAIP (and related functional and neurophysiological measures) or changes in these measures across the first hour of Sound Sweeps **predict greater sensitivity** to amphetamine-enhanced clinical, neurocognitive or functional gains among schizophrenia patients receiving combined amphetamine+TCT.

Research Strategy: A. Significance: Chronic psychotic disorders, including schizophrenia (SZ), affect 2% of the world's population, causing suffering and severe disability. Among the consequences of these disorders, psychosocial disability is strongly correlated with neurocognitive impairment[18,42,118]. The primary treatment for these disorders over the past 60 years has been antipsychotic (AP) medications, which produce only marginal gains in neurocognition[49]; by contrast, specific cognitive therapies significantly improve neurocognition and outcome in SZ patients, with effect sizes of d≈0.40 vs. APs alone[8,30,40,110-1]. Many studies document the safety, acceptability and efficacy of cognitive therapies in SZ with benefits often lasting years[30,40,66-9]; benefits are achieved with both "top-down" therapies, that engage higher order cognitive mechanisms, and "bottom-up" cognitive and basic sensory training delivered via computerized cognitive remediation programs[31-2,115].

One "bottom-up" cognitive therapy, Targeted Cognitive Training (TCT), is a "neuroplasticity-based" computerized approach to cognitive remediation[31]. In TCT, the user performs progressively more difficult learning trials to improve pitch and temporal acuity of processing in auditory sensory, attention-related and working memory systems. The goal of TCT is to foster the recovery of key neurocognitive functions by harnessing mechanisms of neuroplasticity under carefully controlled conditions, rather than to promote the development of compensatory cognitive or behavioral operations. TCT relies on *repetitive practice and procedural learning* - mechanisms that are relatively intact in SZ patients - by providing auditory training exercises that are: 1) *intensive*: thousands of trials per exercise; 2) *attentionally engaging*: self-paced initiation of each trial; 3) *adaptive*: the difficulty of each training task adjusts trial-by-trial based on performance; and 4) *rewarding*: entertaining animations reinforce correct responses[3]. In several reports[31-2,115], Vinogradov and colleagues have shown that after 30-50 hours (h) of TCT, SZ patients have large effect size gains (d≥0.86) in auditory-dependent cognitive domains (verbal learning and memory), global cognition and quality of life that persist for at least 6 months post-TCT.

While TCT is highly efficacious at the group level, individual gains from TCT vary considerably: up to 45% of SZ patients fail to benefit (d ≤ 0.2)[72], even after an extended 100h course of TCT[33]. Multi-site findings are more promising, with significant gains in MATRICS Consensus Cognitive Battery (MCCB) composite and verbal learning scores after 20h of training[51]. While these gains no longer reached statistical significance after 40h of training due to subject attrition, the effect size (d≈0.39) remained non-trivial but modest. Still, given the high rate of TCT "non-response", and the modest overall effect sizes, the costs and logistical impediments associated with getting severely ill SZ patients to complete three 1h sessions of TCT per week for 10-20 weeks can be prohibitive. *Per RFA-MH-18-705, this application seeks to "pilot test" a practical means to augment, accelerate and/or prolong the benefits of TCT in SZ patients, in order to inform a future, fully-powered "Confirmatory Efficacy trial".*

B. Innovation: In **P**harmacologically **A**ugmented **C**ognitive **T**herapies ("PACTs") for SZ [24,89-90], as first proposed by the PI[90], drugs with pro-cognitive effects are used specifically, and perhaps synergistically, to augment the clinical benefits of a range of cognitive therapies. These drugs do not replace APs, which remain essential for limiting active psychotic symptoms that impede a patient's ability to participate in cognitive therapy. While neither the proposed use of pro-cognitive drugs, nor TCT, are independently innovative in the treatment of SZ, combining these treatments within a PACT design to augment the gains from TCT - as described in this application - is highly innovative and responds to the FOA's goal to support *"the development… of novel… interventions… as augmentations to a standard treatment."* This application must be limited to the use of one pharmacologic agent, and the PI has carefully selected this agent based on > 18 years of meticulous "foundational" parametric dose-response and time-course studies in healthy subjects and SZ patients, that included several potential neuro- and psychophysiological biomarkers[95-8,103-4,106]. Nonetheless, it is anticipated that the PACT design tested in this application will be applied to many other medications, and the PI has studies in progress to establish parametric data for other classes of putative pro-cognitive agents. Thus, it is anticipated that **findings from this application will advance an innovative treatment strategy that will have implications well beyond its focused scope**.

A major challenge to the PACT approach is the availability of drugs with evidence-based pro-cognitive effects in SZ patients; in fact, trials of potential pro-cognitive agents in SZ have largely yielded negative results [eg. 4,19,35-7,41]. However, these "negative" studies generally share two important weaknesses. First, they were not conducted in the context of cognitive therapy, and *drugs designed to enhance specific domains of cognition, e.g. attention, might not yield clinical benefits unless paired with interventions that access those components, i.e. utilize/place demands on enhanced attention.* An analogy is seen in the effects of anabolic steroids, which produce minimal gains in muscle mass unless *paired with an exercise* that puts "demands" on that muscle. In many "negative" studies, the candidate pro-cognitive agent was simply added to a *passive* daily medication regimen, without any new cognitive "load"[35-7]. A "proof of concept" for the PACT approach of pairing a drug that has a target pro-cognitive mechanism with a therapy that demands that mechanism is seen in the use of pro-extinction drugs to selectively enhance the therapeutic impact of exposure therapy for anxiety disorders[22,84].

A second weakness of most "negative" studies of pro-cognitive agents for SZ is that these trials suffer from the lack of biomarkers that identify sensitive "enriched" clinical subgroups of patients[43,47,60]. Given the range of neurocognitive and symptom profiles across chronic psychotic disorders, reflecting the heterogeneous

neurobiology of these disorders, it is not surprising that a drug acting through one mechanism to enhance one neurocognitive domain might not generate significant improvement in a non-stratified patient cohort.

The PACT approach in general, and in this application specifically, diverges from past "negative" pro-cognitive trials in these two critical ways. First, PACTs pair a putative pro-cognitive agent with a cognitive "load" that puts demand on cognitive resources that are augmented by that drug. For example, as described below, this PACT application proposes to combine a drug that enhances attention with a TCT task that is attentionally demanding, and in which performance is associated with attentional capacity[105]. By pharmacologically enhancing attention, we have evidence[98,104] (see below) that we can enhance TCT learning in an optimized laboratory setting; if this finding is confirmed in Aim 1, we will test the hypothesis that such enhanced learning translates into greater clinical gains from TCT (Aim 2). Second, PACT designs incorporate biomarkers to identify individuals who are most likely to benefit from the pairing of drug and cognitive therapy. In the PACT design described herein, potential biomarkers range from neurophysiological measures of forebrain mechanisms that regulate early auditory information processing, to performance markers of sensitivity to a "test dose" of a drug+TCT pairing.

This application uses an **experimental therapeutics approach** in an "efficient pilot test" of the hypothesis that the pro-attention psychostimulant, amphetamine (AMPH), will augment TCT-induced learning, and thereby clinical, neurocognitive and functional gains, in AP-medicated SZ patients. In so doing, this application will advance a PACT model for TCT in two specific ways: 1) building on strong preliminary findings (below), this application will confirm target engagement and identify predictive biomarkers that predict the effectiveness of AMPH-enhanced TCT learning, and 2) this application will provide the first randomized controlled trial to assess the ability of medication-enhanced TCT learning (target engagement) to produce significant and lasting clinical, neurocognitive and functional gains in biomarker-stratified SZ patients. In this way, this application responds to RFA-MH-18-705, "Development of Psychosocial Therapeutic and Preventive Interventions for Mental Disorders", which supports *"efficient pilot testing of novel psychosocial therapeutic and preventive interventions for mental disorders… using an experimental therapeutics approach*." Moreover, in this application, "*results, whether positive or negative, will provide information of high scientific utility and… support 'go/no-go' decisions about further development or testing of the intervention.*" The application uses a "*novel intervention strategy"* - the PACT model - in a design that will "*replicate target engagement and relate change in the… target/mechanism to clinical benefit."* Findings from this pilot study will **inform a future, fully-powered Confirmatory Efficacy trial.**

The proposed use of EEG and objective behavioral biomarkers will produce system-level mechanistic insights, e.g. regarding the relationship of early sensory processing, target engagement, auditory discrimination and attentional capacity to clinical and neurocognitive benefits of pharmacologically augmented TCT. This approach is consistent with the NIMH goal to *"identify reliable and stable biomarkers that… are correlated with individual treatment response, or identify subjects that would most benefit from the intervention"* (NOT-MH-14-007). In a future, larger trial, these biomarkers may be implicated as mediators of PACT clinical gains, as in[108].

"Does this application challenge... current research/clinical practice?" As noted above, the PACT strategy in this application fundamentally challenges current treatment models for SZ. In a successful use of PACT, there is a specific pairing of drug and cognitive "load": a drug that enhances specific neurocognitive domains is paired with a cognitive therapy that utilizes/places demands on those domains. At a mechanistic level, PACT challenges existing clinical practice by proposing treatments that target spared, healthy circuitry in patients rather than pathological circuitry per se (which is widely distributed and highly variable among psychosis cohorts[123]). Ultimately, treatment choice will be guided by biomarkers that might include laboratory-based measures, perhaps including a patient's neurophysiological and TCT performance response to a challenge-dose of a pro-cognitive agent. A "deliverable" innovation of this application will be a novel PACT "prototype": a validated paradigm through which AMPH will enhance the therapeutic benefits of TCT in biomarker-identified SZ patients.

Approach: The choice of the dopamine (DA)- and norepinephrine (NE)-releaser, AMPH, for this PACT approach is based on: 1) extensive experience with AMPH in the treatment of attentional and other cognitive deficits: because pro-attentional effects are "known", it will be easier to interpret "negative" findings; 2) robust evidence that AMPH enhances neurocognitive performance in AP-medicated SZ spectrum patients at doses that are safe, well tolerated[6,38,54,79-80,87,117] and reduce negative symptoms[57,73]; 3) a rich cross-species literature of AMPH effects that can inform us about mechanisms of action; and 4) novel and compelling findings from the PI's R01 (MH59803) of AMPH effects in healthy subjects (HS) and SZ patients[104] (below, Fig. 2). This choice is also informed by the PI's MH59803 studies in HS with pergolide, bromocriptine, pramipexole, amantadine, memantine and tolcapone, in addition to AMPH[14,91,97,100,102]. Neither "selective" DA- nor NE-receptor agonists have comparable evidence-based pro-cognitive effects in SZ patients, and thus cannot yet be used to test the main hypothesis in this application. A systematic review and meta-analysis of 22 studies investigating psychostimulant effects in patients with SZ determined that methylphenidate but not AMPH worsened symptoms. Exposure to AMPH in this study and in the proposed PACT design is **very limited**: 5 mg, 3 times per week, for approximately 10 weeks. However, implicit in this choice is the fact that future applications of PACT for SZ – even involving

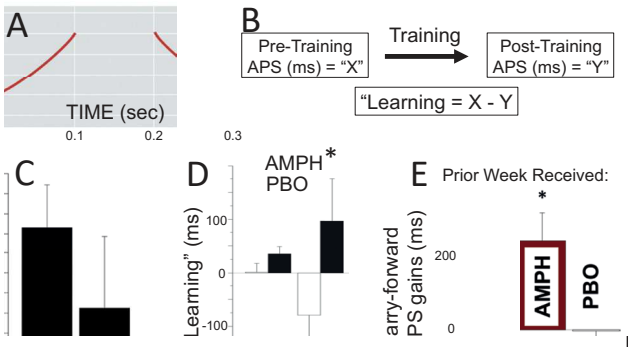
TCT – might ultimately utilize different classes of medications. Specific issues regarding the clinical safety and tolerability of AMPH in antipsychotic-medicated SZ patients are very important and are addressed in detail below.

We reported that TCT performance is significantly associated with measures of auditory attention, among other cognitive domains[105]. We hypothesize that, based on its pro-attentional effects: 1) AMPH will augment and/or accelerate implicit learning processes in TCT, and their effects on higher order cognition; 2) AMPH-enhanced TCT **learning** will be detected in 1-h of TCT, via augmented gains in a quantifiable target (**auditory processing speed (APS)**); and 3) AMPH-enhanced TCT learning will augment, accelerate or make more durable the therapeutic effects of TCT via a convergence of "top-down" AMPH effects and "bottom-up" TCT effects, by helping patients sustain or direct attention towards task-relevant TCT stimuli. Consistent with the RFA for this experimental therapeutics design, this application proposes clear hypotheses *"about how an intervention directed at changing the target can lead to functional improvement and/or clinical benefits*." We do not exclude a "partial mediation model", i.e. the possibility that other pro-TCT effects might be mediated by AMPH-enhanced associative learning, reinforcement or neuroplasticity[29]. Lastly, the proposed mechanism is not specific to patients with the diagnosis of SZ, but rather is *"directed towards an operationally defined, empirically-supported **(RDoC) functional domain**"*, i.e. **cognition**, and the specific construct of **attention** and its impact on learning.

Fig. 1. Proposed 4-step model for PACT as tested in this application: AMPH-enhanced therapeutic effects of TCT

1. AMPH → ↑ **attention/vigilance**, especially in individuals with low attention/vigilance[23];
2. ↑ attention/vigilance → ↑ **auditory discrimination** (Fig. 3C)[105];
3. ↑ auditory discrimination → ↑ **auditory learning** (e.g. ↑ APS learning; Figs. 2C, 3A,B)[98,104];
4. ↑ auditory learning → ↑ **clinical, neurocognitive and functional gains from TCT** (Aim 2)

A prerequisite for AMPH's utility in a PACT application is that it have appreciable pro-cognitive effects in patients. As noted above, the literature provides evidence that a single small oral dose of AMPH can modestly enhance neurocognition in SZ- and SZ-spectrum patients, without adverse effects, and our findings confirmed this with 5 and 10 mg doses[98,104]. However, there are limitations to this literature. First, the magnitude of pro-cognitive effects of AMPH in most studies is modest. AMPH-induced gains in non-motor measures in Goldberg et al.[38] reached "trend" levels; in Barch & Carter[6], they reflected planned contrasts and the loss of trend-level deficits in patients vs. HS; in Petrzak et al.[79] they were robust in one report with 10 mg po, but moderate in another with 20 mg po (*d*= 0.63[80]). Second, meaningful comparisons across these studies, and with subsequent studies of other putative pro-cognitive agents, are confounded by a lack of shared performance measures. Until recently, no studies had tested the effects of AMPH on neurocognition in SZ patients using the MCCB, considered the "gold standard" for repeatable measures of pro-cognitive drug effects in SZ; nor had any studies in SZ patients assessed the utility of biomarkers to identify patients most likely to exhibit AMPH sensitivity, as discussed below. And of greatest relevance to this application, until the PI's studies supported by MH59803, no study had tested the effects of AMPH on learning processes specifically engaged by cognitive training in SZ patients.



2. Preliminary studies[104]: AMPH effects on Sound eps learning. A. Subjects identify "sweep direction" of ency modulated tones; adaptive trials increase in ulty as subject learns. B. Auditory Processing Speed , in ms; smaller # = better discrimination) is calculated pre- and post-training. APS "learning" is defined as pre minus APS post". C. At screening, healthy subjects tend to "learn" more than SZ patients. D. In a within- ct design, 10 mg AMPH enhanced APS learning in both nd SZ patients. E. AMPH-induced gains in APS learning ed forward" to pre-testing 1 wk later; this did not happen ner no pill or PBO was received the previous week.

Preliminary Studies: 1. Amphetamine effects on auditory frequency modulation learning in SZ patients[104].

MH59803[98,104] tested the hypothesis that AMPH will enhance learning of auditory frequency modulation in "Sound Sweeps" -- a major component of the Posit Science TCT program known to enhance clinical, neurocognitive and functional status in SZ patients[31-2,115]. We reported that performance in this Sound Sweeps task is dependent on attention[105], and we hypothesized that gains in the main performance metric of auditory processing speed (APS) would be augmented by the pro-attention drug, AMPH. APS was measured in 24 AP-medicated SZ patients and 35 healthy subjects on 3 days, each separated by 1 week. Specific candidate biomarkers were assessed as potential predictors of sensitivity to AMPH-enhanced gains in APS among patients, including prepulse inhibition (PPI) of startle, specific event-related potentials (ERPs), neurocognition (MCCB) and the rs4680 polymorphism of catechol-O-methyltransferase. On two test days, subjects ingested either PBO or 10 mg AMPH po, in a double-blind, balanced order design; TCT, PPI and MCCB measures were repeated on each test day.

Auditory system "learning" (APS pre- vs. post-training) 210 min post-pill was significantly **enhanced by 10 mg AMPH (p<0.002), particularly in SZ patients** (Fig. 2D); rs4680 status did not moderate AMPH effects on APS. Among patients, more APS learning was associated with **AMPH-induced increases in attention** (MCCB "A/V" domain: r=0.34, p<0.05) and **shorter latency of the P3a ERP** (r=-0.43, p<0.035). There were no significant "order effects": AMPH enhanced APS learning whether it preceded or followed placebo testing. AMPH-enhanced learning was **not state-dependent**: it "carried forward" to the next testing day, 1 week later (Fig. 2E). There were no adverse effects of AMPH, consistent with our experience with higher doses of AMPH (20 mg po) in HS[23,94,97,103,106]. Subjectively, participants could not guess pill identity at greater than chance levels, while objective / blind measures of alertness, hedonia and autonomic function confirmed AMPH bioactivity.

Based on these findings, we submitted an R61/R33 application (MH112742); the primary goal of the R61 was to both confirm "target engagement" (AMPH effects on APS learning) and optimize AMPH dose and post-AMPH time interval for an R33 "pilot" trial of an AMPH/TCT PACT design in SZ patients. The major critiques of this application were that the proposed R61 scope (parametric dose- and time-course optimization) was 1) "incremental" (not novel); and 2) not "significantly distinct from [the scope of] MH59803". Seeing no other viable path forward, over the next 2 years we used carry-over funds from MH59803 and funds from a NARSAD Distinguished Investigator Award to complete the previously proposed R61 parametric studies (target n=36 SZ patients; current n=30), in addition to relevant "foundational" studies of TCT in SZ patients, described below.

These studies (Fig. 3; reported in[98]) use a within-subject 4-week design to test dose-response effects of AMPH (0, 2.5, 5 or 10 mg po) on APS learning, given 60 (current n=12) or 210 min (n=18) prior to Sound Sweeps. AMPH significantly enhanced APS learning at both time-points, with an inverted-U dose-function reflecting maximal gains with 5 mg (d=0.85; Fig. 3A). APS learning gains with AMPH were greatest among patients in the lowest 50% of attention/vigilance (A/V) scores (the highest 50% scored in a "normal" A/V range), consistent with our findings that low baseline attention/ vigilance predicts greatest AMPH-enhanced attention[23]. AMPH-induced gains in auditory discrimination (assessed by the QuickSIN "Speech-in-Noise" measure) and sensorimotor gating (prepulse inhibition) in SZ patients parallel those in APS learning, both in terms of optimal dose (5 mg) and attention-dependence (greatest in patients with low MCCB "A/V" scores) (Fig. 3C,D). We have preliminary[92] evidence for similar findings with memantine, a drug pharmacologically distinct from AMPH, and collectively these findings are incorporated into our working mechanistic models for PACT effects on TCT (e.g. Fig. 1).

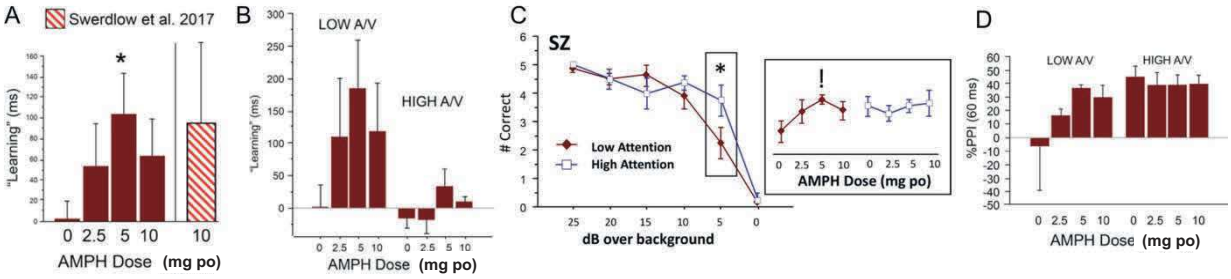


Fig. 3. Preliminary studies: AMPH dose-effects[98]. A. Maximal APS learning with 5 mg AMPH (d=0.85); hatched bar shows 10 mg data from Fig. 2D. Similar effects of 5 mg were detected 60 and 210 min post-pill. B. AMPH gains in APS learning in patients with impaired-range A/V scores. C. QuickSIN detected deficits at 5 dB in low-attention patients (*) corrected by 5 mg AMPH (!). D. Similar inverted-U AMPH effects on prepulse inhibition (PPI) in low-attention patients.

Safety of AMPH in AP-medicated SZ patients: Over the course of studies in Figs. 2-3, we accumulated enough experience to publish findings on the safety of AMPH in antipsychotic-medicated SZ patients[95]. We assessed autonomic, subjective and clinical measures after acute (same day) and subacute exposure (across 4 weeks of repeated within-subject dosing), and were able to recontact and clinically assess 19 subjects with an average post-AMPH interval of 17 months. AMPH was associated with no detrimental subjective, autonomic or clinical changes. Symptoms assessed acutely, sub-acutely or long-term were either unchanged or reduced. Reductions in BPRS psychosis scores were noted across each test day; long-term, psychosis symptoms declined (SAPS: p<0.009) and function increased (Scale of Function: p<0.015). Anecdotally, 4 subjects participated in both single and multi-dose studies, resulting in a cumulative AMPH dose of 27.5 mg; in these subjects, long-term reductions in SANS and SAPS were *d*=1.11 and 0.93, respectively. Among the 19 recontacted subjects, antipsychotic dose (chlorpromazine equivalents) declined for 6 subjects by an average of 411 mg/d, increased in 2 subjects by an average of 146 mg/d, and was unchanged in 11 subjects. **No subjects experienced any adverse effects of AMPH after 1 dose, 3 weekly doses over 4 weeks, or both, assessed daily, weekly or 17 months later.**

For perspective, the 5 mg dose proposed in this application is a conservative starting dose for **children**, ages 6 and older, for the treatment of ADHD, who then titrate to substantially higher doses taken daily for years; this application proposes this 5 mg dose for **adults** who are taking medications (antipsychotics) known to block many adverse effects of amphetamine[70,95,104], and these patients will have a total exposure of 30 pills over 10 weeks.

Prelim. Studies: 2. TCT effects on neurophysiological, neurocognitive and functional measures in SZ patients

In the past 3 years, the PI and Co-PI (Dr. Light) assessed biomarker predictors of TCT response in 46 severely ill SZ patients at a residential treatment facility. Findings from these studies are published[45,48,77-8,107,109]. In brief, patients were assessed in measures of neurocognition and early auditory information processing, and then randomly assigned to TCT (1-h, ≈ 3 times/week, total ≈ 30 sessions) or treatment as usual (TAU) groups. As seen in Fig. 4, compared to TAU, TCT patients exhibited significant gains in neurocognition (verbal learning, the most disabling neurocognitive deficit of SZ), reduced symptoms (auditory hallucinations) and enhanced function (engagement and participation in psychosocial groups and activities); compared to TAU, gains in function by TCT patients over 10-weeks translated to 1 full extra week of clinical rehabilitation[45,107,109]. Importantly, gains in neurocognition and symptoms correlated significantly with (i.e. were predicted by) 3 EEG-based measures (discussed below). As it relates to the feasibility of this application, these findings demonstrate that: 1) a trial of TCT is feasible in patients with chronic psychotic disorders; 2) TCT is well-tolerated, even among severely disabled, functionally impaired patients; 3) TCT produces quantifiable gains in clinical, neurocognitive and functional metrics; 4) adding high-density EEG testing to a TCT protocol is feasible and well-tolerated; and 5) changes in functional EEG biomarkers of auditory system target engagement predicted TCT-induced gains.

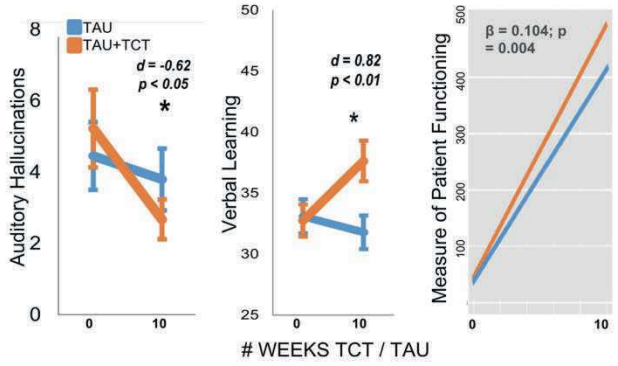


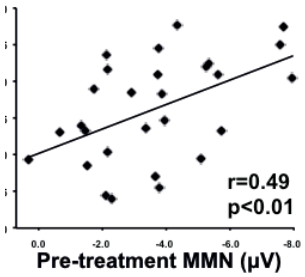
Fig. 4. TCT effects on symptoms (Scale of Positive Symptoms auditory hallucinations ($p<.05$) and voices conversing $p<0.01$), neurocognition (MCCB verbal learning, $p<0.01$) and function ($p<0.005$) in SZ patients over 10 weeks of TAU (n=22; blue lines) or TAU+TCT (n=24; orange lines)[45,107,109]. Findings confirm feasibility of quantifying significant gains from TCT in the same population to be used in this application. Larger effects were detected in biomarker-identified subgroups, but there is clearly "room" for AMPH-enhanced effects on these and other symptoms, neurocognitive domains and functional metrics, as proposed here, as well as the rate and durability of these changes (not assessed in our previous studies).

Target Engagement: APS learning is the **target to be engaged** in this application. Compared to healthy subjects, APS learning is impaired in SZ patients[104]. We hypothesize that this impaired learning is one factor that prevents SZ patients from benefiting fully from TCT; by enhancing APS learning, patients will benefit more from TCT. Consistent with the experimental therapeutics model supported by this RFA, TCT "learning", as detected by gains in APS, is the *"factor that an intervention intends to modify, based on a hypothesis that [its] modification will result in improvement of symptom, behavior, or functional outcomes."* This choice of targets is consistent with this RFA instruction, *"Targets might include…potentially modifiable…cognitive processes…"* We hypothesize and will test in this application that AMPH-enhanced learning during TCT – **of which APS learning is an accessible, quantitative metric** - will amplify, accelerate or make more durable the clinical, neurocognitive and functional gains after a 30-h course of TCT, i.e. *"test the hypothesis that the target is relevant to the clinical problem under study."* In addition to TCT Sound Sweeps used in target engagement, clinical delivery of TCT involves training modules that engage auditory sensory processing in ways that are distinct from Sound Sweeps. Nonetheless, we predict that AMPH-enhanced gains in APS learning reflect processes that will generalize to AMPH-enhanced gains in the therapeutic impact of these other auditory sensory-based tasks. Other potential measures of target engagement, including "APS plateau"[16] will also be explored as secondary outcomes.

More generally, our findings have led us to develop working mechanistic models of PACT effects on TCT (e.g. Fig. 1). PACT works when a medication engages brain substrates regulating neurocognitive resources that are demanded by the form of learning being applied in cognitive therapy. With enhanced neurocognitive resources, greater learning is possible; in some cases this enhanced learning is associated with (and potentially mediated by) an identifiable intermediate neural mechanism. With greater learning, the learning-based therapy has an enhanced clinical impact. In the present application, AMPH enhances attention, most prominently among patients with the lowest basal attentional levels. Enhanced attention mediates greater auditory discrimination; this is evident both in gains in EEG metrics of early auditory information processing, and in enhanced speech discrimination in QuickSIN testing[98] (Fig. 3C). Patients able to better discriminate sounds are able to more quickly discriminate and learn to correctly identify Sound Sweeps (and learn other TCT components), and the therapeutic impact of learning to detect tonal frequency modulation (e.g. a critical feature of prosody that allows an individual to better interpret the affective content of speech) is augmented. Based on this model, we acknowledge that – in addition to gains in APS learning - "target engagement" could be demonstrated either via gains in attention (e.g. MCCB scores in "A/V" domain) or auditory discrimination (QuickSIN score), but feel that the target that is most proximal to the therapeutic impact of TCT in this model is learning, i.e. gains in APS. Because of its "proximity" to the therapeutic impact of PACT, APS learning should be a target that provides a robust engagement signal and that strongly predicts the clinical consequences of the PACT intervention.

Biomarkers are critical to a PACT strategy: An explicit feature of a PACT intervention is that it incorporates one or more biomarkers that distinguish subgroups of individuals whose biology is more vs. less sensitive to the ability of a drug to magnify, accelerate or make more durable the clinical gains from cognitive therapy. **Indeed, we predict that not every patient will gain from either TCT or the addition of AMPH to TCT**, and thus a critical feature of both PACT and this application is the development of reliable, quantitative predictive measures. The PI and Co-PI have written elsewhere about the optimal features of such predictive measures[59,93]. Our preliminary studies have identified strong candidate biomarkers that may predict: 1) the amount of APS learning in the initial hour of Sound Sweeps exposure; 2) an individual's sensitivity to the ability of AMPH to enhance APS learning; and 3) an individual's sensitivity to neurocognitive and clinical gains from TCT.

1) Predictors of **APS learning** in the initial hour of Sound Sweeps? We reported that APS gains in the first hour of Sound Sweeps training are predicted by a measure of early auditory information processing, **mismatch negativity** (MMN) (Fig. 5). This is one of several findings from our group (detailed below), suggesting a strong connection between measures of early auditory information processing, and learning mechanisms engaged via auditory TCT.



ig. 5. Biomarker predictor? Mismatch Negativity (MMN) rior to Sound Sweeps redicted APS learning here as % baseline gains) n 31 SZ patients[60], using ne 64-Channel BioSemi ctive Two system roposed in this application.

2) Predictors of **AMPH-induced gains in APS learning**: While studies to date have not been fully powered to assess mediators or moderators of AMPH effects on APS learning, we have nonetheless identified two predictors of an individual's sensitivity to AMPH-enhanced APS learning.

First, data support a relationship between **attention/vigilance** (MCCB "A/V" scores) and AMPH effects on APS learning. In our initial study, the MCCB was administered on PBO and 10 mg AMPH test days; AMPH-induced gains in MCCB A/V scores were significantly associated with AMPH-induced gains in APS learning ($r=0.34$, $p<0.05$)[96]. In our dose-response study, the MCCB was administered only on the screening day; patients with low screening MCCB A/V scores gained the most from AMPH in terms of APS learning, seen in Fig. 3B. One parsimonious explanation for these two findings is that patients with low A/V scores: 1) perform poorly on Sound Sweeps because attention is critical for APS learning[105], and 2) are most sensitive to the A/V-enhancing effects of AMPH (as we reported in healthy subjects[23]); and hence 3) gain the most in terms of APS learning as a result of their gains in A/V scores (as we reported in[98]). *Even if this "PACT" approach "only" benefits SZ patients with impaired attention, this would be an important advancement, and one that could be easily "personalized".*

Second, in our initial study, AMPH-induced gains in APS learning were associated with shorter latencies of the P3a event-related potential ($r=-0.43$, $p<0.035$). Shorter ERP latencies are generally considered to reflect more efficient information processing; though clearly a post-hoc observation, it may be that individuals who - by this metric - are least efficient at early auditory information processing are also least able to benefit from AMPH's impact on APS learning. This application will test the "reproducibility" of this observation and potential biomarker.

3) Predictors of **gains from 30-h of TCT**: Neurocognitive (primarily but not exclusively verbal learning) and/or clinical gains after 30 sessions of TCT were predicted by both baseline levels and changes in specific EEG measures after 1 hour of Sound Sweeps. First, baseline (pre-TCT) levels of the Auditory Steady State Response (gamma power) and theta activity both predicted post-TCT gains in neurocognition[46]. Second, gains in P3a amplitude over the course of the first hour of Sound Sweeps significantly predicted both gains in verbal learning ($r=0.58$, $p<0.025$) and reduced hallucination (SAPS; $r=-0.54$, $p<0.04$) after 30-h of TCT[45].

PACT predictors? Compared to biomarker predictors of a TCT response, or a drug response, predictors of a PACT response – i.e. the ability of a drug to augment the therapeutic effects of TCT - might reflect more complex mechanisms, e.g. related to: 1) an individual's sensitivity to either pro-cognitive or adverse effects of the drug; 2) the specific "match" between the pro-cognitive mechanisms of a drug and an individual's cognitive profile/deficits or capacity for TCT-based learning/neuroplasticity; 3) disease-related factors influencing capacity for clinical change over 30-h of TCT, or to some combination thereof. This application (Aim 3) will pilot the use of several specific biomarkers and outcome measures to identify patients most sensitive to the ability of AMPH to augment TCT benefits; most promising measures will be applied in a subsequent "Confirmatory Efficacy trial". Biomarker findings will also inform models for system-level mechanisms (Fig. 6) whereby: 1) basic information processing capacity moderates the impact of drug-enhanced attention on procedural learning, and 2) enhanced "bottom-up" sensory learning promotes higher order changes in neurocognition, symptoms and function.

AMPH enhances simple sensory-based learning and its underlying cortical reorganization[29]; such processes might be responsible for the observed facilitation of TCT-based sensory discrimination learning. As noted above, a more parsimonious (but not mutually exclusive) explanation for AMPH-enhanced "learning" in this TCT

paradigm is that AMPH enhances attentional engagement with the auditory discrimination task. Anecdotally, test subjects (particularly patients) are challenged to maintain full attention throughout the hour-long Sound Sweeps task, and conceivably, a low dose of AMPH might help subjects stay "on task". Nonetheless, both our empirical data and conceptual models leave us well short of a neural or molecular mechanistic explanation of AMPH's actions in a PACT model, and it is not realistic to suggest that such mechanisms will be fully explicated via the present application. However, if utility of an AMPH PACT regimen is confirmed in this R33, we plan to develop these models within subsequent clinical trials (of AMPH and perhaps memantine), and in a separate application focused on basic mechanistic analyses of TCT learning.

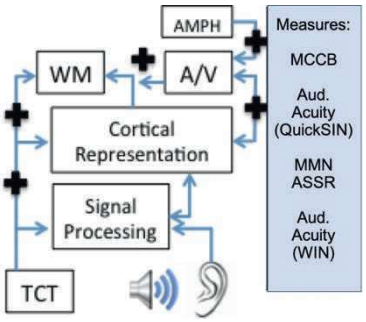


Fig. 6. Simplified schematic of a system-level mechanistic model informed by this application. **Cognitive constructs** and **circuits** map onto an **RDoC matrix**. Biomarkers/ outcome measures probe different system levels; some circuit-level information will come from pre- vs. post-TCT changes in EEG source dynamics. "**+**" = convergent gains from TCT and AMPH.

Critical next step: Our preliminary findings from MH59803 provide evidence of target engagement for this PACT model: compared to PBO, AMPH was associated with greater APS "learning" across 1-h of TCT. However, this evidence is inadequate to justify a Confirmatory Efficacy trial with PACT, since AMPH may enhance TCT-induced APS learning, but still not enhance TCT-induced clinical, neurocognitive or functional gains. Even with evidence of target engagement, and its replication and optimization in MH59803, it is only a *hypothesis* that enhanced learning during TCT will augment its clinical benefits. *Consistent with this RFA-MH-18705* ("*replicate target engagement and relate change in the… target/mechanism to clinical benefit"),* **testing this hypothesis, with specific "Go/No Go" criteria, will be the most critical development of the present application.** Beyond this critical step, this application will leverage a substantial foundation of findings from MH59803, to explore (i.e. "learn/confirm") mature hypotheses related to mechanisms (e.g. Fig. 1) and predictors of pro-cognitive therapeutics for SZ.

Six potential limitations: It is important to acknowledge and address the potential limits of this application.

Limitation #1? It might not work: Some evidence suggests that drug-enhanced APS learning, symptom reduction and neurocognitive gains from TCT may be dissociable phenomena, i.e. AMPH might enhance APS learning but have no impact on PACT-induced neurocognitive gains. Cain et al.[20] reported that SZ patients taking the pro-extinction NMDA agonist, D-cycloserine (DCS) – but not those taking PBO - exhibited significant gains in APS learning and negative symptom reduction during an 8-week trial of TCT; DCS-enhanced APS learning was evident at the first time point (1 week). Interestingly, PBO- but not DCS-treated patients exhibited significant gains in MCCB performance. Thus, enhanced APS learning was associated with symptom reduction but not neurocognitive gains. This R33 application differs from the Cain et al.[24] study in several specific ways, including: 1) this application uses a detailed conceptual framework for PACT design and implementation; 2) it benefits from dose/time optimization studies (Fig. 3) to maximize drug effects on APS learning; 3) AMPH is a pro-attention DA releaser, while DCS is a pro-extinction NMDA agonist. Clearly, better attention (after AMPH) might augment the neurocognitive effects of TCT, while better extinction (after DCS) might not; 4) the present study uses a suite of hypothesis-driven biomarkers to identify potentially sensitive patient subgroups; and 5. The present patient cohort might have more "room to move" in outcome metrics. Nonetheless, it is clear that AMPH-enhanced TCT gains might be most evident in some but not all metrics (symptoms, neurocognition, function), even in the face of robust target engagement. With this understanding, we will carefully track and dissect these distinct outcome measures over the course of the R33 (Fig. 7), as we have in our published studies[45,48,77-8,107,109 .]

One possible basis for a lack of PACT response might be that, over a 30-session trial, enhanced learning with AMPH may be state-dependent (to some degree). Evidence from our preliminary study suggests that AMPH-enhanced APS learning was not "state-dependent": APS gains from training done under AMPH conditions **"carried over"** to the pre-assessment phase of a subsequent test, 7d later (Fig. 1F). However, this finding does not guarantee that clinical, neurocognitive or functional gains from an AMPH PACT regimen would not exhibit some state-dependency, i.e. be less robust when patients are assessed in the absence of AMPH. In practical terms, it matters less whether there is some degree of state-dependent learning in this process, as long as "enough" learning and the associated clinical changes do generalize to a non-AMPH state. Outcome measures after sessions 10, 20 and 30, and 12 weeks later (Fig. 7), will be acquired in the absence of AMPH.

Limitation #2? Even if AMPH is safe in SZ patients after 1-3 doses, is it safe if used 30 times over 10 weeks in this R33? Even with the stress of neurochemical imaging, and/or a bolus i.v. infusion[1,2,27,56,65,113], in **AP-unmedicated** SZ patients, high doses of AMPH have mixed and transient clinical effects, often improving symptoms and neurocognition. A recent meta-analysis documents the safety of AMPH in antipsychotic-medicated SZ patients[88], and studies (Fig. 2-3) confirmed that AMPH is well-tolerated and enhances learning in such patients. However, our 2 studies involved only 1-3 doses of AMPH, while in this R33 PACT paradigm, AMPH will be taken 30 times over ≈10 weeks, each pill paired with a session of TCT. Thus, it would be reassuring

to find evidence that comparable dosing with AMPH, followed by its discontinuation, is safe in AP-medicated SZ patients. The recent meta-analysis[73] cites many such studies; one recent example is described here:

Lasser et al.[57] reported the safety of daily lisdexamfetamine (ld-AMPH), an AMPH pro-drug (Vyvanse 20-70 mg/day; equivalent AMPH dose = 5.9–20.8 mg/d), in 92 antipsychotic-medicated SZ outpatients, in a 10-week trial, followed by abrupt discontinuation and a 4-week follow-up. Daily ld-AMPH for 10 weeks significantly reduced negative symptoms but did not increase adverse events; abrupt discontinuation of ld-AMPH did not lead to an increase in adverse events. These data support the safety of 10 weeks of daily AMPH use, in doses that far exceed those proposed herein, followed by abrupt drug discontinuation. Total AMPH exposure in that study greatly exceeded the amount proposed in this application (e.g. 70 consecutive days of 5.9–20.8 mg/d vs. 30 days over ≈10 weeks of 5 mg/d). Still, patients in this application are **carefully monitored** as described below, and assessed by a licensed clinician 3 times each week, and tested on a range of clinical scales including **RFA-mandated suicidality scales**, throughout the full course of the study.

Importantly, while daily AMPH in the Lasser et al.[57] study reduced negative symptoms in SZ patients, we do not predict that the more limited TCT-paired use of AMPH in the present study will reproduce these effects. In fact, we predict that AMPH will primarily exert its therapeutic effects by **augmenting the impact of TCT**, which should result in reduced negative **and** positive symptoms, as well as neurocognitive and functional gains (see Fig. 4).

Limitation #3? This application will not pinpoint molecular or neural circuit-level mechanisms of AMPH, TCT or PACT effects, in a biologically heterogeneous group of medicated psychotic patients. **This is true.** Nominally, circuit-based models may help frame the PACT construct within the RDoC matrix. In the simplest model, neurocognitive deficits in SZ patients caused or exacerbated by low PFC DA tone will be "rescued" by AMPH-induced PFC DA release; potential adverse effects of AMPH-induced subcortical DA release will be blunted by antipsychotics via D2 blockade, with relatively weaker blockade of PFC D1 receptors[26,44]. In this model, AMPH might be most beneficial to patients whose forebrain DA systems, including PFC and subcortical regions working in concert, are most sensitive to pro-neuroplastic effects of AMPH. We reported circumstantial support for this model, based on levels of positive symptoms, positive hedonic effects of AMPH, AMPH-enhanced PPI and attention, AMPH-enhanced APS learning and antipsychotic dosing in SZ subjects, as well as related animal models[93]. **However,** the hypothesized ability of AMPH to enhance TCT performance in SZ patients is first and foremost based on empirical evidence (e.g. Figs. 2-3), independent of unproven circuit- or pathophysiological models involving DA, NE or other brain substrates. The explicit primary goal of this application is to provide the first-ever test of a novel, evidence-based therapeutic model, starting with confirmation of target engagement, but not to investigate the pathophysiology of SZ; system-level mechanisms will be modeled (e.g. Fig. 6).

Limitation #4? This PACT is stacked: This R33 design is optimized: a) patients are carefully characterized as part of a clinical trial; b) AMPH dose and timing are optimized based on MH59803; c) potential logistical hurdles that might cause subject attrition (transportation, food, reimbursement) are minimized; and d) biomarker assessment uses high fidelity lab-based measures that are not readily available in community-based settings for mental healthcare delivery. While this optimized design is feasible in our on-site laboratory (see below, "Feasibility"), a robust PACT design will face challenges in implementation in the "real world". Importantly, different PACT delivery models are being studied by the PI and Co-PI, and we are in discussions with a local Intensive Outpatient Program (IOP) (comparable to "Day Treatment"). The IOP model has been particularly successful in San Diego, and could be adapted to incorporate PACT into an integrated treatment, along with standardized biomarkers for personalized regimens, careful monitoring of clinical state and antipsychotic adherence, and individual and group supportive therapies. If this and a Confirmatory application support PACT efficacy, it will be "scalable."

Limitation #5? Control groups? Adding control "computer game" groups might reveal if PACT benefits reflect 3x/week AMPH use independent of TCT, computer use independent of TCT, and/or interactions of AMPH+computer use. These are 3 very-low probability outcomes. We opted against this since: 1) efficacy of TCT is already known, so our primary aim is to assess the impact of added AMPH vs. PBO; 2) recruitment demands for 4 groups will not yield "n's" needed to detect meaningful Go/No-Go criteria; and 3) requiring patients to complete 30-h of non-therapeutic games for 10 weeks, or exposing patients to AMPH under conditions that are unlikely to have lasting clinical value, **is not ethically justified**. Fisher et al.[33] found that patients randomized to computer game groups exhibited significant declines in verbal memory. Healthy subjects are not studied since no likely PACT effects on such subjects would alter the clinical implications of either positive or negative findings in SZ patients.

Limitation #6? Ceiling effects? TCT effects on neurocognitive and clinical metrics might be "at ceiling", and thus insensitive to further gains from AMPH. Compared to treatment as usual, 30-h of TCT in our studies resulted in medium-to-large effect size gains in Verbal Learning (d=0.65) and auditory discrimination ("Words-in-Noise"; d=0.67), and in reductions of auditory hallucinations (d=-0.64)[139a]. However, TCT did not produce gains in other MCCB domains (e.g. Cohen's d's for processing speed, attention/vigilance and working memory were -0.1, -0.3 and -0.29, respectively), or in broader symptom profiles (e.g. SANS or SAPS). Thus, despite robust gains in some areas after TCT, **there is clearly "room to move"[93] for added PACT-induced gains**. Furthermore, while

past studies assessed the magnitude of TCT effects at a single point (after 30 sessions), the proposed study will assess both the onset and durability of PACT effects. It is possible that AMPH will accelerate and/or prolong the gains from TCT, in ways that were not assessed in our previous studies, but which are certainly of clinical importance. The small sample size of this "pilot" study will not easily detect traditional ($p<0.05$) statistically significant group differences, but "Go/No-Go" decisions will be based on "clinically meaningful" Cohen's $d=0.5$.

Will "negative results… guide further intervention development"? This R33 has clear *'Go/No-Go'* criteria. **If target engagement is not confirmed**, we will conclude that this design setting is unsuitable for detecting robust AMPH group effects on APS learning. Based on the data (e.g. evidence of AMPH bioactivity), we will develop testable hypotheses (e.g. cohort differences) that might account for differential outcomes in the present application vs. studies in MH59803. Even if there are not robust AMPH effects on APS learning (target engagement), it is possible that heterogeneity in AMPH APS sensitivity might reflect meaningful subgroups of patients (e.g. low vs. high attention/vigilance), and that APS AMPH sensitivity might still predict (correlate with) AMPH enhancement of TCT therapeutic effects. In other words, a lack of a group difference (placebo vs. AMPH) would not preclude the utility of AMPH APS sensitivity as a predictive biomarker. Conversely, even if target engagement is confirmed, it is possible that group differences (placebo vs. AMPH) in therapeutic gains might not be detected. A "valid" negative outcome (e.g. lack of positive AMPH effects on outcome measures despite evidence of target engagement and adequate TCT exposure) will indicate that AMPH-enhanced APS learning is not sufficient to enhance TCT effects in a **clinically**-defined SZ cohort. Analyses will then determine if AMPH enhances TCT effects in **biomarker**-defined SZ subgroups. A failure to detect such subgroups would suggest a dissociation between target engagement in the first Sound Sweeps session and therapeutic benefit after 30-h of TCT. Factors contributing to this dissociation might include (among other possibilities): 1. Tolerance to the "pro-learning" properties of AMPH (unexpected, since AMPH retains pro-attentional effects, even after years of daily use); 2. State-dependent learning (discussed above); 3. Adverse effects of AMPH on psychosis, akathisia or other symptoms; such effects will be assessed via clinical metrics (below). Analyses of these and other factors that might impede AMPH-induced gains will guide further development of both TCT and PACT interventions.

Feasibility: Our research team includes a Board Certified Psychiatrist (NS) with SZ clinical trial experience, a licensed Clinical Psychologist/Neurophysiologist and PI of a BBRF-funded trial of biomarker predictors of TCT in SZ patients (GL), an expert statistician with a career focus on analytic pathways from biomarkers to clinical function in SZ (MT), a UCSD SZ Research Program with a >25 y history of recruiting and testing thousands of psychosis patients in studies with ERPs and other biomarkers proposed in this R33 (published retest stability with 1-year follow-up[61]), as well as double-blind, PBO-controlled trials of putative pro-cognitive agents (including AMPH) in SZ patients and HS[13,23,91,104]. We have completed and published extensively on a 30-session clinical trial of TCT in the same general population and with many of the same biomarkers proposed herein.

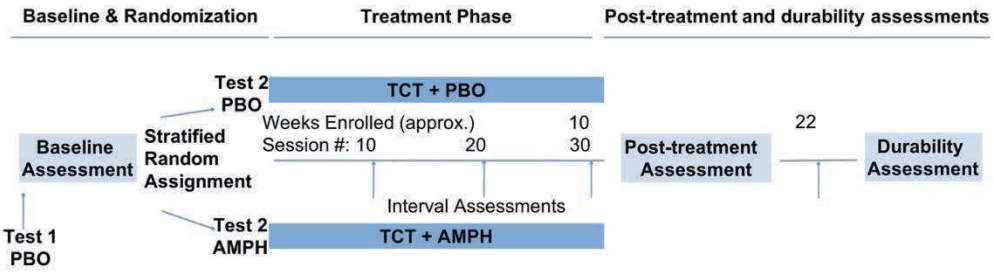
In summary, this application will confirm target engagement by demonstrating that AMPH (5 mg po, 60 min prior to TCT) enhances APS learning in a Sound Sweeps session in biomarker-characterized AP-medicated SZ patients; these patients will then be randomized to a 30-session RCT of TCT+AMPH (n=27) vs. TCT+PBO (n=27). Findings will determine whether AMPH augments the known neurocognitive and clinical benefits of TCT, and whether APS "AMPH sensitivity" - based on APS gains in 2 test sessions - predicts the therapeutic impact of AMPH over a 30-session TCT regimen. Other predictive biomarkers will be explored, including baseline neurocognitive (MCCB A/V scores), ERP (P3a, MMN) / EEG (ASSR, theta band power) measures, and AMPH effects on auditory discrimination and on ERP changes across the first Sound Sweeps sessions.

General Methods: Environment**:** Subjects are screened, tested and undergo TCT at the UCSD Medical Center. Recruitment will enroll ≈ 23 patients/year. Participants are 18-55 y.o. AP-medicated (stable regimen ≥1 month, in active outpatient treatment) patients with a primary diagnosis of SZ or schizoaffective disorder (depressed type), recruited and consented at UCSD as per [91,101,104]. Study inclusion/exclusion criteria are detailed in **"Protection of Human Subjects"**; all subjects with stimulant abuse or dependence histories are excluded. Screening includes a confirmatory diagnostic assessment (M.I.N.I. 6.0), a general medical, psychiatric and substance history, physical exam by an M.D., EKG, vision and hearing tests, urine toxicology and pregnancy test (UTox/P). All medications and changes are recorded (AP doses in chlorpromazine equivalents; quantifying anticholinergic burden[116] as in[13,48,91]). Medication patterns of our last ≈ 100 SZ subjects are found in[91,95,104].

Design (Fig. 7). Test 1: Enrolled patients complete post-PBO clinical, neurocognitive and functional measures and candidate biomarkers (EEG, QuickSIN, WIN); they are tested in Sound Sweeps, and then assigned to PBO vs. AMPH arms (n=27/arm) using stratified random sampling (over sex, age and high/low Test 1 (baseline) APS learning) blind to arm identity, similar to[107]. Stratifying for baseline APS learning should increase the sensitivity of the primary target engagement metric. Test 2 follows ≈ 5-7 days later, after either PBO or AMPH (5 mg po). Tests 1-2 are used to assess target engagement (Aim 1: AMPH-enhanced APS learning) and AMPH effects on ERP/EEG, auditory discrimination (QuickSIN, WIN) and neurocognitive measures (Aim 3: Biomarkers). Our design allows for 20% attrition from enrollment (n=69) to completion of target engagement testing (n=54).

For Aim 2, TCT is scheduled 3 d/week (M-W-F) for 1-h/d, recognizing the need for flexibility (T-Th are "make-up days"), and continues until a subject completes 30-h (≈ 10-12 weeks). TCT is delivered by trained staff (see below). 60 min prior to each TCT session, patients take either PBO or 5 mg AMPH, as per arm assignment. Patients and staff are blind to study arm; staff are blind to patients' baseline or post-intervention assessments.

Fig. 7. Study Phases: Baseline & Randomization includes 2 Sound Sweeps tests: Test 1 with PBO and ≈ 5-7 days later Test 2 with either AMPH or PBO. Treatment Phase includes 30 TCT sessions with outcome measures after 10, 20 and 30 sessions. Post-treatment tests assess both immediate biomarker changes and 12-week durability of outcome gains.



Assessments: 30 sessions of TCT will be completed, based on our findings (Fig. 4) and evidence that TCT efficacy is dose-dependent[16,32,114]. Assessment dates could be based on either: 1. session # (10, 20 and 30 and 12 weeks later); or 2. Time (days) since starting TCT. In our experience[45,107,109] TCT rates closely match 3/week (30 sessions mean = 65 days; 90% of subjects completed their 30 TCT sessions within 11 weeks. Primary analyses will be based on session #, but session dates are recorded and confirmatory analyses will define assessment points based on time passage. Candidate predictive biomarkers are re-tested after session 30.

General Clinical Monitoring: In addition to their established ongoing care, patients are carefully monitored at each session as per our well-established procedures, and through to the week-22 follow-up, for any clinical changes. Each week, a member of our research staff checks vital signs and weight, does a detailed assessment of symptom changes, focusing on psychosis, depression, suicidality and abnormal movements, and tests UTox and pregnancy. A designated unblinded staff member processes UTox results in the event that a PBO-arm subject tests positive for amphetamine; any clinical worsening or UTox positive for recreational drugs (other than AMPH in AMPH-arm subjects) or a positive pregnancy test is promptly reviewed with the on-site Psychiatrist; any "yes" on the Columbia Suicide Severity Rating Scale[81] (C-SSRS) "Since Last Visit", or an exacerbation of psychotic symptoms, prompts detailed review, with appropriate clinical interventions. Patients testing positive for recreational drugs will be retested in 1 week; patients with 3 positive tests no longer continue in the study. **Data from subjects who, for this or other reasons, do not complete the full study are carried forward in an "intent to treat" design, and their data are analyzed using linear mixed models.**

Fig. 8. "Go" criteria: #1, plus at least one of #'s 2, 3 & 4 (d>0.5)
1. **Target engagement:** APS learning, AMPH > PBO, p<0.05
2. **Greater** clinical, neurocognitive **or** functional gains:
   - ↓PANSSt, ↑MCCB-C **or** ↑Fnxn: AMPH+TCT > PBO+TCT
3. **Faster** clinical, neurocognitive **or** functional gains:
   - drug group x session interaction (p<0.05) followed by AMPH+TCT > PBO+TCT at specific session # or combination;
4. **More durable** clinical, neurocognitive **or** functional gains:
   - AMPH+TCT > PBO+TCT at post-TCT week 12.

PANSSt: Positive & Negative Symptom Scale total; MCCB-C: MATRICS Composite; Fnxn: Function (assessed via the World Health Organization Disability Schedule 2.0 (WHODAS)

Outcome and "Go Decisions". In addition to confirming "target engagement", this application tests the hypothesis that SZ patients given AMPH +TCT will exhibit greater, faster and/or more durable improvements (change from baseline) in symptoms, neurocognition and/or function compared to patients given PBO+TCT, and that this enhanced clinical response will be associated with greater AMPH-enhanced TCT learning.

The small "n" necessitated by the 3-year timeline and demanding treatment schedule greatly constrains the total number of outcome measures. Moreover, the plan to assess not only magnitude but also rate and durability of PACT gains triples the number of primary analyses. Thus, we selected only one **primary** clinical, neurocognitive and functional outcome measure (Fig. 8) – recognizing that they are relatively "blunt" metrics - but will track several other, more focused, measures as well as inter-measure correlations in exploratory analyses to inform future studies.

A "Go" decision requires: 1) confirmation of target engagement (APS learning, AMPH>PBO, p<0.05); 2) evidence of gains from PACT ($d \geq 0.5$ (AMPH > PBO)) in primary clinical, neurocognitive and/or functional measures (Fig. 8), and 3) the absence of adverse effects of AMPH that are significantly greater than PBO levels. The decision to not use traditional statistical significance as "Go" criteria for Aim 2 reflects this RFA's call for "Pilot" studies, the need to identify candidate treatments for a subsequent larger "n" Confirmatory Efficacy R01 study, and the limits in sample size resulting from the 3-year R33 duration. Cohen defined a medium effect size (d=0.5) as one that is "visible to the naked eye," and this amount of change is viewed as clinically meaningful in trials targeting negative symptoms.[25,63-4] This d=0.5 "Go" threshold for Aim 2 corresponds to a "number needed to treat" (NNT) value ≈ 3.62. While a "Go" decision does not require identification of a biomarker predicting greater PACT

sensitivity (Aim 3), the identification of one or more meaningful predictors that could be incorporated into a Confirmatory Efficacy trial would favorably impact a "Go" decision.

Staff assessing outcome measures are blind to treatment arm, and for some measures receive training using videotaped and practice interviews until achieving high (ICC≥.80) reliability based on 20 assessments by 2 raters. We achieve high inter-rater reliability (e.g., ICC>0.85 for PANSS total[14]), and check for rater drift each 90d.

Specific Procedures: TCT is completed with a dedicated room and equipment. Staff trained with a UCSD-developed "TCT Clinician Competence Assessment" monitor TCT, clarify instructions and provide encouragement as needed. **In the initial "biomarker testing" session (Test 1), all subjects receive a PBO pill and complete** 1-h of Sound Sweeps to generate a "PBO APS score" as described previously (Fig. 2A,B). Treatment group assignment (PBO vs. AMPH) is then made using stratified random sampling (above), and 5-7 days later patients ingest either PBO (n=27) or 5 mg AMPH (n=27) 60 min before completing the Sound Sweeps session ("Test 2"). AMPH effects on APS learning are assessed both within-subject (APS (Test 1 - Test 2) for AMPH group subjects: a key measure of **AMPH sensitivity**) and between subjects (APS Test 2, PBO vs. AMPH groups). For all other sessions, subjects receive either PBO or AMPH 60 min before TCT, which includes 5 modules of auditory/verbal processing exercises. Each module increases in difficulty as performance improves: 1) Sound Sweeps; 2) Syllable Identification: Patients distinguish between 2 similar phonemes (e.g., "ba" vs. "da"), differing only in their voice onset time; 3) Word Matching: Subjects match short similar-sounding consonant-vowel-consonant words (e.g., bad, dad); 4) Listen & Do: Subjects reconstruct a spoken series of instructions and use a computer mouse to click icons on the screen in a specified order. This exercise is designed to stimulate verbal WM processes supported by the lateral PFC as well as premotor and motor processes. 5) Rhythm Recall: Subjects listen to and replicate a short rhythmic sequence. This task is designed to stimulate both basic auditory processes supported by primary auditory cortex, and non-verbal auditory WM.

Symptoms are assessed (Fig. 4B) to track clinical status, and TCT response. TCT reduces both positive and negative symptoms of psychosis, and we predict that AMPH will augment these effects **via enhanced TCT learning** (i.e. not via a lasting direct pharmacological effect of AMPH), detected by the Positive & Negative Syndrome Scale. For this reason, and based on the need to limit total outcome measures, **PANSS Total Score** is the primary clinical outcome measure. Positive and negative symptom subscales, as well as PANSS factor-derived measures, will be assessed in exploratory analyses. Other secondary clinical measures will include: 1) Psychotic Symptom Rating Scales (PSRS; assesses auditory hallucinations); 2) Young Mania Rating Scale; 3) Patient Health Questionnaire-9 (PHQ-9; current depressive symptoms); 4) Abnormal Involuntary Movement Scale (AIMS); 5) C-SSRS; "Lifetime/Recent version" at screen; "Since Last Visit" at follow-up visits). The C-SSRS is a reliable, valid and sensitive measure of suicidal ideation[81]; *any "yes" in C-SSRS prompts an immediate full evaluation/action plan by a study M.D.; and* 7) AMPH Cessation Symptom Assessment (ACSA).

Neurocognition: Change in MCCB Composite performance from baseline is one outcome measure. The MCCB measures 7 cognitive domains: SP, A/V, WM (verbal and nonverbal), verbal learning, visual learning, reasoning/problem solving and social cognition. Details are found in[50,52,74]; past studies by the PI of drug effects on MCCB performance include[13,23]. Since the MCCB is assessed multiple times, alternate forms of the HVLT-R and BVMT-R are used in counterbalanced order. MCCB Global Composite T-score (MCCB-C) is the primary neurocognitive outcome measure. Individual MCCB domain T-scores are used in secondary analyses to determine whether an overall effect is driven by specific aspects of neurocognition; TCT effects on verbal learning performance are known to be robust[31], and should be augmented by AMPH. Baseline and AMPH-enhanced (Test 2 vs. 1) MCCB performance (A/V subscale) will also be tested as potential biomarkers/moderators of AMPH PACT efficacy.

Function is assessed via the World Health Organization Disability Schedule 2.0 (WHODAS)[112] at baseline, after sessions 10, 20 and 30, and week 12 post-TCT. WHODAS 2.0 is a 12-item patient-rated measure (< 15 min) using a 5-point Likert scale focusing on cognition, mobility, self-care, getting along with people, life activities and participating in society; it was recommended by the DSM-5 Task Force committee to replace the global assessment of functioning scale[55]. NIH "PhenX Toolkit" scales of Impairment, QOL and Social Isolation will also be used. After session #30, the assessment will include a 14-item 7-point Likert scale of treatment satisfaction.

Biomarkers from Tests 1-2 will be assessed as predictors of target engagement (Aim 1) and PACT sensitivity (Aim 2); in some cases, these measures will also inform mechanistic models for PACT: 1. AMPH-enhanced APS learning is both an outcome measure (Aim 1, "target engagement") and candidate predictor of clinical outcome (Aim 2); 2. Baseline and AMPH-enhanced MCCB A/V scores are associated with APS AMPH sensitivity[96,98], and thus may predict clinical outcome (Aim 2); 3. ERP measures of early auditory information processing variably predict response to early APS learning[60] , AMPH-enhanced APS learning[104], and TCT outcomes[45]. EEG/ERPs are acquired via 64-channel recording systems and assessed in the same order, as per[53,91]: MMN/P3a/Theta power/Phase locking (25 min; Oddball Paradigm), ASSR (6 min). 4. Auditory discrimination: Words-In-Noise (WIN; NIH Toolbox) and Speech-In-Noise (Quick-SIN; Etymotic Research) are acquired at Tests 1-2, TCT hour 30 and week 22. Both measures assess the ability to recognize speech over background noise, mimicking a

conversation in a noisy environment, and are thought to index peripheral (WIN) vs. more central (QuickSIN) auditory processing. AMPH-enhanced auditory discrimination (Test 2 vs. 1) may predict PACT outcome (Aim 2); gains in auditory discrimination over 30 hours of TCT, and their augmentation by AMPH, will be tracked to inform evolving models of PACT mechanisms (e.g. Figs. 1 & 6). **Predictions:** First and foremost, target engagement (AMPH-enhanced APS learning) will predict AMPH-enhanced TCT outcomes (Aim 2) as described below. Exploratory analyses will test secondary predictions: for example, high vs. low baseline P3a amplitude and faster P3a latency will predict greater target engagement (Aim 1), and greater AMPH-enhanced TCT outcome (Aim 2). AMPH-enhanced (Test 2 vs. 1) ERPs, auditory discrimination and neurocognitive (A/V) measures will also be explored as outcome (Aim 2) predictors; significant pre- vs. post-TCT changes in ERP source dynamics will also be examined for mechanistic characterization[77]. Robust biomarker predictors will be examined as moderators of both indirect and direct paths between treatment and outcome in a future Confirmatory Efficacy trial.

Data Analysis: "Go/No Go" decisions are based on traditional statistical significance (Aim 1) and effect sizes (Aim 2). Formal statistical testing is conducted using linear mixed-effects (LME) models; hypothesis tests are 2-sided (α=.05). Model parameters are estimated via the R lme4 package and Cohen's d is estimated via the EMAtools package. Type I errors are minimized by constraining the number of primary analyses; secondary analyses use false discovery rate corrections. Expected attrition rates are described above. Because outcome measures involve a "change from baseline", baseline metrics are compared between PBO and AMPH arms, and any baseline differences are addressed in the outcome analyses. Differential drop-out rates from PBO vs. AMPH arms are monitored. Data are assumed to be missing at random; full information maximum likelihood estimators are used, and all data/cases are included in analyses. Clinical follow-up is pursued with all patients exiting the study through post-TCT week 12. Cohort differences: For between-subject contrasts (main effect of drug), differences in age, antipsychotic and anticholinergic loads are tested and used as covariates[48,107,116]. Sex differences are tested for all measures based on known sex differences in AMPH sensitivity[10,71]. NIH Data Harmonization: 3 "PhenX Toolkit" (NOT-MH-15-009) measures of function are used; see above and "Resource Sharing Plan".

Aim 1 – Confirm target engagement: The primary dependent measure of target engagement is AMPH-enhanced APS learning. APS learning is defined as the reduction in Sound Sweeps APS threshold (ms) pre- to post-assessment. Target engagement was demonstrated in MH59803[98,104], and will be confirmed if APS learning is increased by AMPH either in a within-subject comparison (AMPH group, "Test 2 vs. 1"), or in a between-subject comparison (AMPH group vs. placebo group change "Test 2" vs. "Test 1") (note that AMPH and PBO groups are matched by Test 1 PBO performance via stratified randomized assignment). Effect sizes and inferential statistics are based on LME models with random intercepts. A statistically significant main effect of drug (PBO vs. AMPH) on APS learning in either within- or between-subject contrasts is a "Go" criteria and confirms target engagement.

Aim 2 – Test clinical, neurocognitive and functional impact of AMPH on TCT, and its relationship to target engagement: We will determine if AMPH+TCT produces greater, faster or more durable clinical, neurocognitive or functional gains from baseline, compared to PBO+TCT, over a 30-session course of TCT. A Cohen's $d \geq 0.5$ for the main effect of drug (PBO vs. AMPH) or drug x session (#10, 20, 30) interaction in an LME model is the primary "Go" criteria. The main effect of drug assesses "greater" gains. Reverse Helmert contrasts for session assesses "faster" gains. A separate model comparing differences in outcomes at 12-weeks post-TCT assesses "more durable" gains. Secondary regression analyses will examine whether change in AMPH-enhanced APS learning ("within-subject" target engagement; Aim 1) predicts gains in Aim 2 outcome measures.

Aim 3 – Biomarkers of AMPH-induced gains: We will determine if baseline levels of specific neurocognitive or EEG-based measures, or changes in specific measures with initial AMPH exposure (Test 2 vs. 1), predict greater sensitivity to AMPH-enhanced neurocognitive, clinical or functional gains over 30-h of TCT. Regression analyses will assess whether specific candidate biomarkers predict AMPH-enhanced gains in outcome measures.

Subject "throughput": We will enroll and screen 23 subjects/yr, test target engagement in 18 subjects/yr, and (conservatively) complete TCT training in 12 subjects/yr. This will yield 2 "target engagement" Aim 1 arms of n=27, and (conservatively) 2 TCT completion Aim 2 arms of n=18. Training capacity (2 TCT stations with morning and afternoon sessions on M, W and F, with T and Th "make-up" days for missed appointments, 48 weeks/year) allows for a "maximum throughput" of 19.2 subjects/yr. To reach the target of **12 TCT-completing subjects /year**, we would need to maintain training rates of **62.5% capacity**. This is well within our historical testing levels.

Power analyses: Consistent with the FOA, this study will adequately power tests of target engagement (Aim 1) for traditional significance, while the "Go" signal for therapeutic impact (Aim 2) is based on effect size (d=0.5). To detect target engagement with d=0.5, 80% power, alpha=0.05, test-retest correlation =0.8, and a linear treatment effect, n=27 randomized participants are required per group. This is a very conservative estimate of d for target engagement, since empirically, d for target engagement with 5 mg amphetamine was 0.85 (Fig. 3A). A future Confirmatory Efficacy trial will be powered to apply more robust approaches to Aim 2, e.g. Path Analysis[108] to study moderating effects of APS AMPH sensitivity and biomarkers on both indirect (moderated-mediation) and direct paths between treatment and outcome.

Inclusion of Women, Minorities and Children

Inclusion of women: Women will be included in this study. There are sex differences in the DA-releasing effects of AMPH[10,71], that might impact the effects of AMPH on a number of behavioral measures that are relevant to this application. Thus, while no sexual dimorphism has been reported in the therapeutic effects of TCT, and none were noted in our study of AMPH effects on APS learning, we will strive to include enough men and women in the study to conduct meaningful analyses of sex effects on both AMPH sensitivity and biomarker predictors of AMPH effects on APS learning. To control for potential effects of menstrual cyclicity on biomarkers or drug sensitivity, Aim 1 drug testing will begin within days 1 - 7 of menses onset (our standard protocol for over a decade [e.g. 106]). There is a strong rationale for assessing the predicted drug effects in both men and women, because these findings will have implications in terms of the potential clinical applications of this PACT design.

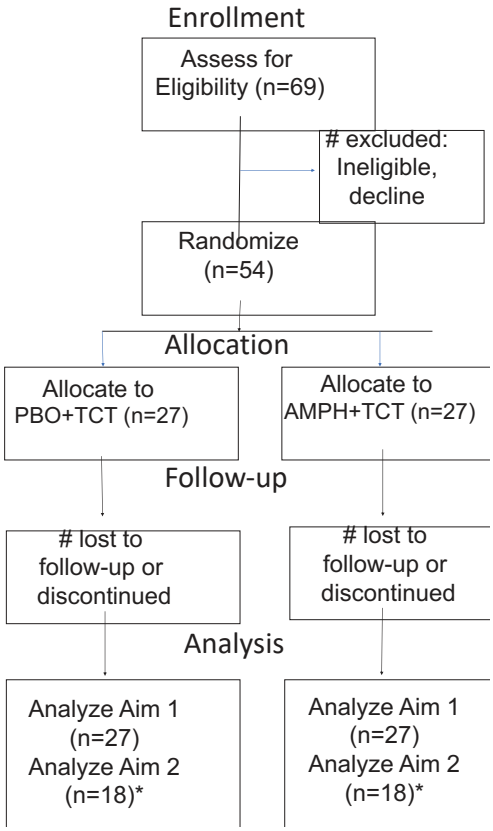
Several steps will be taken to avoid exposure of any fetus to amphetamine. First, females who are pregnant, nursing, imminently planning pregnancy or have a positive urine pregnancy test on screen day or any test day will be excluded from this study. Second, female subjects of childbearing potential (defined here as any female who has not had a total hysterectomy and/or bilateral oophorectomy, or who has had a menstrual cycle within the past year) will have urine pregnancy tests weekly through the 10th week of TCT ("Surecheck Early Pregnancy Test"). Second, in all subjects of childbearing potential, Aim 1 testing will begin within days 1 - 7 of menses onset. Third, to participate in this study, females of childbearing potential must agree to use a double-barrier method of contraception when participating in sexual intercourse (regardless of other methods of contraception). If a female of childbearing potential becomes pregnant during the study, the subject will be exited from the study. The investigator will determine whether the subject was exposed to active study drug or placebo, and notify the subject of this information.

Inclusion of minorities: Ethnic representation is based on recruitment response, with every effort made to include minority groups. Exclusion criteria are not based on ethnicity. Minority participation should thus reflect the ethnic make-up of the San Diego community. Based on our experience, the following ethnic percentages are expected in the study sample, based on the past 4 years of subject recruitment: White, not of Hispanic origin = 54%; Hispanic = 9.5%; Black, not of Hispanic origin = 3.2%; Asian = 32%; American Indian or Alaskan native = 0%. The source of recruitment information is recorded for each subject (e.g. website, fliers, newspaper advertisements, etc.), providing us with ethnic “success rates” for particular means of recruitment. Ethnic representation is then reviewed with annual progress reports. Recruitment efforts are adjusted, based on “success rates” of specific recruitment means, to respond to any significant deviation from the projected ethnic recruitment rates. The UCSD Medical Center is an equal opportunity employer; pursuant to state legislation, the University of California no longer applies affirmative action criteria in the student application process.

Inclusion of Children: Children younger than 18 are not included because of the diagnostic complexities and clinical heterogeneity introduced by studying psychosis in that population, as well as the ethical considerations involved in the administration of psychoactive drugs to children. The primary therapeutic intervention (TCT) has not been thoroughly studied in psychosis spectrum patients younger than 18 years of age; one small report was “negative” but likely under-powered; one larger report detected positive effects. Because the key question in the present R33 application will be confounded by a lack of therapeutic response to the TCT intervention, it was felt that inclusion of this younger cohort should await more definitive evidence for such an effect. In addition, several key “biomarker” measures are either highly variable and not fully developed or not established in younger children.

Recruitment and Retention Plan

We anticipate that over the course of this study we will consent 69 SZ individuals for screening, from whom we will advance 54 individuals to in-laboratory baseline testing and randomization into two arms with n=27 per arm. After study attrition, we conservatively expect that 36 individuals will complete 30 hours of TCT and longitudinal (12 week post-TCT) testing, and that attrition will be roughly balanced to arrive completed samples of n=18 per study arm.



Example of CONSORT Diagram of proposed R33 study
* Conservative estimate of final n=18/arm for Aim 2 analyses

To meet these recruitment and retention needs, men and women with a SZ disorder are recruited from the San Diego community using our long-established network and recruiting procedures, as per[13,58,61,91,101,104]. Our full-time patient recruiters have established longstanding relationships with club houses and board-and-care facilities in San Diego County that serve this patient population. Our laboratory participates in events at these facilities (e.g. MHA Visions Clubhouse in Chula Vista recently hosted a “What Wellness Looks Like” Mental Health Awareness and Creative Arts show to celebrate Mental Health Awareness Month), as well as recruitment events (e.g. “NAMI Walks”) hosted by NAMI-San Diego. The PI is a former member of the NAMI-SD Board of Directors and Chair of their Medical Advisory Board, and has maintained strong relationships with this organization that facilitate recruitment. Study advertisements are placed in local newspapers, and on relevant websites, including the PI’s website dedicated to this study. The URL for this site (http://www.psychiatry. ucsd.edu/research/Pages/psychiatryresearch.aspx) can be accessed through links entitled “Psychiatry Research” on our Department’s website (http://www.psychiatry.ucsd.edu/research/Pages/default.aspx) and on the UCSD CTRI website for “Studies Recruiting Volunteers” (http://ctri.ucsd.edu/community/Pages/studies-recruiting-volunteers.aspx). Our studies are also listed on ResearchMatch, and Clinicaltrials.gov. The lead Co-Investigator, Dr. Light, has ongoing funded collaborations with local residential treatment facilities, as described in this application, and patients who do not participate in TCT studies at these facilities are eligible for participation in this application. Other recruitment sources include the UCSD Medical Center Outpatient and Inpatient Psychiatric Services (both of which are staffed by Psychiatry Residents in the UCSD Psychiatry Research Residency Training Program, for which the PI serves as Director), as well as outlying community clinics staffed by UCSD Residents.

Study enrollment is reviewed at weekly diagnostic consensus meetings, and is documented in quarterly milestone reports. There are expected seasonal differences in recruitment patterns, based on University Holidays (e.g. Winter Holidays, during which time no TCT training takes place), and Resident caseload transfers (July, when a “bolus” of referrals can be expected). Nonetheless, any deviation from expected recruitment targets is identified, analyzed and addressed. Primary responsibility to track and retain participants is delegated to Ms. Joyce Sprock.

Study retention is enhanced by: 1) transportation provided to and from each laboratory visit; 2) careful attention to participant needs including schedule flexibility; 3) a comfortable laboratory environment, including availability of healthy meals and snacks; 4) reminder phone calls for all post-TCT visits; 5) careful follow-up protocol for all missed visits; 6) subject payment.

Recruitment of subjects and informed consent procedures will follow Dr. Swerdlow's established methods. For all subjects we will have a consent form describing all laboratory measures and any potential side effects they may expect from AMPH. Specifically, all subjects will be asked to read a description of AMPH, which includes the following information: 1) the typical indications for this drug; 2) the recommended starting dose for this drug, and details regarding typical maintenance doses and schedules; 3) common side effects experienced by individuals taking this drug, based on trials with in SZ patients; and 4) an assessment of the likelihood that they will experience significant side effects from this drug, in the dose to be used in this study. In all cases, fully informed consent will be obtained and a study M.D. will be directly available to clarify any questions raised by a subject. Signed and witnessed consents will be kept on file with other patient data. The UCSD IRB application is under review; in our past protocols for AMPH studies in this population, we have had no waivers or modifications of normal procedures.

Subjects will be carefully screened to ensure their ability to comprehend study procedures, risks, and benefits. Potential participants will be fully informed of all risks and benefits prior to giving their written informed consent and prior to enrollment in the study. Participants will be asked to repeat back understanding of this material, and if there is any question as to whether a person is able to provide informed consent then they will not be permitted to participate. A copy of the signed consent form will be stored in a separate locked filing cabinet from other de-identified coded materials, and a copy will be given to the study participant.

All study personnel involved in obtaining written informed consent will have completed a web-based course with post-test on Human Subject Research Protections and Good Clinical Practice, in addition to being trained by the PI on obtaining informed consent. These study personnel will also be authorized to obtain informed consent by the IRB and Human Studies Subcommittee. Informed consent will be documented using standardized IRB-approved forms. The forms will be presented to all potential participants at the initial visit. Briefly, the informed consent form will describe the purpose of the study, procedures and participant involvement, nature of assessments and treatments, potential risks, alternatives to participation, costs and compensation, confidentiality, right to withdraw, potential benefits, relevant contact personnel, and information regarding the Health Insurance Portability and Accountability Act (HIPAA) of 1996. Because participation in the proposed study is entirely voluntary, patients can choose to discontinue the study at any point for any reason and this will in no way affect future medical treatment decisions or practices.

Payment is $15/hr. This equates roughly to $45 for completion of the screening visit, $45 per visit for each of the 30 TCT sessions, except sessions 10, 20 and 30 ($75), $60 for post-week 30 biomarker testing and $45 for week 22 testing. For the full R33 screening, testing, training and follow-up, subjects are paid a total of $1590. This payment is required to: 1) maintain subject flow and thereby avoid cost-ineffective “down time”; 2) attract subjects from non-indigent populations, and thereby avoid high rejection rates due to health and drug exclusion criteria and subject.

Protection of Human Subjects

The subject population for the present application will include approximately 69 individuals diagnosed with Schizophrenia or Schizoaffective Disorder, Depressed Type (collectively referred to as "SZ" patients) (ages 18-55). These numbers represent the estimated samples that will be screened in order to yield a final sample size of 54 SZ patients who will complete Aim 1, of whom 36 will also complete Aim 2. Subjects are recruited from the San Diego community, and their ethnic/ racial characteristics are described elsewhere.

Specific inclusion and exclusion criteria are as follows:

Inclusion criteria: 18-55 y.o. AP-medicated (stable regimen ≥ 1 month; current active outpatient treatment) outpatients with a primary diagnosis of SZ or schizoaffective disorder (depressed type) for ≥2 years, clinically stable (non-acute phase ≥12 weeks; not hospitalized in ≥2 months; all "no" responses on C-SSRS items 1-5 (1 month) and behaviors (3 months), never treated with TCT.

Exclusion criteria: premorbid IQ <70, substance abuse (past month; positive UTox), history of stimulant dependence, pregnant or nursing (women of childbearing potential consent to double-barrier contraception), history of significant medical/ neurologic illness (e.g. cancer, diabetes, CVA, heart disease, HIV, tuberculosis), history of seizure, open head injury or closed head injury with loss of consciousness > 10 min, R-hand injury), vital signs (VS): SBP<90 or >160; DBP<45 or >95; HR<55 or >95, hearing deficit (>40 dB @ 1000 Hz), corrected visual acuity < 20/40[12], color blindness; inability to provide informed consent or to complete visits needed for this application; past or current treatment with TCT; current medications include psychostimulants, monoamine oxidase inhibitors, or dopamine agonists (including bromocriptine and amantadine).

Patients are typically first screened by a trained laboratory assistant, who will exclude them based on the above criteria. Importantly, all SZ participants must be taking an antipsychotic medication on an ongoing basis (including depot preparations), with a stable dose for at least 1 month prior to study participation, and must be maintained on that medication throughout the study. Dose adjustments by the treating physician will be recorded. SZ patients cannot be taking a concomitant dopamine agonist medication (e.g. amantadine or bromocriptine). For appropriate subjects, the study is described again, and subjects sign consents for participation.

This age range was selected to avoid ethical and interpretative concerns associated with drug effects on symptoms and biomarkers in children and adolescents, as well as diagnostic uncertainties in younger individuals exhibiting psychotic symptoms. There will be a roughly equal representation of males and females; sample size is based on power analyses described in this application. The difference between the size of the anticipated screened population and anticipated final sample size (n=69 vs. n=36 SZ patients) reflects predicted rates of subject screen failure and attrition.

Records and data will be rigorously protected, as described below. Historical and questionnaire data, biomarker and related measures will be obtained; urine will be obtained for toxicological analysis as part of the subject exclusion process and with each study visit to reduce risk of interactions with the study drug and of uncontrolled effects on TCT performance and outcome measures.

Subject recruitment and informed consent procedures follow the PI's established methods, approved by the UCSD Human Subjects IRB. In all cases, fully informed consent is obtained by a trained technician or the PI, and the PI will be directly available to clarify questions. Signed and witnessed consents are kept on file with other subject data. The UCSD IRB has authorized no waivers or modifications of normal procedures.

Study governance follows our successful model: the PI provides study oversight, runs weekly diagnostic consensus / clinical monitoring meetings, oversees IRB and DSMB interactions, insures recruitment / testing milestones, among other roles; Co-I's oversee all biomarker testing, data fidelity and analyses (GL, MT), participate in clinical consensus meetings (GL). Our DSMB, through the UCSD CTRI, ensures patient safety and data validity and integrity (see Letter).

Potential risks are minimal. The rating scales and questionnaires are innocuous. ERP testing exposes subjects to the application of scalp electrodes and to brief sounds, which in >25 years of testing have caused no side-effects. Alternative measures have been considered; the selection of these specific ERP measures reflects the significant advantages of applying towards these studies the substantial body of information generated by > 25 years of systematic studies of ERPs in healthy and clinical populations. All other measures require only computer keyboard or paper-pencil use and involve no risk.

The AMPH dose (5 mg po) is low in terms of clinical use ("starting dose for a 6 year-old with ADHD"), and based on our substantial experience with higher doses in healthy (20 mg) and SZ populations (10 mg) (see citations in "Research Strategy"), including studies with multiple doses administered over 4 weeks, adverse reactions are not likely (never seen in our experience with over 120 HS given 20 mg p.o., or in > 70 SZ patients tested thus far with 10 mg AMPH). Furthermore, higher daily doses of AMPH in SZ patients

administered over a 10-week clinical trial followed by rapid discontinuation yielded adverse event rates comparable to those of placebo[57]. No consistent subjective effects have been associated with the 5 mg dose of AMPH in our studies, nor has 5 mg produced any statistically significant autonomic changes. Alternative drugs have been considered, and the proposed drug was selected, based on a rationale clearly described in "Research Strategy".

The use of AMPH as a daily augmentation medication for SZ patients has been reviewed in systematic meta-analyses, revealing no adverse effects (but some benefits) with AMPH; by contrast, methylphenidate was associated with adverse effects.[88] The use of AMPH to study neurocognition and brain imaging in antipsychotic-medicated and unmedicated SZ patients has been described in numerous published reports, cited in this application[1,2,27,56,65]. A 1982 review[145] of the use of high doses of AMPH in about **300 unmedicated SZ patients** – mostly via an i.v. route – produced mixed changes, with most patients having no symptomatic changes, and with more patients showing improvement than worsening of symptoms. More recent case series[e.g. 21] identify predominant symptomatic improvement in AP-medicated SZ patients prescribed high daily doses of AMPH (40-80 mg po) for periods of years. In controlled trials, adverse effects after an oral dose of 10 mg AMPH, or even with 10 weeks of higher daily doses in antipsychotic-medicated SZ patients[57] are extremely rare. Our recent review of our laboratory's experience supports the safety of AMPH in the same population to be recruited for the present application[95]. For perspective, the present study proposes to use 5 mg AMPH, about 3 times per week, for about 10 weeks. Nonetheless, clinical state will be carefully monitored in all test subjects via symptom ratings scales described in the application. All testing will be monitored by a licensed physician, who will remain on site for the entire test day, until subject discharge; R33 patients will be evaluated by a trained Research Associate during 3x/week visits for TCT, with a specific focus on suicidality and psychotic symptoms via both unstructured and structured clinical assessment (e.g. including use of the Columbia Suicide Severity Rating Scale[113] (C-SSRS)). Any increase in symptoms is reviewed immediately with a study Psychiatrist, who will make appropriate clinical interventions, potentially including an Emergency Room evaluation for hospitalization. Electrocardiograms will be administered at the onset, mid-point and end of the study. Follow-up contact will be attempted with all patients who miss scheduled visits. These are standard practices in the PI's laboratory, where studies of acute drug effects (e.g. memantine, AMPH) on the proposed measures in SZ patients are commonly conducted.

The overall risks of this proposal are small. AMPH will not be administered to subjects in whom it is medically contraindicated, such as subjects with known cardiovascular or neurologic disorders or diagnoses of stimulant dependence (although it is notable that oral AMPH, at doses up to 60 mg, has been investigated as a treatment for cocaine dependence[39]). The dose selected for use in these studies is in the low- or below-therapeutic range for AMPH. Studies will be conducted under the direct supervision of a licensed physician. To address the potential for AMPH to produce changes in blood pressure, all subjects' vital signs will be carefully monitored, and subjects will not be released from the laboratory until their vital signs are within normal limits; it is notable that the dose of AMPH in this application has been tested in SZ patients in the PI's laboratory and produced minimal autonomic activation. Drugs will be dispensed by a licensed physician or pharmacist, and a licensed physician or nurse will be present on the premises at all times during testing to assess and address potential adverse drug effects, and if needed, to administer medical assistance to the test subject. Protection of subject confidentiality and privacy will be rigorously guarded by the assignment of coded numbers to each file in the computer analysis and database.

Risk/benefit ratio: Both study arms include an active intervention with documented efficacy in reducing symptoms and improving neurocognition in SZ patients. Thus, it is a reasonable likelihood that many study participants will benefit clinically from completing this study, regardless of their arm assignment. The hypothesis being tested is that these benefits will be augmented by AMPH. It is anticipated that the proposed study will yield important, new information about a new therapeutic approach in SZ patients, as well as systems-level neural information of direct relevance to several neuropsychiatric disorders. Thus, this study has a significant potential for providing major gains in our treatment and understanding of the brain basis for disorders that are severe and common. It is possible that the information obtained, and the treatment administered, in this R33 with individual subjects will be of direct benefit to them. In addition, subjects will benefit indirectly - through a cascade of familial and societal benefits - from the information generated by these studies. Furthermore, based on their awareness of the potential importance of this work to their community, subjects will benefit in areas of self-esteem and self-understanding. Information from physical examinations, and screening measures, may also be of direct benefit to test subjects. The overall risks of the proposed studies are low, as described above. Thus, on balance, the risk/benefit ratio of the proposed studies is very low.

Data and Safety Monitoring Board and Plan:

The Data and Safety Monitoring Board (DSMB) is an independent group of three UCSD experts established through our UCSD CTRI, based on a Data and Safety Monitoring Plan (DSMP) specific to this R33 application. Our UCSD CTRI is partially funded by a Clinical and Translational Science Award (CTSA) from the National Institutes of Health. The DSMB comes at no cost to this application.

The DSMB consists of 3 CTRI multidisciplinary leaders, free from any conflicts of interest or direct involvement with the academic or other credit resulting from this study, who advise both the PI and the NIMH, based on their expertise. The primary responsibilities of the DSMB are enumerated below; they include to periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and efficacy, and to make recommendations to the NIMH concerning the continuation, modification, or termination of the R33 trial. The DSMB considers study-specific data as well as relevant background knowledge about the treatments (TCT and AMPH) and patient population under study (chronic psychotic disorder).

The DSMB is also responsible for maintaining the confidentiality of its internal discussions and activities as well as the contents of reports provided to it. The DSMB will review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. The CTRI has specific guidelines that ensure a comprehensive study protocol for timely DSMB notification by the PI related to any adverse events (AEs), serious adverse events (SAEs) or unanticipated problems (UPs). As part of this responsibility, DSMB members must be satisfied that the timeliness, completeness, and accuracy of the data submitted to them for review are sufficient for evaluation of the nature of the event and the safety and welfare of the study participants. The DSMB will also assess the performance of overall study operations and any other relevant issues, as necessary. **A letter of support from Dr. Kathryn Gold, DSMB Chair, is attached.** The “primary responsibilities” of this DSMB include:

1. Conducting an initial review of the proposed research to assure quality study conduct;
2. Reviewing study procedures to assure quality of study conduct, including SOPs for data management and quality control procedures;
3. Evaluating the quality of the ongoing study conduct by performing quarterly evaluations of the study accrual, compliance with eligibility, participant adherence to study requirements, and accuracy and completeness of data;
4. Considering factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the study;
5. Recommending appropriate study review or temporary halting for any SAE, and termination due to the occurrence of 3 SAEs (symptom exacerbation or suicidality associated specifically with active treatment vs. PBO), or inability of PI to provide necessary assessment information or to answer study questions;
6. Recommending continuation of ongoing studies at quarterly reviews;
7. Considering the overall picture, including need to pursue both primary and appropriate secondary analysis, and making these recommendations during the final months of PY3 (see “Timeline”);
8. Consider modifying sample sizes based on unexpectedly robust therapeutic benefits; and
9. Reviewing final results, via DSMB report by PI within 90 days of completion of final R33 subject.

The DSMP proposes both the “process” and “content” of the DSMB, including its deliberative processes, event triggers that would call for an unscheduled review, stopping guidelines, unmasking (unblinding) and voting procedures prior to initiating any data review. Elements of the DSMP include:

1. How risks are minimized (e.g. see “Protection of Human Subjects” section on inclusion and exclusion criteria, careful clinical monitoring including specific scales for suicidality and psychosis and specific criteria for interventions based on these scales);
2. How risks are reasonable in relation to anticipated benefits (see “Protection of Human Subjects” re: risk/benefit ratio);
3. Plan to monitor progress and safety (see below for description of adverse events and related protocol);
4. Assessments of data quality, timeliness, participant recruitment, accrual and retention;
5. Plan to assure compliance with reporting of adverse events and/or unanticipated problems involving risk to participants or others (see below for details):

a. Process for detecting and reporting serious and unexpected adverse events and/or unanticipated problems involving risk to participants or others;
b. Who will be monitoring and collecting the adverse events;
c. Who will be notified of an adverse event;
d. The timing of reports;
e. Annual reporting of adverse events.

This DSMP will be approved by our UCSD IRB and CTRI DSMB in advance of enrolling any R33 study subjects.

Adverse Events

Definition of Adverse Events (AEs): An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Causal relationship of AEs: Medical judgment will be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, confounding factors such as concomitant medication, concomitant diseases and relevant history, and reported as such to the DSMB.

Vital signs (measurements of systolic/diastolic blood pressure and pulse rate as outlined below) will be recorded at each study visit and at specific time points after AMPH/PBO ingestion. BP is measured using a brachial cuff on the non-dominant arm; pulse is measured manually for 30 seconds and multiplied by 2.

Assessment of suicidality: Suicidality will be monitored closely during the study period. Suicidal thoughts and behavior will be assessed by Columbia-Suicide Severity Rating Scale (C-SSRS). The C-SSRS is a questionnaire assessing both suicidal behavior and suicidal ideation. It consists of five questions related to suicidal behavior and five questions related to suicidal ideation, evaluated as either present or not. The C-SSRS will be administered by qualified clinicians and will be assessed at the screening visit with the aim to exclude patients with active moderate or severe symptomatology prior to the Screen Visit, or recent (or current) suicidal or suicide attempt according to the C-SSRS (baseline/screening version). Subsequently, the C-SSRS “since last visit” assessment will be performed at each visit as shown in the study Schematic. If there is a positive response of suicide attempt or suicidal ideation by the patient during the administration of the C-SSRS during the treatment period, a study MD will immediately interview the patient during the visit and determine if the patient will be discontinued from the trial and appropriate actions for the patient’s safety have to be initiated. For assessment of the C-SSRS paper forms will be used and results will be transcribed into the DSMB report.

Definition of a Serious Adverse Event (SAE): A serious adverse event is defined as any AE which results in death, is life-threatening, requires inpatient hospitalization, results in persistent or significant disability or incapacity or is to be deemed serious for any other reason if it is an important medical or psychiatric event when based upon appropriate medical judgment which may jeopardize the patient and may require medical, psychiatric or surgical intervention.

For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity:

- Mild – Events require minimal or no treatment and do not interfere with the participant’s daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant’s usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

The PI's assessment of an AE's relationship to the study interventions - TCT and AMPH - is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported. All AEs will have their relationship to TCT and AMPH assessed. To help this assessment, the following guidelines are used:

- Related – The AE is known to occur with TCT or AMPH, there is a reasonable possibility that TCT or AMPH caused the AE, or there is a temporal relationship between the use of TCT or AMPH and the event. Reasonable possibility means that there is evidence to suggest a causal relationship between the TCT or AMPH and the AE.

- Not Related – There is not a reasonable possibility that the administration of TCT or AMPH caused the event, there is no temporal relationship between the use of TCT or AMPH and the event onset, or an alternate etiology has been established.

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the known risks of TCT or AMPH.

AE's will be identified either 1) if alerted by study subject, their representative (relative, physician) between study visits, or 2) by careful clinical assessment at a study visit or follow-up visit. All subjects are evaluated clinically at every visit (approx. 3 times per week), and any deviation from their expected baseline clinical state will warrant a more detailed clinical assessment, documentation and intervention as necessary.

Any medical or psychiatric condition or symptom that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The PI will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation (12 weeks post-TCT). At each study visit, the investigators will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

AE's suspected by study staff are immediately reported to a study MD. A study MD (typically the PI, but other licensed MD's are also listed on this PI's IRB protocols and can provide back-up coverage) is on the premises at all times that experiments and TCT training are in progress, and study staff have cell phone access to study clinicians at all times, including weekends and holidays. If an AE is confirmed, the PI is notified immediately; study staff and clinicians have cell phone access to the PI at all times, including weekends and holidays.

The PI will convene a phone- or face-to-face meeting of all study clinicians 24 hours to discuss the implications of the AE and all necessary follow-up and interventions. A full report to the DSMB and IRB will be made within 7 days of the AE. The PI is responsible for signing off on all AE reports. Reporting lines are as follows:

Reporting Source $\rightarrow$ Research Staff $\rightarrow$ Study MD (PI) $\rightarrow$ DSMB, IRB

Reporting lines will be as above, for AEs. However, the PI will notify the DSMB and IRB in real-time in the event of any SAE; in addition, the PI will complete an SAE Form within the following timelines:

All deaths and immediately life-threatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to the NIMH within 24 hours of site awareness. Other SAEs regardless of relationship, will be submitted to the NIMH within 72 hours of site awareness.

All SAEs will be followed until satisfactory resolution or until the PI deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the NIMH as soon as possible.

Incidents or events that meet the OHRP criteria for unanticipated problems (UPs) require the creation and completion of an UP report form. It is the PI's responsibility to report UPs to the UCSD IRB and to the NIMH. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.
- UPs that are SAEs will be reported to the UCSD IRB and to the NIMH within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the UCSD IRB and to the NIMH within 72 hours of the investigator becoming aware of the problem.
- All UPs will be reported in real time to the DSMB

Pregnancy: As described in "Protection of Human Subjects", women of childbearing years participate in the present study only under specific conditions designed to minimize the possibility of pregnancy, and with weekly or more often monitoring of urine pregnancy tests. Any patients testing positive in this surveillance will receive further study drug. The study blind will be broken; if the subject was receiving active drug, they will be referred for appropriate pregnancy-related care and follow-up will be maintained with the subject through to completion of pregnancy.

Amphetamine carries a teratogenic risk classified as Pregnancy Category C. However, the level of exposure in the present study is very low and likely to be greatly exceeded by the teratogenic risk of other medications being taken by schizophrenia patients. TCT has no known teratogenic risk.

Study Halting: Administration of study agent will be halted if three grade 3 AEs determined to be "probably related" are reported to the DSMB. The DSMB will notify the NIMH immediately when the third grade-3 event is reported and enrollment screens will stop accepting new study participants. The DSMB will convene an ad hoc meeting by teleconference or in writing as soon as possible. The DSMB will provide recommendations for proceeding with the study to the NIMH. The NIMH will inform the FDA of the temporary halt and the disposition of the study.

Section 4 - Protocol Synopsis (Study 1)

4.1. Brief Summary

Current therapies for chronic psychotic disorders such as schizophrenia include antipsychotic medications, which do not significantly improve function or correct cognitive deficits in this disorder, and cognitive therapies, which produce only modest benefits to most patients. We hypothesize that medications that specifically target neurocognitive processes like attention and vigilance will significantly augment the clinical benefits of cognitive therapies in schizophrenia. Here, we will confirm that the pro-attention psychostimulant, amphetamine, enhances learning of an auditory processing task in a computerized targeted cognitive training (TCT) program in antipsychotic-medicated schizophrenia patients, and complete a randomized, double-blind clinical trial in antipsychotic-medicated schizophrenia patients, comparing TCT (30 sessions) plus amphetamine vs. TCT (30 sessions) plus placebo.

4.2. Study Design

4.2.a. Narrative Study Description

Screened, eligible patients complete clinical, neurocognitive and functional measures and candidate biomarkers (EEG, QuickSIN, WIN). Aim 1 is completed in 2 tests, approximately 1 week apart. In Test 1, Sound Sweeps are tested after PBO for all subjects, who are then randomized to TCT+PBO vs. TCT+AMPH arms (n=27/arm) using stratified random sampling (over sex, age and high/low Test 1 APS learning) blind to arm identity, similar to our previous studies. Test 2 follows approximately 5-7 d later; this test is identical to Test 1, except that subjects receive their assigned study drug (PBO vs. AMPH (5 mg po)) 1 hour prior to Sound Sweeps. Tests 1 and 2 are used to assess target engagement (Aim 1: AMPH-enhanced APS learning) and AMPH effects on auditory discrimination (QuickSIN, WIN). Our design allows for 20% attrition from enrollment (n=69) to completion of target engagement testing (n=54). For Aim 2, TCT in these same subjects is scheduled 3 d/week (M-W-F) for 1-h/d, recognizing the need for flexibility (T-Th are “make-up days”), and continues until a subject completes 30-h (approximately 10-12 weeks). TCT is delivered by trained staff. 60 min prior to each TCT session, patients take either PBO or 5 mg AMPH, as per arm assignment. Patients and staff are blind to study arm; staff are blind to patients’ baseline or post-intervention assessments. Outcome metrics assess symptom, neurocognitive and functional changes after 10, 20 and 30 TCT sessions, and 12 weeks post-TCT. Candidate biomarkers are re-tested after completion of 30 sessions of TCT.

4.2.b. Primary Purpose: Treatment

4.2.c. Interventions

Type	Name	Description
Behavioral (e.g., Psychotherapy, Lifestyle Counseling)	Targeted Cognitive Training	Thirty, one-hour sessions over approximately 10 weeks, of computerized cognitive training modules.
Drug (including placebo)	amphetamine	The pro-attentional medication, amphetamine (placebo vs. 5 mg) will be administered orally, 1 hour prior to targeted cognitive training, in a double-blind, randomized design.

4.2.d. Study Phase: Phase 2/3

Is this an NIH-defined Phase III Clinical Trial? ○ Yes ● No

4.2.e. Intervention Model: Parallel

4.2.f. Masking: ● Yes ○ No

☑ Participant ☑ Care Provider ☑ Investigator ☑ Outcomes Assessor

4.2.g. Allocation: Randomized

4.3. Outcome Measures

Type	Name	Time Frame	Brief Description
Primary	Auditory Processing Speed (APS) learning	Test 1 and Test 2, one week apart	APS is measured before and after the TCT "Sound Sweeps" frequency modulation session, to determine the amount of "learning", based on the reduction in detection gap (ms). More learning (greater gain in processing speed) with amphetamine vs. placebo confirms target engagement, which is the primary outcome of Aim 1.
Primary	PANSSt: Positive & Negative Symptom Scale total	baseline vs. post-TCT session 10, 20 and 30 (approximately 10 weeks), and 12 weeks post-TCT	TCT reduces both positive and negative symptoms of psychosis; we predict that amphetamine will augment these effects via enhanced TCT learning, detected by the PANSS. For this reason, and based on the need to limit total outcome measures, PANSS Total Score is the primary clinical outcome measure. Positive and negative symptom subscales, as well as PANSS factor-derived measures, will be assessed in exploratory analyses. Other secondary clinical measures will include: 1) Psychotic Symptom Rating Scales (assesses auditory hallucinations); 2) Young Mania Rating Scale; 3) Patient Health Questionnaire-9 (current depressive symptoms); 4) Abnormal Involuntary Movement Scale; 5) Columbia Suicide Severity Rating (C-SSRS); “Lifetime/Recent version” at screen; “Since Last Visit” at follow-up visits). The C-SSRS is a sensitive measure of suicidal ideation; any “yes” in C-SSRS prompts an immediate full evaluation/action plan by a study M.D.; and 7) AMPH Cessation Symptom Assessment
Primary	MATRICS Consensus Cognitive Battery Global Composite T-score (MCCB-C)	baseline vs. post-TCT session 10, 20 and 30 (approximately 10 weeks), and 12 weeks post-TCT	The MCCB measures 7 separable cognitive domains. Details are found in cited reports including past studies by the PI of drug effects on MCCB performance. Since the MCCB is assessed multiple times, alternate forms of the HVLT-R and BVMT-R are administered in counterbalanced order. MCCB Global Composite T-score (MCCB-C) is the primary neurocognitive outcome measure. Individual MCCB domain T-scores are used in secondary analyses to determine whether an overall effect is driven by specific aspects of neurocognition; specifically, TCT effects on verbal learning performance are known to be robust, and should be augmented by AMPH. Baseline MCCB performance (attention/ vigilance subscale) will also be tested as a potential biomarker/ moderator of AMPH efficacy.
Primary	World Health Organization Disability Schedule (WHODAS 2.0)	baseline vs. post-TCT session 10, 20 and 30 (approximately 10 weeks), and 12 weeks post-TCT	Function will be assessed via the World Health Organization Disability Schedule 2.0 (WHODAS 2.0)at baseline, after sessions 10, 20 and 30, and week 12 post-TCT. WHODAS 2.0 is a 12-item patient-rated measure (< 15 min) using a 5-point Likert scale focusing on 6 domains: cognition, mobility, self-care, getting along with people, life activities, participating in society; it was recommended by the DSM-5 Task Force committee to replace the global assessment of functioning (GAF) scale.

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