Human models as tools in the development of psychotropic drugs

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Phase 1 studies constitute a pivotal step in drug development. Their goal is to gather enough information to warrant the scientific value of phase 2 studies. The information to be collected includes the pharmacological actions of the drug, its side effects with increasing doses, its pharmacokinetics (PK) and metabolism, its mechanisms of action, and, if possible, early evidence of effectiveness.[1] The classic method of conducting phase 1 studies is much more limited *(Table I)*. First-time-in-man, single-dose, and repeated-dose studies are carried out in healthy volunteers (HV), according to a parallel, double-blind (DB), placebo-controlled design. They are focused on PK, safety, and tolerability, seeking the maximal tolerated dose (MTD), which will be the basis for the choice of doses in subse-

Despite the growing means devoted to research and development (R & D) and refinements in the preclinical stages, the efficiency of central nervous system (CNS) drug development is disappointing. Many drugs reach patient studies with an erroneous therapeutic indication and/or in incorrect doses. Apart from the first clinical studies, which are conducted in healthy volunteers and focus only on safety, tolerability, and pharmacokinetics, drug development mostly relies on patient studies. Psychiatric disorders are characterized by heterogeneity and a high rate of comorbidity. It is becoming increasingly difficult to recruit patients for clinical trials and there are many confounding factors in this population, for example, those related to treatments. In order to keep patient exposure and financial expenditure to a minimum, it is important to avoid ill-designed and inconclusive studies. This risk could be minimized by gathering pharmacodynamic data earlier in development and considering that the goal of a phase 1 plan is to reach patient studies with clear ideas about the compound's pharmacodynamic profile, its efficacy in the putative indication (proof of concept), and pharmacokinetic/pharmacodynamic relationships, in addition to safety, tolerability, and pharmacokinetics. Human models in healthy volunteers may be useful tools for this purpose, but their use necessitates a global adaptation of the phase 1 scheme, favoring pharmacodynamic assessments without neglecting safety. We are engaged in an R & D program aimed to adapt existing models and develop new paradigms suitable for early proof of concept substantiation.

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Selected abbreviations and acronyms

AD	*Alzheimer's disease*
BZD	*benzodiazepine*
DB	*double-blind (study)*
fMRI	*functional magnetic resonance imaging*
HV	*healthy volunteer*
MTD	*maximal tolerated dose*
PD	*pharmacodynamics*
PK	*pharmacokinetics*
POC	*proof of concept*

quent patient studies. Using this scheme, many drugs have been developed in the wrong indication[2] or using inappropriate doses,[3] which led to failures or irrelevant studies, which then had to be replicated leading to delays, increased costs, and overexposure of patients to drugs.

It seems clear that gathering data on pharmacodynamics (PD) and PK/PD relationships earlier would minimize these risks, bearing in mind that, in any case, further steps will face other major issues such as patient heterogeneity and placebo response.

Our usual way of conducting phase 1 studies takes these needs into account *(Table I)*. As early as in the first-in-man study, in addition to PK and safety/tolerability evaluation, we collect basic, central nervous system (CNS) PD data, as well as peripheral PD data (eg, evidence of blood–brain barrier crossing, QTc or cardiac rhythm changes, minimal active dose, and dose effect), and attempt to sketch PK/PD relationships. This information is expanded in repeated-dose studies, which can be followed by PD studies in HV, conducted according to a crossover, DB, placebo-controlled design and using the most appropriate tools, such as wake or sleep electroencephalography (EEG), cognition or functional imaging according to the molecule and its putative indication (see, for example, references 4 to 10). This allows patient studies to be undertaken with a better knowledge of the drug profile and the most appropriate doses.

In the last years, the necessity for a proof of concept (POC) approach has emerged. Simply stated, POC means that at some stage of the development, before launching large patient studies, it should be demonstrated that the drug does what it is supposed to do. Classically, POC studies are patient studies. Psychiatric disorders are highly heterogeneous syndromes, with a high rate of comorbidity (eg, dementia or schizophrenia coexist with affective or anxiety disorders, affective disorders with anxiety disorders, different anxiety disorders together, etc). Therefore,

	Classic	Current (usual)	Enhanced
Single-dose study			
Population	Young, healthy volunteers	Young, healthy volunteers	Young, healthy volunteers
Design	Parallel, double-blind, vs placebo	Parallel, double-blind, vs placebo	Parallel, double-blind, vs placebo
Objectives	• Safety/tolerability (MTD) • PK	• Safety/tolerability (MTD) • PK • Basic PD* • PK/PD relationships	• Safety/tolerability (MTD) • PK • Basic PD* • PK/PD relationships
Repeated-dose study			
Population	Healthy volunteers	Healthy volunteers	Healthy volunteers
Design	Parallel, double-blind, vs placebo	Parallel, double-blind, vs placebo	Crossover, double-blind, vs placebo
Objectives	• Safety/tolerability (MTD) • PK	• Safety/tolerability (MTD) • PK • Basic PD** • PK/PD relationships	• Safety/tolerability (MTD) • PK • Refined PD (model)*** • PK/PD relationships
Next step			
Population	Patients	Healthy volunteers	Patients
Design	Parallel, double-blind, vs placebo	Crossover, double-blind, vs placebo	Parallel, double-blind, vs placebo
Objectives	• Safety • Efficacy	• Refined PD • PK/PD relationships	• Safety • Efficacy

Table I. Three ways of conducting phase 1 studies. MTD, maximal tolerated dose; PK, pharmacokinetics; PD, pharmacodynamics; BBB, blood–brain barrier. *Basic PD includes BBB crossing, minimal active dose, dose effect, and non–central nervous system (CNS) PD. **Basic PD without BBB crossing. ***Refined PD (model): proof of concept, minimal active dose, dose effect, and non-CNS PD.

essentially two strategies are possible to improve patient recruitment. The first is to recruit small, homogeneous groups of highly characterized patients (no comorbidity, homogeneous symptomatic profile, imaging or biological characteristics, such as genotype, if applicable, etc), which is an ambitious and lengthy operation. The second is to increase the sample size, with the hope that number will compensate for heterogeneity. This also makes the trial longer and more expensive, and there is no guarantee that the compensation will be obtained. In addition, concern about withdrawing an ongoing treatment on the part of ethics committees, physicians, nurses, families, and patients further hampers recruitment.

Studies in HVs have advantages that compensate for these difficulties. HVs are easier to recruit. They make more homogeneous—or less heterogeneous—populations than patients and, since more subjects are available, homogeneity can be improved through specific selection criteria. By definition, these subjects are healthy, have a lower risk of complications, and tolerate procedures better. In addition, they have no expectations about the treatment, which can minimize placebo/nocebo effects. By definition, they are also volunteers and get paid, and are thus more compliant.

Conducting POC studies in HVs implies the recourse to models or symptom provocation. These challenges can be understood as the provocation not of a complete clinical picture, but of some core signs and symptoms. The goal can be to produce and study functional markers because they are often more sensitive—and hopefully more reliable—than clinical signs and symptoms. Therefore, it is possible to use less stressful provocative procedures, which further increases subjects' comfort and compliance. Symptom provocation in HVs must comply with some basic rules *(Table II)*, as stated by D'Souza et al.[11] In the context of drug development, a model must also induce target signs and symptoms in a reasonable proportion of HVs. These signs and symptoms must be accompanied with reliable functional changes, which can be used as biomarkers and display low interindividual and mostly intraindividual variability, to warrant good test–retest reliability and permit the assessment of drugs effects in a crossover, placebo-controlled design.

- The safety and protection of subjects is ensured
- The study is expected to provide information of critical value
- The proposed methodology is undoubtedly adequate to answer the question (testable hypotheses, reliable and valid measures, adequate power, appropriate data analysis, and relevant controls)
- The study is the best or only feasible method of answering the question

Table II. Criteria to justify symptom provocation in humans.[11]

Although the principle of a POC approach in HVs is appealing, we must be cautious in putting it into practice. Even when the provocation procedure is simple (eg, a single agent with well-known neurochemical properties, in the case of a pharmacological model), the totality of the neurochemical consequences of its administration are seldom known. The same holds for the new compound studied and for its interaction with the challenge. As a consequence, a positive result (ie, reversal or prevention of the challenge's effects by the new drug) is undoubtedly a clue to efficacy, but a negative result can hardly be taken as the basis for a "no-go" decision. This often makes pharmaceutical companies reluctant to add a POC study in HVs to their development plan, arguing that, in case of negative results, it could merely delay it and increase costs. In fact, introducing POC studies in HVs implies further enhancing the global phase 1 scheme *(Table I)*. In this "enhanced development plan," the single-dose study has the same design and goals as the regular one. The repeated-dose study merges the former repeated-dose and PD HV studies, ie, it is conducted according to a crossover (per dose), placebo-controlled design. Provided that a single administration study has shown good tolerability in an HV group close to the target population (eg, elderly HVs for cognitive enhancers), this study can be conducted in such a group. A model, if available, can also be used in this study, by adding an administration the day after the classic PK and PD assessments. This avoids wasting HVs and resources, and maximizes the chances of positive results; however, it requires paying close attention to tolerability and safety, which must be verified before a challenge is added to a repeated-administration study.

Models at FORENAP

Few models are available for routine use in drug development. We have launched a program to adapt existing models for this purpose *(Table III)*, following the principles described above. Below we discuss the rationale for each of these models, as well as preliminary results when available, at least those which are not covered by confidentiality agreements.

Alzheimer's disease and age-related cognitive impairment

The scopolamine model

The scopolamine model is based on the cholinergic hypothesis of aging and Alzheimer's disease (AD). Its theoretical drawback is that scopolamine is a nonselective muscarinic blocker, whereas selective muscarinic M_1 blockade could be considered to better modelize the status of the cholinergic system in AD.[12] Nevertheless, it is a well-established model, producing cognitive defects close to those observed in mild AD and EEG changes consisting of an increase in δ and—to a lesser extent—Θ bands, and a decrease in α and β power.[13] The scopolamine model has been widely used in clinical experimental pharmacology,[14-23] as well as in the assessment of cognitive enhancers.[24-40] In our hands, a 0.5-mg subcutaneous injection of scopolamine in young HVs induced impairment in immediate and delayed word recall, multiple choice reaction time and accuracy, and the digit symbol substitution test. In quantified EEG, it reduced total power and induced an increase in δ and a decrease in Θ, α, and β absolute power; in relative power analysis, the δ and β band activity was increased and that of the Θ and α bands decreased *(Figure 1)*. An interesting feature of this model is that is can be reversed or prevented not only by cholinomimetic drugs, but also, as we have found, by compounds without direct cholinergic effects.[30,31,38,41]

The lorazepam model

Benzodiazepines (BZDs) are known to induce sedation, psychomotor impairment, and anterograde amnesia, leaving retention and retrieval spared.[42] Although cognitive impairment is a class effect, differences between different BZDs have been reported, independently of their elimination half-lives.[43-45] A dissociation between the cognitive and sedative effects of drugs has also been described.[46] Lorazepam has dose-related memory- and attention-impairing effects.[43,44,47] It has been suggested[48] that the profile of lorazepam-induced cognitive impairment is close to that observed in Korsakoff's syndrome, whereas scopolamine rather mimics AD. Some studies[47,49] were unable to distinguish the effects of lorazepam from those of scopolamine. Both drugs were shown to have similar effects on verbal priming[50] and in a face–name associative encoding task,[51] and as well as on associated functional magnetic resonance imaging (fMRI) activation patterns. On the other hand, differential effects were found on logical reasoning, immediate and delayed recall,[52] and priming for human faces.[53]

BZDs have well-known effects on EEG. Changes in β amplitudes seem to reflect their interaction and intrinsic efficacy at the $GABA_A$-BZD (GABA, γ-aminobutyric acid) receptor complex; their effects on β and α activity their anxiolytic, anticonvulsant, and sedative properties; and δ-induced changes their hypnotic action.[54]

In our hands, an oral dose of 2 mg lorazepam impaired immediate and delayed word recall, multiple choice reac-

Indication	Method	Marker	Status
AD/cognition			
	Scopolamine	EEG/ERPs	Routine
	Lorazepam	EEG/ERPs	Routine
	Low-dose ketamine	EEG/MEG	Validation underway
	Nonpharmacological method	fMRI	Validation underway
Anxiety			
Panic	CCK-4	fMRI	Validation underway
Anticipatory	Behavioral	fMRI	Validation underway
Depression			
	Tryptophan depletion	Sleep EEG	Validation completed
Schizophrenia			
	Apomorphine	EEG	Routine
	Ketamine	EEG/MEG	Validation underway

Table III. Models available or in development at FORENAP. AD, Alzheimer's disease; CCK-4, cholecystokinin tetrapeptide; EEG, electroencephalography; ERP, event-related potential; fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography.

tion time and accuracy, and digit symbol substitution test, but had no effect on flicker fusion frequency. In quantified EEG, lorazepam's effects were dose-dependent in length and intensity, increasing δ and β power, and decreasing the power of the Θ and α frequency bands *(Figure 2)*.

The low-dose ketamine model

Ketamine infusion produces positive, negative, and cognitive symptoms reminiscent of those observed in schizophrenia.[55-65] A hypoglutamatergic state has also been proposed as the substratum of late-stage AD.[66] Studies focused on ketamine-induced cognitive impairment should separate the latter from the psychotomimetic effects of ketamine, which is possible using lower doses.[64]

Nonpharmacological approaches

Functional (positron emission tomography [PET] and fMRI) studies on the neural correlates of cognitive aging basically describe two cases.[67] In one, performance and brain activation during the task are lower than in young controls; this is also the case for episodic memory and conflict resolution tasks. The second consists of preserved performances associated with enlarged activation, engaging more brain regions, such as during working memory tasks. Our fMRI activation maps, obtained during a spatial "n-back" working memory challenge are in agreement with these data *(Figure 3)*. Our hypothesis is that activation patterns in elderly volunteers should be closer to those of young volunteers after administration of a

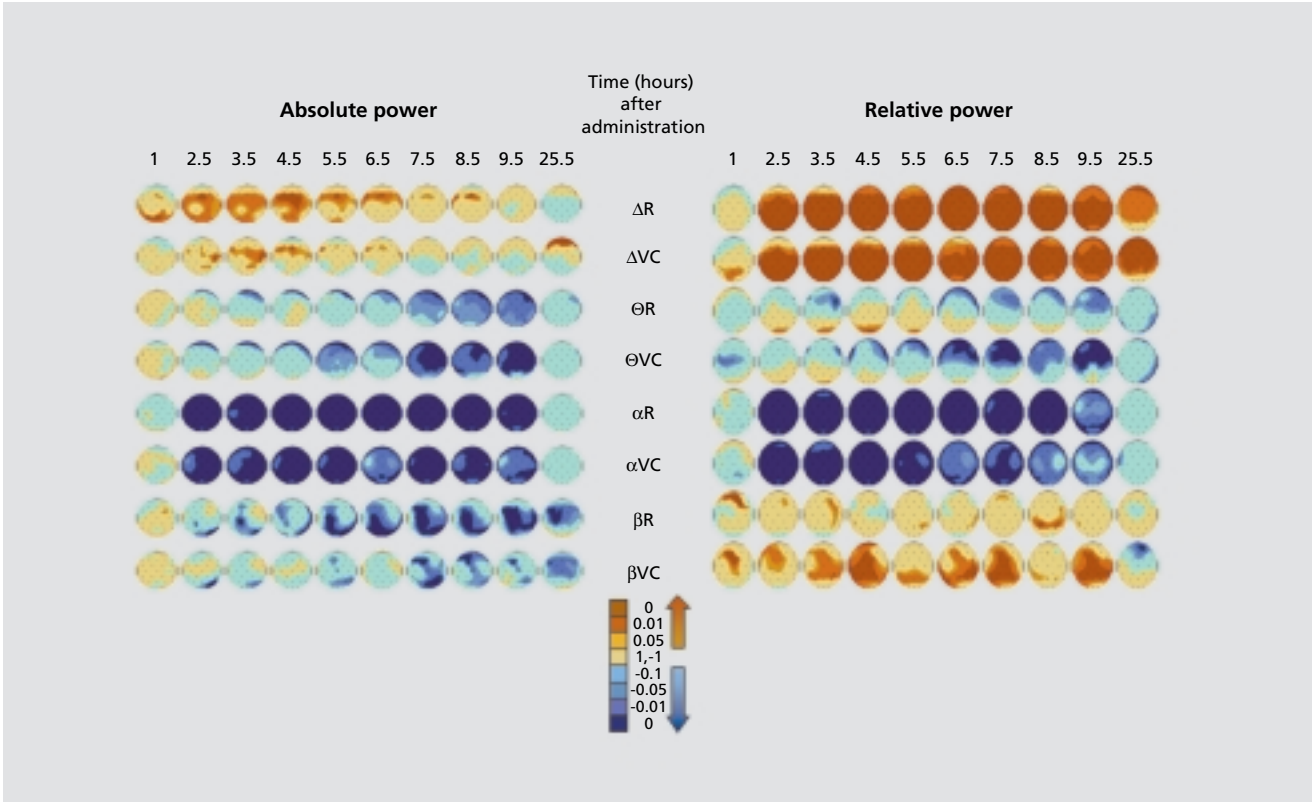

Figure 1. Effect of scopolamine (0.5 mg subcutaneously) on electroencephalogram (EEG) in 12 healthy young men. Placebo and scopolamine were administered according to a crossover, double-blind design. EEG was recorded from 28 electrodes during the first 3 min in vigilance-controlled conditions, and then at rest. Analog filtering 1 to 70 Hz, 12 dB/octave; digitalization with a 256-Hz sampling frequency; fast Fourier transform on each 2-s artifact-free epochs. δ, 0.5-3.5 Hz; Θ, 4-7.5 Hz; α, 8-12.5 Hz; β, 13-32 Hz. Maps displayed are *P* values after scopolamine–placebo comparison. Scopolamine reduced total power (not shown) and induced an increase in δ and a decrease in Θ, α, and β absolute power; in relative power analysis, the δ and β bands' activity was increased and that of the Θ and α bands decreased. R, at rest; VC, in vigilance-controlled conditions.

cognitive enhancer. Indeed, PET scan and fMRI studies in young volunteers have shown that physostigmine infusion improved working memory performances and reduced task-related activation.[68-70]

Anxiety

Panic attack model: CCK-4

The idea of using cholecystokinin tetrapeptide (CCK-4) as a panic probe came from experiments showing that BZDs antagonized CCK-8S in the rat,[71] as well as from the serendipitous finding that a 70-µg CCK-4 injection produced panic-like feeling in healthy humans.[72] In subsequent studies,[73-91] CCK-4 induced panic attacks in 0% to 70% of HVs and these attacks were quantitatively and qualitatively similar to those reported by patients. Attack incidence and severity of symptoms were dose-dependent, although discordant results have been described with the same dose and a considerable overlap exists in the rate of response to different doses. The dose of 50 µg seems to give the most homogeneous response rate, ranging from 47% to 65%. Test–retest reliability has been poorly assessed. Two studies—although not specifically designed for this purpose—reported a decrease in the number and intensity of panic symptoms,[79,88] as well as in the incidence of panic attacks.[79]

In HVs, lorazepam prevented CCK-4–induced panic,[73] as did the CCK-4 receptor antagonist CI988,[80] propranolol,[87] ondansetron after acute but not repeated administration,[88] atrial natriuretic peptide,[89] and vigabatrin.[90] PET scan studies found an increased cerebral blood flow concomitant of anxiety response in the claustrum-insular-amygdala region bilaterally and in cerebellar vermis and anterior cingulate gyrus.[92,93] Our fMRI results confirm these data.

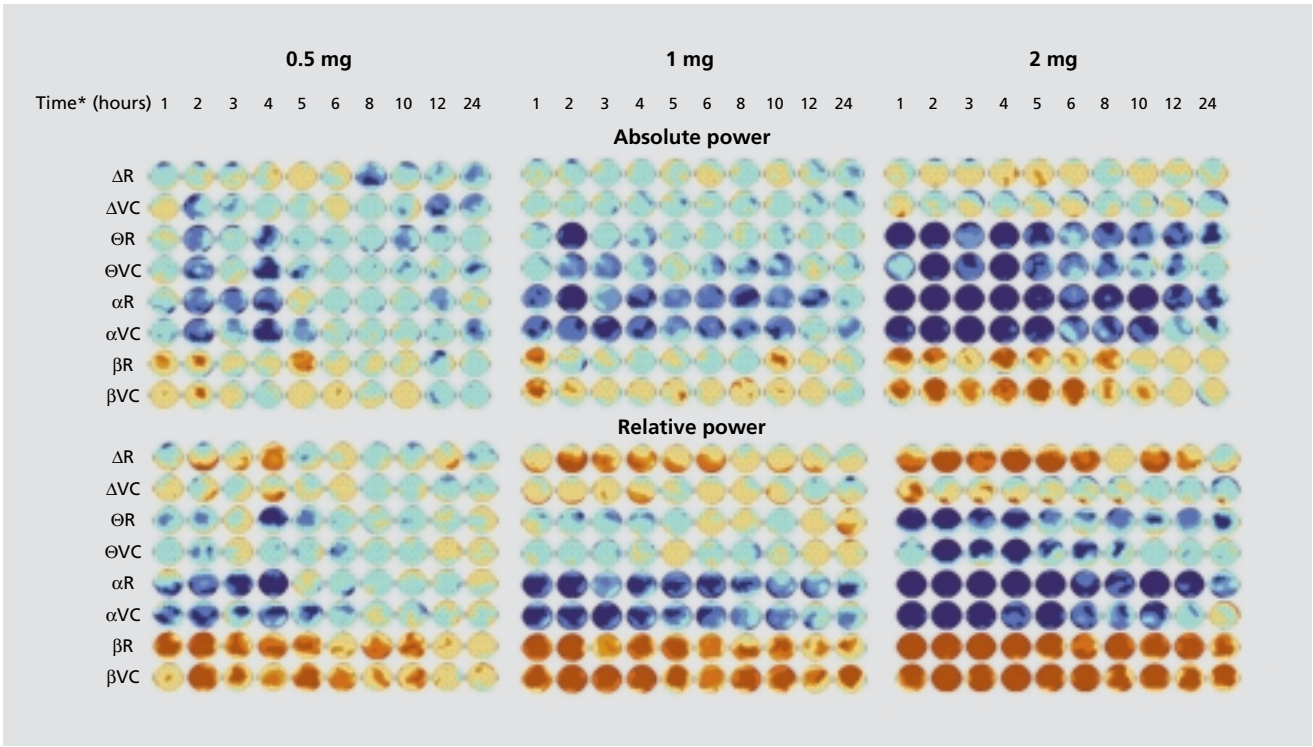

Figure 2. Effects of three oral doses of lorazepam on electroencephalogram (EEG) in 20 young healthy male volunteers. Lorazepam 0.5 mg, 1 mg, and 2 mg, and placebo were administered according to a crossover, double-blind design. Maps displayed are *P* values after lorazepam–placebo comparison. In absolute power analysis, lorazepam dose-dependently decreased Θ and α power, and increased β activity. Relative power disclosed an additional effect on δ power which was, also dose-dependently, increased. See *Figure 1* for methods and maps color code. *Time post-administration. R, at rest; VC, in vigilance-controlled conditions.

Anticipatory anxiety: behavioral model

Recent research suggests that the neurophysiological mechanisms underlying anxiety disorders are closely related—if not identical—to those underlying the emotion of fear.[94] This provides the rationale for using behavioral models based on fear induction or anticipation of an aversive stimulus. In behavioral models, an anxious state is induced by presentation of stimuli having an aversive emotional content, via any sensory modality. A major drawback of using intrinsically fearful stimuli is that the fear or aversion elicited can vary according to volunteers' traits and experiences. Aversive conditioning (in which an emotionally neutral or conditioned stimulus [CS] is paired with an aversive—or unconditioned—one [UCS], usually in different sensory modalities) allows for a more homogeneous response within the subject population by adjusting the aversive nature of the UCS on an individual basis. Although amygdala activation is considered to be central to anticipatory anxiety,[94-96] other regions are also activated during classical conditioning, eg, right orbitofrontal, dorsolateral prefrontal, inferior and superior frontal, inferior and middle temporal cortices, and left superior frontal cortices,[97,98] anterior cingulate, and insula,[99] according to the paradigm used. The study of many regions together can lessen the consequences of "missing" the amygdaloid complex activation, which is transient even when the UCS continues to be presented in association with CS.[95,98,99] Our results confirm the merits of this approach.

Depression: the tryptophan depletion challenge

The rationale and results of a recent study with this model are given elsewhere in this volume.[100]

Schizophrenia

The apomorphine model

For decades, dopamine transmission abnormalities have been thought to be involved in the pathophysiology of schizophrenia,[101] justifying the stimulation of dopaminer-

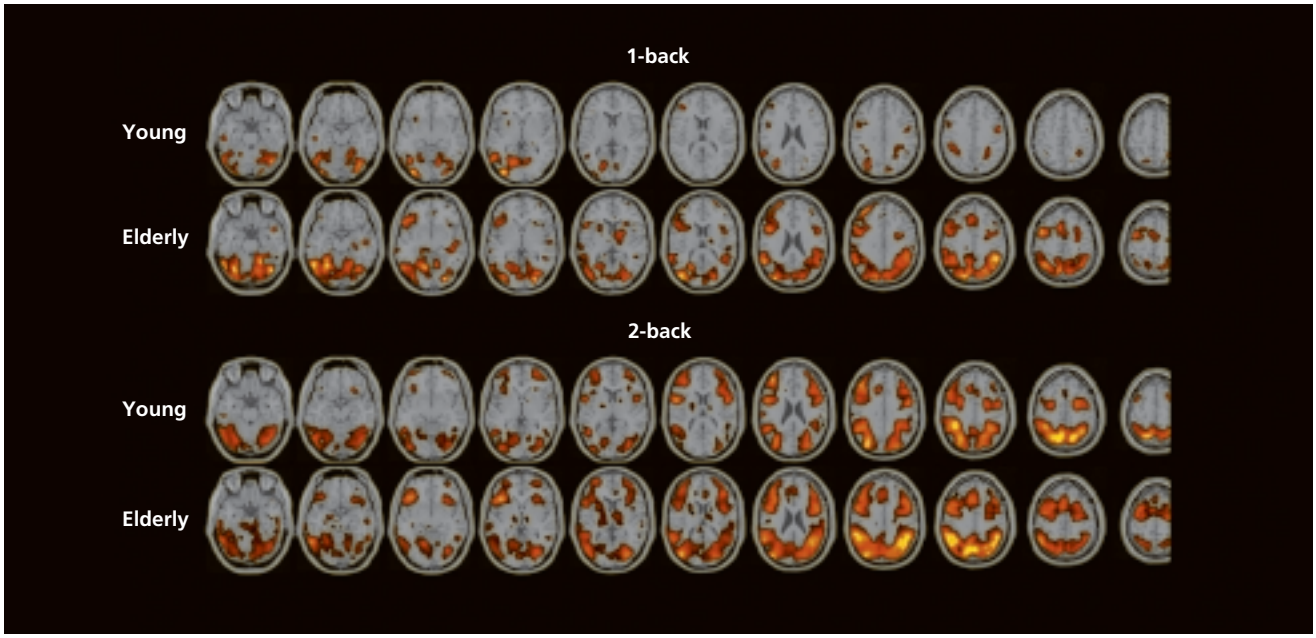

Figure 3. Statistical parametric maps (SPMs) of the group analysis (4 young and 4 elderly healthy male volunteers, 3 functional magnetic resonance imaging [fMRI] exams per subject) during "n-back" spatial working memory task versus control. In the control condition ("0-back"), subjects had to respond when a square appeared in a given position on the computer screen; in the "1-back" condition, when it appeared in the same place as 1 screen before; in the "2-back" condition when it appeared in the same place as 2 screens before. In both the 1-back and the 2-back tasks, accuracy score was similar in elderly and young subjects. Reaction time was similar in the two groups during the 1-back task, but significantly longer in the elderly group during the 2-back task. Significant activity (t-score>4) is displayed upon anatomical axial T_1 images after being transformed to standardized Talairach space.

gic pathways as a model of schizophrenia in HVs. Apomorphine, a nonselective dopaminergic agonist, has a rapid phase of absorption and distribution in the periphery (20 min) as well as the brain compartment (30 min) in humans[102] and is an ideal pharmacological tool because it has minor psychotropic effects in both HVs and psychiatric patients. We have characterized apomorphine-induced topographic changes in neurophysiological markers using a 28-lead multielectrode montage in HVs. To ensure that observed modifications are of central and not of peripheral origin, subjects were pretreated with domperidone, a dopamine antagonist that does not cross the blood–brain barrier. We assessed drug-induced modifications in EEG/event-related potential measurements at different time points after subcutaneous injection of apomorphine.[103] As expected, the effects of apomorphine on EEG were partially opposite to those reported for classic[104] and atypical[105,106] neuroleptics, with an increase in fast β power and decrease in Θ relative power. This model was validated using haloperidol, which antagonized the acute effects of apomorphine.[107]

The ketamine model

N-Methyl-D-aspartate (NMDA) receptor blockade by ketamine infusion in HVs is acknowledged to be a good model of schizophrenia, reproducing positive, negative, and cognitive symptoms.[55-65] Despite evidence that ketamine modulates dopamine striatal concentration,[108-111] its clinical effects were not reversed by haloperidol in patients[112] or in HVs,[61] or olanzapine,[113] but were blunted by clozapine in patients with schizophrenia.[114] This inconsistent effect of antipsychotics could be dose-related. The above studies used ketamine doses of 0.1 to 0.9 mg/kg in bolus or 1-h infusion, whereas we use 0.16 to 0.54 mg/kg in a 2-h infusion.

Conclusion

There is an agreement on the need to increase the efficiency of drug development. Whatever the improvements in the chemical and preclinical steps, clinical development strategy remains critical. Human models in HVs are obviously not a panacea. They are not applicable to any situation and the validity of the different provocation procedures is uneven. Their optimal use is within what we call an "enhanced development plan," which requires improvements in safety data processing. Nevertheless, when properly used, human models can secure phase 1 study results, be of help in a "go" (more than in a "no-go") decision, and therefore improve the safety and efficiency of patient studies, leading to a reduction in both time and resources. ❑

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Modelos humanos como herramientas para el desarrollo de fármacos psicotrópicos

A pesar de los crecientes recursos dedicados a la investigación y desarrollo, y al refinamiento en las etapas preclínicas, la eficiencia del desarrollo de fármacos para el sistema nervioso central (SNC) ha desilusionado. Muchos fármacos llegan a estudiarse en pacientes con una indicación terapéutica errónea y/o en dosis incorrectas. Además de los primeros estudios clínicos que se realizan en voluntarios sanos y que se enfocan sólo a la seguridad, tolerancia y farmacocinética, el desarrollo de fármacos depende principalmente de los estudios en pacientes. Los trastornos psiquiátricos se caracterizan por su heterogeneidad y la alta proporción de comorbilidad. Cada vez es más difícil reclutar pacientes para ensayos clínicos y hay muchos factores de confusión en esta población; por ejemplo, los relacionados con los tratamientos. A fin de reducir al mínimo la exposición del paciente y el gasto financiero, es importante evitar estudios mal diseñados y no concluyentes. Este riesgo podría ser minimizado al obtener datos precozmente durante el desarrollo y al considerar que el objetivo en la fase 1 del plan es llegar a los estudios en pacientes con las ideas claras acerca del perfil farmacodinámico del compuesto, su eficacia en la probable indicación (proof of concept)*, y relaciones entre farmacodinámica y farmacocinética, además de la seguridad, tolerancia y farmacocinética. Los modelos humanos en voluntarios sanos pueden constituir herramientas útiles para este propósito, pero su empleo necesita de una adaptación global del esquema de la fase 1, favoreciendo las evaluaciones farmacodinámicas sin descuidar la seguridad. Nosotros estamos comprometidos en un programa de investigación y desarrollo orientado a adaptar modelos existentes y a desarrollar nuevos paradigmas que se adecuen a una precoz verificación de la* proof of concept.

Les modèles humains comme outil du développement des médicaments psychotropes

Malgré l'augmentation des moyens consacrés à la recherche et au développement (R et D) et au perfectionnement des phases précliniques, l'efficacité du développement des médicaments du système nerveux central (SNC) est décevante. De nombreux médicaments atteignent le stade d'étude chez le sujet malade avec une indication thérapeutique fausse et/ou des doses incorrectes. En dehors des premières études cliniques, qui sont conduites chez le volontaire sain et mettent l'accent uniquement sur la sécurité, la tolérance et la pharmacocinétique, le développement des médicaments repose principalement sur les études cliniques chez le sujet malade. Les troubles psychiatriques se caractérisent par une hétérogénéité et un taux élevé de comorbidité. Le recrutement de patients pour des essais cliniques devient de plus en plus difficile et il existe de nombreux facteurs confondants dans cette population, par exemple ceux liés aux traitements. Il est important d'éviter les études mal conçues et peu concluantes pour limiter au maximum l'exposition des patients et les dépenses financières. Ce risque peut être minimisé en recueillant des données pharmacodynamiques plus tôt au cours du développement et en considérant que l'objectif des études de phase 1 est d'aboutir à des études chez le sujet malade avec des idées claires en ce qui concerne le profil pharmacodynamique du composé, son efficacité dans l'indication probable (preuve de concept), et les relations pharmacocinétique/pharmacodynamie, en plus de la sécurité, de la tolérance et de la pharmacocinétique. À cet effet, les modèles humains chez le volontaire sain peuvent être un outil utile, mais leur utilisation nécessite une adaptation globale du schéma de phase 1, favorisant les évaluations pharmacodynamiques sans négliger la sécurité. Nous sommes engagés dans un programme de R et D visant à adapter les modèles existants et à développer de nouveaux paradigmes capables d'établir à un stade précoce la preuve de concept.

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