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Using neuroimaging to predict relapse to smoking: role of possible moderators and mediators

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Abstract

Background and aims: *Preclinical animal studies have established stressors, substance use associated cues, and priming as distinct triggers of relapse in substance dependence. These triggers seem to induce relapse by activating distinct brain pathways. In order to test these findings in humans, it is necessary to establish new human research paradigms. Neuroimaging may help to study brain regions involved in mediating the effects of these distinct triggers of relapse and to further delineate mediators of these pathways. In order to understand individual differences it is crucial to assess the impact of moderators on these pathways to relapse.* Methods: *Paradigms to study distinct relapse triggers are currently being set up for tobacco dependence. It is practically impossible to study human relapse and specifically its neurobiological pathways in the natural surrounding. Instead we aim to establish vulnerability patterns in a laboratory environment, applying functional magnetic resonance imaging (fMRI) assessments during trigger exposure. Brain activation determined by fMRI may constitute a sensitive measure to assess responses to cues, stress, and priming. Establishing these paradigms will then allow to further delineate the role of possible mediators (e.g. attention, inhibition) and moderators (e.g. sex, genetic factors) underlying relapse to smoking.* Results: *Initial results are encouraging, but this approach needs further studies to proof its usefulness.* Conclusions: *We outline an approach to study nicotine relapse within a laboratory environment, using fMRI assessments during trigger exposure. The long term goal is rational treatment development. To reach this goal it is crucial to identify, include and investigate critical moderators and mediators of relapse within this approach. Copyright © 2008 John Wiley & Sons, Ltd.*

Key words: moderators, mediators, functional magnetic resonance imaging (fMRI), neuroimaging, smoking

Background and aims

Substance use disorders (SUDs) constitute a major public health burden. Among those tobacco dependence has the highest prevalence (Grant et al., 2004), the highest associated mortality (WHO, 1997), the earliest age of onset (DiFranza et al., 2000; Storr et al., 2004), and the highest rate of progression to dependence among those initiating use (Anthony et al., 1994).

Tobacco dependence constitutes a chronic and relapsing disorder (O'Brien, 1997). Thus, once cessation of use has been established, preventing relapse is the major goal of treatment. For this reason, relapse and reinstatement of use constitute major foci for addiction treatment research. Rational treatment development calls for an elucidation of underlying etiological and patho-physiological mechanisms, based on genetic, imaging, and animal studies.

Currently studies into brain mechanism of relapse and reinstatement predominantly rely on animal studies. A body of preclinical research has lead to the establishment of a concept that differentiates three groups of triggers to relapse (Stewart, 2004): Exposure to drug-related cues ("cue-reactivity"), exposure to

stressors, and the application of small doses of the drug itself ("priming"). Each group of triggers is mediated by a brain pathway, which shows specificity, while allowing some overlap. Preclinical studies have further demonstrated effects of medications on relapse for one group of triggers (e.g. cues), with no effect on the others (Shaham and Hope, 2005). These three groups of triggers have intuitive appeal for the clinician, but their value for development of specific treatments in humans has yet to be demonstrated.

Animal models are essential to develop and test medications and behavioural treatment approaches (O'Brien and Gardner, 2005). But, treatments which have been demonstrated to be effective in animal models, so far have not necessarily been effective in humans (Vocci et al., 2005). A major setback of animal models has been our lack in understanding how well they resemble human behaviour and human behavioural pathology. A recent review concluded that there is a "remarkable paucity of overlap between the approaches used in reinstatement research [in animal models] and in clinical research on relapse prevention" (Epstein and Preston, 2003). It has also been pointed out, that there still is a lack of "crosstalk", between preclinical and clinical researchers and that contrary to many statements, the infrastructure and mediating research necessary for "translational work" is almost always lacking (Birmingham, 2002).

One of the major problems of clinical relapse studies constitutes the problem of studying relapse within its natural surrounding. For a number of reasons it is not possible to conduct neurobiological studies with human subjects, while relapsing within their natural surroundings. Studies have used retrospective recall to analyse relapse situations, but the shortcomings of recall have been demonstrated. A promising new approach has been to use ecological momentary assessment (EMA) (McKay et al., 2006). This approach also has problems and limitations, e.g. it has limited value in studying brain function. It may have its value though in the process of validating laboratory paradigms, which we strive to establish.

These laboratory assessments will consist in a set of relapse trigger exposures of subjects initiating treatment, in this case smoking cessation treatment. These relapse trigger exposures will be conducted within the magnetic resonance imaging (MRI) device, allowing to assess brain activation patterns during exposure. Once these paradigms have been established and validated, it will be possible to further delineate the impact of specific possible mediators. Mediators may be of psychological (e.g. attention, emotional response) or physiological nature [e.g. hypothalamic-pituitary-adrenal axis (HPA) activation, amygdale activation]. Differences between individuals may be based on moderating factors such as sex, history of exposure to substances, etc. Thus we assess factors, which might be important moderators, basically consisting in DNA (allowing to study genetic predisposition) and environmental factors, including socio-demographic factors, major life events, substance use history, etc. Moderators and mediators are established concepts of treatment studies (Kraemer et al., 2001). Their specific application in the context described later has not been established.

Research concept and methods

A smoking cessation clinic has been set up at the University Psychiatric Hospital to conduct research within the framework of the "North Rhine Westphalia Addiction Research Consortium". Funding was provided by the German Federal Ministry of Education and Research. One of the major research foci has been the initiation and development of the standardized intermediate phenotype assessment, which we named the functional MRI (fMRI) assessed relapse proness intermediate phenotypes project (FARPIP).

Within the FARPIP project the aim is to establish fMRI assessed relapse proness intermediate phenotypes in subjects entering treatment. Assuming that results from preclinical work can be transferred to human research, we should be able to differentiate three different brain activation patterns: the fMRI assessed relapse proness intermediate phenotype stress (FARPIP-S), the fMRI assessed relapse proness intermediate phenotype cues (FARPIP-C), and the fMRI assessed relapse proness intermediate phenotype priming (FARPIP-P). The feasibility of assessing three different intermediate phenotypes needs to be demonstrated and the relevance of these activation patterns needs to be tested in studies on relapse under natural conditions.

We conceptualized the activation pattern as intermediate phenotype. In human research the concept of intermediate phenotypes and endophenotypes recently has received increased attention (Gottesman and Gould, 2003). An endophenotype may be an inherited neurophysiological, neuropsychological, neuroanatomical, biochemical or endocrinological trait that may

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assist in the identification of the genetic underpinnings of psychiatric disorders regardless of the disease status. The concept of an intermediate phenotype has been applied less stringently. It can be defined as a neurophysiological, neuropsychological, neuroanatomical, biochemical or endocrinological trait or stable state, which is associated with the pathophysiology of a syndrome or specific aspect of a syndrome. Such phenotypes are putatively closer to the underlying neurobiology than the clinical phenotype.

In studies using fMRI we so far have assessed groups of smokers participating in a standardized six months smoking cessation programme. In the fMRI study participants watched video sequences with smoking-related cues or neutral control videos. Other research groups have studied cue induced fMRI assessed brain activation patterns before, but the activations were not studied in relation to relapse or treatment success. Some studies have looked at craving as a proxy for relapse, but craving and relapse are less than well associated (Miller and Gold, 1994).

The second paradigm currently being tested is exposure to a stressor. Establishing this paradigm is more challenging, but again a number of groups have started to apply different paradigms, in order to assess the response to stressors within the MRI device. Studies have applied paradigms such as arithmetic tests (first part of the Trier task), imaging (recall of stressful situations) and physiological stressors (cold pressor).

Priming so far has received the least attention, since it involves the application of the substance, in this case nicotine. Given the restrictions of human research and the restrictions of human laboratory assessments this paradigm will be the most challenging to establish.

Preliminary results and perspective

Brain regions associated with reactivity to smoking cues were differentially more activated in smokers who relapsed (Landsberg et al., submitted for publication). Differences could be demonstrated in regions classically associated with visuospatial attention, motivational processing of reinforcement values, and

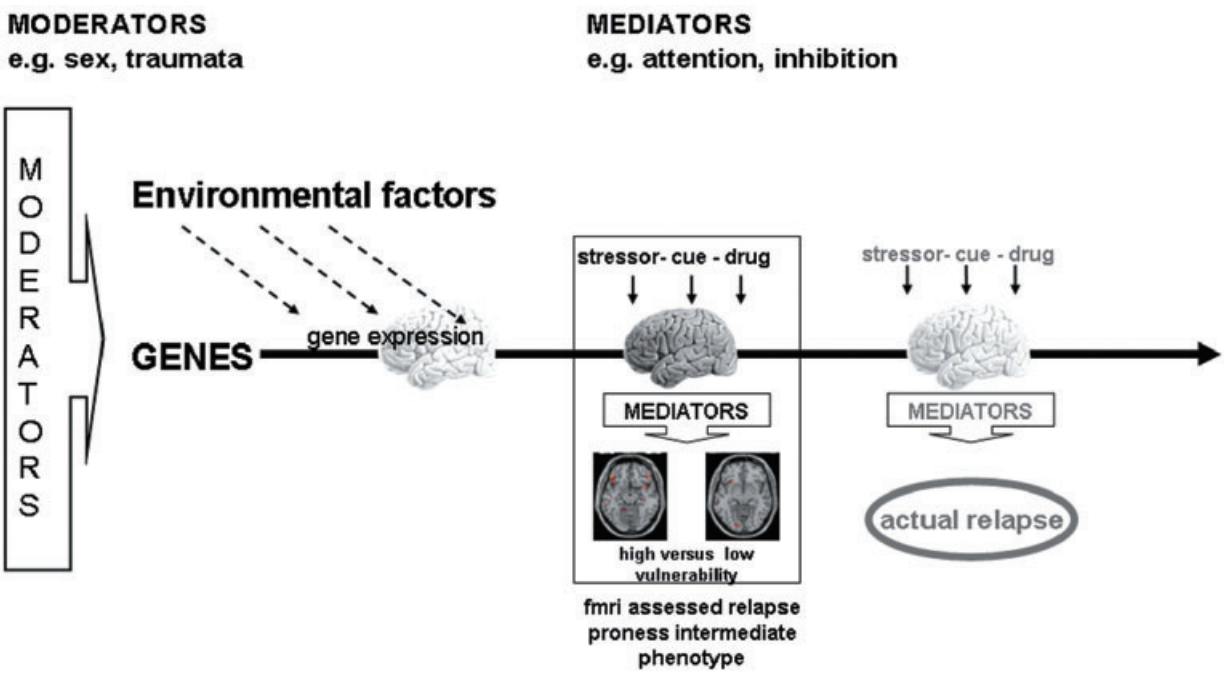

Figure 1. A conceptual integration of moderators, mediators and intermediate phenotype assessment for treatment development.
In the current paradigm the fMRI assessed intermediate phonotypes allow specific relapse proness patterns to be assessed in smokers presenting for a smoking cessation programme. The paradigms allow moderators and mediators to be tested. Concurrent genetic assessments further investigate if these intermediate phenotypes fulfil the criteria of endophenotypes.

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behavioural response preparation. While this functional role can only be inferred from the specific area activated, activation patterns can help to develop hypotheses about possible mediator mechanism through which relapse (or treatment success) might be brought about (see Figure 1). These mechanisms are the causal links between relapse triggers and reinstatement of consumption (e.g. attentional processes, motivational attribution). Whether specific functions inferred from activation of brain regions do actually mediate relapse needs to be investigated in further studies, applying paradigms designed to measure these specific processes. A major advantage of this approach is the fact that the assessment of functional mediators is based on assessment of brain functions and not on assessment of conscious self-reports of individuals.

We have further conducted studies using a stress paradigm. In a preliminary analysis we found a specific pattern to predict relapse (Schütz et al., 2006). These stress associated fMRI activation shows overlap with activations which previously have been reported to be associated with negative affect. Negative affect may be a specific stressor, but negative affect also may be a relevant aspect of stressor response. We are just starting to look into these questions in more detail. If negative affect would turn out to be essential for stressor induced relapse, then negative affect may actually be a mediator for stressor induced relapse.

Regarding the last trigger "priming", we are at a very early phase, looking into the possibilities of applying nicotine and finding a measure for a dose considered to be priming dose.

Relapse moderators specify for whom the relapse risk is increased, e.g. sex, genetic disposition, specific exposures such as childhood trauma (see Figure 1). In a first preliminary look we found that subjects with a history of depressive disorders showed increased activation of the amygdala compared to those with no history of depressive disorders, allowing to hypothesize that amygdale related functions might be more important for relapse in this specific subgroup (unpublished observation). This being the case previous history of depression associated difference in response to cues may be considered a moderator.

Conclusion

The presented concept outlines the development of a human fMRI based paradigm to study relapse in humans. The approach aims to rationally develop interventions to prevent relapse. The concept is based on preclinical animal studies, which demonstrate three distinct brain pathways to be responsible for relapse induced by three distinct triggers: cues, stress and priming.

The outlined concept consists in laboratory paradigms to establish profiles (intermediate phenotypes) for these three distinct pathways. They are then the bases for further studies delineating mediators and moderators of relapse.

Currently mediators and moderators are not part of the conceptualization and analysis of neuroimaging studies, but they seem necessary for the development of substance dependence treatment. Thus they are likely to play an essential role in future neuroimaging based treatment developments.

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Declaration of interest statement

No conflict of interest declared.

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