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Central positions and performance in the scientific community. Evidences from clinical research projects

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ABSTRACT

Literature claims for a deeper understanding of which processes shape the evolution of network structures over time. Drawing on the assumption that the "normative ideal" network structure should be understood according to the context in which the network is embedded, we observe collaborative networks generated by the necessity to respond to meeting regulatory requirements. We address the following research questions: What are the effects of centrality on performance in cooperative networks? Which network structural characteristics are relevant in cooperative research networks?

We test our hypotheses in a cooperative network made of 114 clinical trial research projects. We provide evidence that, in collaborative networks, an actor's centrality is likely to increase according to its past structural holes. Moreover, we observe that an actor's centrality has a negative effect on performance.

1. Introduction

Our study is aimed at addressing some critical issues related to a better understanding of how network structures and dynamics impact on network performance. We observe network structures, their antecedents and the subsequent performance. We build on social network arguments and we highlight how certain ego network's structural attributes help in exploiting opportunities arising from the surrounding environment, improving their performance. We address the following research questions: What are the effects of centrality on performance in cooperative networks? Which network structural characteristics are relevant in cooperative, clinical research networks?

Literature is claiming for a deeper understanding of which processes shape the evolution of network structures over time, as the knowledge of networks remains otherwise incomplete (Zaheer & Soda, 2009). We draw on the assumption that the "normative ideal" network structure should be understood according to the context in which the network is embedded, the nature of the actors and the content of the relationships (Ahuja, 2000). While previous studies have extensively focused on network of competitors (Dyer & Nobeoka, 2000; Gargiulo & Benassi, 2000; Gupta & Polonsky, 2013; Obstfeld, 2005; Powell, Koput, & Smith-Doerr, 1996; Rowley, 1997; Uzzi, 1997) we observe collaborative networks generated by the necessity to meet legal and/or regulatory requirements.

Our study is set in the context of clinical research projects carried out in the pharmaceutical industry, a setting subjected to increasing specialization and complexity and characterized by institutional forces that significantly constrain actors. We focus on clinical trials that can be conducted locally or internationally, in a single site or across multiple sites. Accordingly, they may be focused on a single institutional context or they may span multiple institutional environments. When trials are conducted across multiple sites, they are connected by the same protocol, and the network of sites can be considered a research network, or a bundle of "innovating firms working together" (DeBresson & Amesse, 1991).

Research networks in this industry are likely to provide timely access to otherwise unavailable knowledge and resources (Gupta & Polonsky, 2013), stimulate internal expertise, and contribute to learning capabilities (Powell et al., 1996). Such networks are a consequence of the increasing technological, market and research uncertainties witnessed by pharmaceutical companies over the last decades (Xu, 2009), with the subsequent need to leverage upon complementary know-how and other resources.

In this study, successful scientific performance is measured by the citations that the Principal Investigator receives since the start of the trial project he is in charge of.

The Principal Investigator is the coordinator of the whole study and he can be seen as the knowledge and information gatekeeper, monitoring the environment, translating, and collecting the information (Cohen & Levinthal, 1990).

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The investigator's (actor's) centrality across the network may impact on its capability of being an information gateway by disseminating and receiving information and knowledge (Freeman, 1979; Rowley, 1997). By playing a pivotal role, the central actor can be strategically important, enhancing knowledge mobility, ensuring equitable distribution of value, and fostering trust among actors and finally promoting network stability (Dhanaraj & Parkhe, 2006).

In the attempt to explain how certain ego network structural attributes may be relevant in cooperative networks, we focus on the role of structural holes, which represent gaps in information flows between unconnected actors within the network. When the need is fostering the circulation of information, spanning structural holes is strategically important: the more the holes spanned by a certain actor, the richer the information benefits, as an access to a broader information screen enhances the chance to identify opportunities and guarantees a timely gathering of information (Burt, 1992; Powell et al., 1996).

Authors have explored the role of actor centrality in competitive networks but, unless some relevant conceptual contributions (Dhanaraj & Parkhe, 2006; Gnyawali & Madhavan, 2001), the role of centrality in cooperative networks remains largely unexplored. Nevertheless, in these settings the key activity carried out by central actors of assessing the value of relevant knowledge residing in certain network actors and successfully activating the transfer of such knowledge over the network (Dhanaraj & Parkhe, 2006; Gulati, 1999, Hansen, 1999), as well as fostering trust among actors in the network (Dhanaraj & Parkhe, 2006) is critical to create and extract value. In the attempt to explain network evolution, we analyze how the past presence of structural holes impacts on the current centrality of an actor, and the effects of being a central actor on scientific performance, observing that these latter may be negative in cooperative networks.

2. Theory and hypotheses

This study focuses on research networks, consisting of "innovating firms working together" (DeBresson & Amesse, 1991). In contrast to other studies that have focused on competitive dynamics, we investigate networks characterized by co-operative dynamics between actors. Within these networks, facilitating the co-ordination between the competences and assets of nodes serves to enhance the contribution of each node (Powell et al., 1996).

External collaboration is complementary to internal capabilities as it facilitates exploiting and building upon existing knowledge (Ahuja, 2000). Networks offer two substantial benefits: sharing of resources, knowledge and skills, enabling the transfer of know-how and physical assets; and, access to knowledge spillovers, facilitating the transfer of information (Ahuja, 2000). Networks stimulate internal expertise and learning capabilities (Powell et al., 1996). Resources and knowledge sharing account for positive impacts on performance: the network acts as a channel through which partners share the knowledge and experience from their interactions with network partners (Gulati & Gargiulo, 1999).

Studies have demonstrated that the position of firms in inter-organizational networks influences their behavior, benefits and outcomes (Powell et al., 1996). The appropriate network structure that allows catching these benefits may depend on a variety of moderating factors. A contingency view on the benefits of network structure is largely being argued (Ahuja, 2000; Obstfeld, 2005; Uzzi, 1997); we focus on collaborative relationships generated by the necessity (Oliver, 1990) or regulatory/or regulatory requirements as institutional forces rationalize the environment in which the network is embedded (Uzzi, 1997). Moreover, literature is claiming for a deeper analysis of network evolution (Powell, White, Koput, & Owen-Smith, 2005; Zaheer & Soda, 2009) at the dyadic and network level. In this light, authors have explored the role of actor centrality in a longitudinal perspective looking at centrality as an antecedent of specific network structure characteristics (Zaheer & Soda, 2009). Nevertheless, the investigation of the antecedents of actor centrality in network dynamics remains largely unexplored.

In cooperative networks, partners are encouraged to share resources and knowledge (Gargiulo & Benassi, 2000) in order to meet individual and network outcomes. The Principal Investigator (PI) is the coordinator and scientific responsible of the clinical trial project, as defined by the NIH (National Institutes of Health, US Department of Health and Human Services) "PIs are responsible for conducting the trial, have access to and control over the data from the clinical trial and have the right to publish the results of the trial[1]". Therefore, the Principal Investigator can be seen as the knowledge and information coordinator for the whole research group (Cohen & Levinthal, 1990). A higher investigator's centrality favors its capability of being an information gateway, fostering knowledge mobility and trust among other actors in the network (Dhanaraj & Parkhe, 2006). In this setting, other network structural attributes are relevant, such as role of structural holes that are gaps in information flows between unconnected actors within the network. Here, the need to foster the circulation of information, spanning structural holes, is strategically important: the more the holes spanned by a certain actor, the richer the information benefits as the actor is connected to sources of knowledge in the network that would be otherwise difficult to reach (Burt, 1992) and can provide timely gathering of information and referral benefits (Burt, 1992). Despite these benefits, networks rich in structural holes are associated with the execution problem (or "action problem", see Obstfeld, 2005) — while opportunities for the combination and recombination of ideas are higher, due to the increased circulation of resources and information, the chance of acting is lower because of the dispersed nature of the relationships. Nonetheless, we argue that in a context of cooperation in which coordination of action is fundamental to the innovation outcome, actor spanning a structural hole may act as tertius iungens, promoting the creation and facilitation of ties among alters in order to foster the innovation activity and maintaining a *coordination* rather than mediation role (Obstfeld, 2005).

Actors who span structural holes can have a speedy access to recognize diverse information in different parts of the network that might be difficult to reach otherwise. We argue that this may lead the actor – i.e. the Principal Investigator – to increase its centrality, and hypothesize:

H1. In cooperative settings actors spanning structural holes will produce more central positions. Specifically, the higher the past structural holes spanned by an actor the higher is its centrality.

Since the idea of centrality has been proposed by Bavelas (1948), central positions have always been associated to higher influence and privileges (Freeman, 1979), prominence and visibility (Wasserman & Galaskiewicz, 1994), power (Brass & Burkhardt, 1993), or prestige (Bonacich, 1972). The key importance of centrality is related to superior resource and information advantages: the power arising from central position differs from the power obtained by the actors' attributes and confers substantial advantages (Rowley, 1997).

High centrality is associated with higher volume and rapidity of flows of information, resources, and opportunities. Nevertheless, environmental constraints, strategic intent and the actions carried-out by network actors may impact on the benefits arising from network position. Centrality may have two negative consequences: first, a central actor is related to a large number of ties and this can overturn in a highly dependence upon its network; second, each tie represents for the actor a source of information and resources but also a weak point through which those could drain (Gnyawali & Madhavan, 2001).

As centrality increases, projects are likely to experience augmented coordination costs (Gargiulo & Benassi, 2000; Gulati & Singh, 1996), and cognitive limits (Hansen, Mors, & Lovas, 2005) which contribute to decreasing the benefits of centrality. A position of visibility into the

[1] http://grants.nih.gov/clinicaltrials_fdaaa/definitions.htm.

collaboration network may translate into a constraint on the investigator's ability to absorb new information and ideas or to respond as flexibly as other actors with few direct ties. We measure scientific performance through the number of citations accrued by the Principal Investigator following the start of the clinical trial project, thus assessing the effects of centrality on the scientific relevance of the trial is important.

The negative sides of centrality are usually outweighed or balanced by the benefits that the central actor gains for occupying privileged positions. This balance holds for situations in which the actors are not only related by cooperative relations but also by competitive dynamics (Dhanaraj & Parkhe, 2006; Rowley, 1997): as noted by Burt (1992), the position alone does not create the benefit, as the advantages are determined by the entrepreneurial behavior of the actor. Given that in this setting the actor's behavior is significantly constrained, and we do not observe traditional competitive dynamics, but rather cooperative relations, we hypothesize:

H2. In cooperative networks, the higher the centrality of an actor, the lower its scientific performance.

3. Empirical setting and methods

We test our hypotheses in a cooperative network made of 114 research projects carried out in the pharmaceutical industry. Specifically, we look at the clinical trial research networks. Over the last few decades, this setting evolved towards high specialization and high systemic complexity (Szeinbach & Barnes, 1997). Clinical trials can be conducted locally or internationally, in a single site or across multiple sites. When trials are conducted across multiple sites, they are connected by the same protocol, and the network of sites can be considered a research network. Multi-center research affects important aspects of trial performance, as well as the extent to which the study can achieve its aims, by obtaining the maximum amount of data to be collected (Greene, Hart, & Wagner, 2005).

Drug research proceeds through different phases, strictly monitored by regulations. In the pre-clinical phase, the potential lead compounds are synthesized and tested on cultured cells and animals to assess toxicity or efficacy. Once this phase is completed, the lead compounds are reduced to a few useful candidate drugs and advanced to the clinical development stage. Clinical testing proceeds through three phases. In phase I, the compound is tested on a small number of healthy volunteers to establish safe dosages and gather information on possible side and metabolic effects. Phase II consists of randomized, double blind studies to ensure objectivity, evidence on safety, and preliminary data on efficacy. It involves a larger group of volunteers affected by the target disease. Phase III consists of a large-scale study, designed to collect effective information concerning the treatment's safety and effectiveness and involving up to thousands of volunteers. Finally, once the evidence on safety and efficacy is gathered, the developers submit the results to regulatory authorities for marketing approval.

Clinical research trial centers are performed by centers working on common projects on a multi-center basis in order to enroll a sufficient number of patients, share scientific knowledge and carry on the study following a protocol dictated by the sponsor of the trial. Following Huckman and Zinner (2007), each of these investigative sites can be considered as a 'factory', where the end product is a fully evaluated study subject. The protocol and the contract with the sponsor bind the action of sites (Huckman & Zinner, 2007). The former dictates the guidelines of the product (trial), which is identical across all sites in a given trial; the latter defines the product quantities (enrollment goal) and the price (budget provisions for each subject), as well as the expected delivery (enrollment period). Despite the constraints dictated by the agreement, each site maintains the capability of formulating operational and managerial decisions concerning the access to the material (study subjects), allocation of the activities among the team (Principal Investigator, sub-investigators and study coordinators), and the operational execution (enrolling and processing subjects).

The pharmaceutical industry is also characterized by a strong effort in publishing in the scientific literature (Powell et al., 1996), aiming at commercializing the basis of scientific discovery and emphasizing the relation between knowledge and innovation output. Each trial is coordinated by the Principal Investigator, responsible of the study outcome for all the sites involved, as well as the administrative and bureaucratic activities that have to be carried on in order to conduct the trial in respect of the regulation and publicity of the results (NIH). The Principal Investigator is the coordinator of the whole study and assumes the role of the knowledge and information gatekeeper, monitoring translating and transferring information and knowledge across the whole research group (Cohen & Levinthal, 1990).

3.1. Data, variables and measures

Our research uses data gathered from national and international databases on clinical trials, including single and multi-center clinical trials, both national and international. In order to map the full network of actors engaged in research in the same field and time period, 466 projects were identified on Clinicaltrials.gov, according to the specific clinical fields of viral diseases (specifically, Hepatitis-related trials) performed from January 2000 to 1 June 2009. We then analyzed data on the 114 projects sponsored by private industry in which the recruitment of patients has already been closed. These are projects characterized by a "closed recruitment status", allowing for comparison among different levels of study performance.

The analysis focused on projects carried out in centers located in eight selected countries (Germany, France, Italy, Netherlands, UK, US, Canada, and Australia). These countries were selected as the main hosting countries for clinical trials (Thiers, 2006) and major pharmaceutical markets.

Clinical trial projects respect the underlining assumptions that have to be made in order to shift the network level of analysis from individual to organization, as noted by Zaheer and Soda (2009). The content of the ties between projects can be thought of in terms of resources (i.e., basis of enrolled patient), and competences (i.e., procedural competences). First, clinical research projects respect the assumption of network composition – a single link connects one project to the other (i.e., an investigative site) – while coordination processes among sites working on a project are tight and strictly regulated, and therefore a site working within another project is meant to affect the members of the project as a whole. At the same time, as these two dimensions are related, clinical research projects respect the assumption of contagion: if two projects share an investigative site, and one of these two projects shares another investigative site with a third project, then the third project is likely to be affected by practices that are being used in the project with which it is not directly linked. Nevertheless, this process can be mediated by the interfaces and coordination processes within projects, also emphasized by a procedural conformity (Scott, 1987) arising from the surrounding institutional environment. Finally, these projects respect the assumption of causality – i.e. the structural content of the network translates into the performance of each project – along two dimensions: network allows the identification of resource-sharing opportunities and learning processes both in the transfer of knowledge on efficient procedures and institutional opportunities, and knowledge on research-related topics.

Our network is composed of nodes, represented by projects, each lead by a Principal Investigator, connected by ties represented by the sharing of one or more clinical trial center between two different trials. Within the ties between projects there may be different flows, such as scientific knowledge, resources (i.e., basis of enrolled patient) and/or competences (i.e., procedural competences). The Principal Investigator is the pivotal actor within each trial. He/she is connected to other

Principal Investigators when their respective trials share one or more centers. Within centers, in fact, scientific knowledge, competences or resources eventually may flow among researchers via experiences or intended/unintended spillovers.

Data on the 114 projects were gathered from a variety of sources. Data on trials have been collected on Clinicaltrials.gov and its archive (Clinicaltrials.gov archive). ClinicalTrials.gov is a publicly available trial registry developed by the National Library of Medicine (on behalf of the US NIH). It is the most complete source for information about ongoing trials within and outside the US. Publications data were found on Pubmed.gov. Project attributes have been collected on Clinicaltrials.gov (number of location countries, number of sites), while we addressed to the sponsors websites to gather sponsor attributes. Similarly, attributes for each clinical trial center have been collected from the websites of every facility, except for the number of beds, that in some cases is collected nationally on specific databases as in Germany (Kliniken.de and Krankenhaus.net), France (Hopital.fr), Italy (Ministry website) and the US (American Hospital Directory and Hospitaldata.com). Finally, data on the disease incidence have been gathered through specialized websites such as the 'WHO ICTRP' or disease-specific association of practitioners.

Network data were collected through the Clinicaltrials.gov database and integrated with data from the 'WHO ICTRP' and the 'IFPMA' portal; the records for each project contain a list of the sites where the trial is being conducted and the name of the Principal Investigator, which is in charge of the study. The location is easily identifiable in the case of full records; nevertheless, since the specific identity of the medical center in which the site is located is sometimes reported partially, every site has been identified by a research that has cross-referenced facility and a confirmatory research within the website of the facility of current areas of trial investigation.

4. Data analyses

We used a 2SLS model to test our hypotheses. We used a robust variance estimator to control for the effects of correlation between errors across equations due to endogeneity between network structure and performance. We run several tests to check the consistency of our modeling approach. In particular, we run a Durbin–Wu–Hausman χ^2 test: these tests serve to verify or reject the null hypothesis that states that an ordinary least squares (OLS) estimator of the equation would yield consistent estimates, and thus endogeneity among the regressors would not have deleterious effects on OLS estimates. We used the Ivreg2 command in Stata 12 (StataCorp, 2011). The 2SLS model allows us to evaluate at its first stage the endogenous variable *Current Centrality*, testing the first hypothesis. The second stage variable analyzes the dependent variable *Number of Citations* (the scientific performance measure) testing our second hypothesis. First-stage and second stage variables are described below.

4.1. Two-stage Least Square Analysis (2SLS): first stage variables

All network data and measures were analyzed and calculated through the UCINET 6.0 software (Borgatti, Everett, & Freeman, 2002). Network measures for each of the 114 analyzed projects have been calculated over the full network of 466 projects. Network data were first collected in matrices "actor × project" identifying the ties between the sites and the projects. Through the UCINET 6.0, the main matrix was then transformed (cross-products, co-occurrence method) in squared, one mode affiliation matrices "project × project", in order to create primary affiliation data and to calculate specific network indicators referring to the single projects. This network can be considered "isomorphic" with research on individuals as network nodes, as the composition, contagion, and causality assumptions are made (Zaheer & Soda, 2009).

4.1.1. Endogenous variable

Current centrality

To measure our endogenous variable, we considered the measure of closeness centrality. In networks of cooperative research projects, a process of efficient communication, involving fewer message transmissions, shorter times and lower costs to access independently all other members of the network (Freeman, 1979) can be fundamental in order to gain information, resource advantages and foster the innovation performance. This advantage is identified in literature by the idea of closeness centrality (Freeman, 1979) that measures the ability of an actor to reach other actors through a minimum number of intermediary positions (Brass, 1984).

Symmetrically, the central actor spreads information in the network through fewer intermediaries than those actors that occupy a peripheral position: being "close" to all the others, the central actor can quickly access the network (Freeman, 1979), enhancing the mechanism of cooperation. We therefore use closeness centrality as an indicator of centrality. Closeness centrality is based upon "the frequency with which a point falls between pairs of other points on the shortest or geodesic paths connecting them" (Freeman, 1979). In other words, it is based on distance and takes into consideration not only the connections to immediate alters, but the closeness to all network actors.

4.1.2. Instrumental variable

Past structural holes

Our input dataset consisted of 1280 clinical trial centers and 114 total projects. Following Zaheer and Soda (2009), we constructed our past network and calculated past network variables. Their methodology allows to connect each single project to its past network, accounting for the ties to previous projects. Accordingly, we have first composed seven different matrices each corresponding to a two-year project window. We used a time window of two years in order to monitor short-term effects. Each of these 7 matrices (2001–02, 2002–03, 2003–04, 2004–05, 2005–06, 2006–07, 2007–08) represents a "moving" window that allows to split the network with regard to the past and the current time. We moved the two-year windows across multiple years computing our endogenous variable of current structural holes. For each of the projects, excluding those performed in 2001 and 2002 that correspond to the first window and therefore could not be analyzed towards their past network.

Specifically, we constructed an individual vector for each project (1280 centers actors × 1 project), excluding the project of the first window (2001–02). We then created multiple matrices, composed by the past network window to which we added, repeatedly, the vectors, each of them representing a focal project.

Using UCINET version 6.0, each matrix was transformed (co-occurrence method) into squared, one-mode affiliation matrices "project per project". On these co-membership matrices, we calculated the specific ego network indicators. Specifically, we calculated for each of the focal project the measure of past structural holes given by the measure of efficiency of the focal project in its past network.

In the attempt to provide readers with an example, in order to calculate the measure of past structural holes for a project performed in 2004, we took the vector of network relations for that specific project with the clinical trial centers and joined this single vector to the matrix of network relations 2002–03 (projects × clinical centers) creating a new matrix resulting from the matrix 2002–03 + the 2004 project. We then affiliated this latter matrix to make it a co-membership project-by-project matrix and we calculated the past structural holes value for the 2004 project.

We use efficiency as a measure of structural holes, as it relates to the non-redundant contacts of the actor. Efficiency measures the potential for accessing diverse knowledge and information by central nodes playing a brokerage role in network regions rich in holes. According to this logic, the actor's efficiency is higher when the number of its non-redundant contacts to the total number of its relationships is higher,

that is: $CE_i = \frac{NR_i}{N_i}$ where CE_i expresses the efficiency of actor i, NR_i the number of actor i's non-redundant contacts and N_i the total number of actor i's relationships.

4.1.3. Control variables

Clinical center-related variables

We control for alternative factors involving experience or size of network actors as explaining network behavior and performance. Starting from the actor per project matrix, we identified a list of participating centers in the eight analyzed countries, and conducted a specific web-based search to gather information on each site. Specifically we use:

Site Size measured as the number of licensed hospital beds (based on Dranove, 1998, Goodstein, Kanak, & Boeker, 1994; Goodstein, Boeker, & Stephan, 1996; Chadwick, Hunter, & Walston, 2004), a common measure of size for hospitals and healthcare facilities.

Site Experience measured as firm age to capture the effects of firms' prior work experience and learning advantages on facility outcomes, measured as the number of years the facility had been in operation at the beginning of the trial.

These measures are expressed as a measure of the cumulative age and size for each of project, by summing the individual characteristics of the sites participating in that specific project. In order to achieve a better approximation to a normal distribution we used log transformations.

We control for the *Number of Location Countries* in which the trial is taking place, for the *Number of centers participating in the trial*, coordinated by the Principal Investigator.

We also control if the trial is in *Phase 3*, as latest stages of research are usually associated with higher complexity and number of publications.

Project-related indicators

We control for the size of the trial, measured as the *Enrollment target* for the study. The size of the sample enrolled in the specific trial varies across different projects.

Principal Investigator-related indicators

We control for the number of publications issued before the beginning of the trial (*Previous publications*), as this variable may impact on the number of citation accrued by the Principal Investigator, and we also control for the *tenure status* of the Principal Investigator. Specifically, this measure takes into account whether the Principal Investigator is an: Associate Professor (the Principal Investigator has reached the level of Associate Professor), Full Professor (the Principal Investigator has reached the level of Full Professor), and Head or Director (the Principal Investigator has reached the position of head of an academic department or is the director of a specific unit within a pharmaceutical firm).

Sponsor-related indicator

We use the log transformation of the *Years of operations of the firm sponsoring the project* referring to the experience in clinical trials. Firm age is used as a control variable to capture the effects of firms' prior work experience and learning advantages on outcomes. Firm age is measured as the cumulative number of years of operation at the beginning of the trial.

Disease-related indicators

Finally, we controlled for the incidence of the *diseases* for which the trials were testing, using the incidence rate as a measure of the risk of developing a particular disease, calculated as the sum of the incidence rates of the target diseases for each trial we analyzed.

4.2. Two stage Least Square Analysis (2SLS): second stage variables

On the second stage the dependent variable is scientific performance, measured as:

Number of citations The pharmaceutical industry is characterized by a strong effort in publishing in the scientific literature (Powell et al., 1996), and bibliometric measures are widely used to evaluate the impact of research outcomes. The scientific performance is measured trough the number of citations. We use the number of citations (Judge, Cable, Colbert, & Rynes, 2007) accrued for each article published by the Principal Investigator in the two years following the starting date of the trial.

4.2.1. Control variables

The following variables are relevant to control for the role of different factors on the scientific performance of the Principal Investigator:

Project-related indicators In order to control for the complexity of the trial and the coordination activity needed from the Principal Investigator, in the second stage we control for the *Number of Location Countries*, the *Number of centers participating in the trial*, and for the fact that the trial is in *Phase 3*, as latest stages of research.

Principal Investigator-related indicators We control for the number of publications issued before the beginning of the trial (*Previous publications*), and for the *tenure status* of the Principal Investigator.

Disease-related indicators Finally, in the second stage, we also control for the disease incidence.

5. Findings

In order to verify the appropriateness of treating structural holes as an endogenous variable, and to reject the null hypothesis that current structural holes are exogenous to performance, we ran the Durbin–Wu–Hausman χ^2 test [4.40 (1); $p = .04$]. Tests confirm the appropriateness of using a 2SLS specification to address the issue of endogeneity.

We used the Durbin–Watson test to check past structures for autocorrelation with current structures, and the test confirmed that there was no autocorrelation. We corrected for the presence of heteroskedasticity by using the Huber–White sandwich estimator of variance in Stata (Huber, 1967; White, 1980).

Descriptive statistics are reported in Table 1. We report the results of the 2SLS analysis in Tables 2 and 3 of both first and second stages. The second stage of the 2SLS tests the effects of current structural holes on scientific performance. We explain the results of the model below.

The model shows the effect of the instrumental variable past structural holes. The results confirm our first hypothesis as past structural holes impact positively on current centrality, in the 2SLS model $\beta = .12$ significant at $p < .10$. Therefore, we find evidence that in cooperative settings egos spanning structural holes will produce more central positions. Specifically, the higher the past structural holes spanned by an actor, the higher is its centrality. We have interpreted these results on the basis of the peculiar context of cooperation, where the coordination of action is fundamental to the innovation outcome and actors spanning structural holes may act as tertius iungens promoting the creation and facilitation of ties among alters in order to foster the innovation activity

Table 1
Descriptive statistics and correlations.

	Variables	Mean	S.D.	1	2	3	4
1	*Number of Location Countries*	2.86	3.98	1			
2	*Number of centers participating in the trial*	1.51	1.52	0.66***	1		
3	*Previous publications*	25.34	40.69	−0.02	0.05	1	
4	*Disease incidence*	2009.50	13337.27	0.26***	0.13†	0.05	1
5	*Phase 3* study	.62	.49	0.16*	0.18**	0.08	0.1
6	*Tenure status*	.74	.66	0.14	0.04	0.08	0.04
7	*Years of operations of the firm sponsoring the project*	1.90	.44	−0.05	−0.07	0.01	0.08
8	*Cumulative Size of clinical centers participating in the project*	6.31	2.85	0.50***	0.63***	0.01	0.07
9	*Cumulative Years of operations of clinical centers participating in the project*	3.97	3.03	0.55***	0.64***	0.03	0.09
10	*Enrollment target*	655.30	2228.47	0.16*	0.24***	0.12	−0.01

	Variables	5	6	7	8	9	10
6	*Tenure status*	−0.03	1				
7	*Years of operations of the firm sponsoring the project*	0.37***	−0.12	1			
8	*Cumulative Size of clinical centers participating in the project*	0.03	0.16†	−0.11	1		
9	*Cumulative Years of operations of clinical centers participating in the project*	0.01	0.18*	0.14*	0.98***	1	
10	*Enrollment target*	0.15*	0.04	0.11	0.03	0.05	1

† Coefficients are significant at $p < .10$.
* Coefficients are significant at $p < .05$.
** Coefficients are significant at $p < .01$.
*** Coefficients are significant at $p < .001$.

and maintaining a coordination rather than mediation role (Obstfeld, 2005).

Control variables do not show significant effect, apart from the variable *Years of operations of the firm sponsoring the project*, which has a negative coefficient (−.07, significant at $p < .10$), highlighting the possibility that the more the firm sponsoring the project is experienced in clinical trials, the less the project will increase in centrality. This can be interpreted by assuming that sponsoring firms achieve learning advantages on outcomes and may want to avoid having their projects becoming too central in the network.

Table 3 shows the result of the second stage regression model on scientific performance (*Number of Citations*). This model is related to our second hypothesis. We aimed at testing that in cooperative networks, the higher the centrality of an actor, the lower its scientific performance. We argued that, as centrality increases, projects are likely to experience augmented coordination costs (Gargiulo & Benassi, 2000; Gulati & Singh, 1996), and cognitive limits (Hansen et al., 2005) which contribute to decreasing the benefits of centrality.

A position of visibility into the collaboration network may translate into a constraint on the ego network's ability to absorb new information and ideas or to respond as flexibly as companies with few direct ties. Results indicate a negative impact of current centrality (predicted value) on performance ($\beta = -443.36$), significant at $p < .01$, therefore confirming our second hypothesis.

Alternative explanations tested via the control variables confirm positive and significant effects of the Number of *Previous publications* issued by the Principal Investigator (significant at $p < .05$), his *Tenure Status* and the *Number of centers participating in the trial* (both significant at $p < .10$).

The first two control variables account for individual characteristics of the Principal Investigator. Specifically, the higher his past scientific production (*Previous publications*) the higher his scientific performance, as this is likely to impact on the number of citations and on learning effects. Moreover, the higher the experience and status (*tenure status*) of the Principal Investigator, the higher is scientific performance, due to learning and reputational effects.

The latter control variable (*Number of centers participating in the trial*) accounts for scale effects and complexity in the trial, which are likely to impact positively on the scientific impact (*citations*) of the trial itself.

6. Discussion and conclusion

Our analysis, rooted in the social network literature, further contributes to the debate on ideal social structures. We provide evidence that, in collaborative networks, an actor's centrality is likely to increase according to its past structural holes. Moreover, we observe that an actor's centrality has a negative effect on performance.

Table 2
First stage regression (endogenous variable: current centrality).

Variables		
Controls		
Enrollment target	−.00	(.00)
Years of operations of the firm sponsoring the project	−.07†	(.04)
Cumulative Size of clinical centers participating in the project	.01	(.02)
Cumulative Years of operations of clinical centers participating in the project	.01	(.02)
Constant	.58***	(.11)
Instrumental variable		
Past structural holes	.12†	(.07)
F-statistic	2.67**	
N	88	

Standard errors in parentheses.
† Coefficients are significant at $p < .10$.
* Coefficients are significant at $p < .05$.
** Coefficients are significant at $p < .01$.
*** Coefficients are significant at $p < .001$.

Table 3
Second stage regression (dependent variable: number of citations).

Variables		
Controls		
Number of Location Countries	2.53	(3.04)
Number of centers participating in the trial	13.72†	(7.87)
Disease incidence	−.00	(.00)
Previous publications	.53*	(.24)
Tenure status	27.10†	(15.24)
Phase 3 study	18.57	(16.84)
Constant	268.87**	(83.39)
Independent variable		
Current Centrality	−442.36**	(135.89)
F-statistic	3.37**	
N	88	

Standard errors in parentheses.
† Coefficients are significant at $p < .10$.
* Coefficients are significant at $p < .05$.
** Coefficients are significant at $p < .01$.
*** Coefficients are significant at $p < .001$.

These results have implications at the firm, network, and environmental levels. The effects of centrality on performance prompt us to suggest a deliberate shaping of network structures by prominent actors aimed at first abating their central positions in the network and then increasing the benefits arising from the total number of connections existing at the network level. The first point requires a deeper analysis of the explorative and exploitative capabilities (O'Reilly & Tushman, 2008) of the actor. The former legitimate the actor as innovative, therefore potentially trustable as a competent and reliable partner within a knowledge network; the latter demonstrate to the environment that the actor is able to leverage upon its current knowledge base, valuing his past abilities to reach a desired end. Both these capabilities are conducive to more central positions into a collaborative network, as they stimulate to other potential partners to effectively engage in valuable projects. The second action asks for an analysis of the relational capabilities and brokering attitudes of the actor. Literature confirms that centrality is associated with density, which upon certain conditions moderates the effects of centrality (Dhanaraj & Parkhe, 2006; Freeman, 1979; Gnyawali & Madhavan, 2001; Rowley, 1997). The benefits of access to flows of information and resources, and the asymmetries enjoyed by the central actors, can be leveraged by an increase of the cohesion of the network. In order to increase density and create a bigger market for ideas, actors need to rely upon resources able to scan the environment, to seize it, and to reconfigure it in function of the desired end (Teece, 2007). Many companies in the pharmaceutical and in the airline industry (Gulati, Sythc, & Mehrotra, 2008) are staffing their structures with alliance managers who usefully complement the set of capabilities conducive to high performance.

The ability to cope with external constraints and the possession of the necessary capabilities is a central managerial implication from our research. I.e., most research organizations are requiring, in order to be eligible as scientific referent for a study, to possess the capabilities to communicate and diffuse the results of the study itself. The possession of such skills is exactly one of the basic issues to be addressed when checking for the eligibility of a candidate. When the environment is challenging and with fewer rooms to maneuver, the inability to escape from centrality may be a source of either idea and action problems therefore leading to rigidity at the project level. In these cases, ties can bind and might be disentangled to cope with limits posed by an existing environment.

Our results suggest the need for the creation or the affirmation of a behavioral inclination at creating or facilitating ties among firms instead of keeping them far apart (as the tertius gaudens approach would suggest, see Obstfeld, 2005). More precisely and importantly, what seems to matter is the tertius iungens strategic orientation (Obstfeld, 2005) as the means for moderating not only the magnitude of density in a collaboration network, but also for spanning boundaries and realigning the network with the environment in which it operates. Evidences suggest, one more time, how critical is the role of a coordinative agent, in avoiding the fragmentation of ideas, processes, all potentially valuable in the search of fit with the environment.

This study presents some limits, as longitudinal data must be more thoroughly elaborated for a better understanding of how network structures and dynamics would affect on network performance and in order to identify patterns of homogenization among network actors that may arise in these settings. Moreover, a clear definition of the length and strength of relationships, as well as partner characteristics (i.e. size, experience or type) will be beneficial in order to enrich the discussion raised in the paper.

An important and potential future area of analysis is related to the phases following the clinical trial and leading to commercialization of the product. Application filing, competent authority approval and market access could be analyzed via the network perspective, and the success of trials could be observed via other indicators, such as the commercialization of the product, or its time to market. In the clinical trial phases procedural nuances that have to be followed, rules have to be obeyed and many marketing mechanisms and strategies are not allowed, therefore identifying and enrolling the appropriate set of patients for conducting clinical research is not easy given the highly-regulated institutional environment. The underlying commercial resources available to network actors, the flow of knowledge and competences on procedures are likely to exhibit interesting dynamics to analyze, especially if we consider the shift towards competitive dynamics, typical of these latter phases in contrast with the cooperative dynamics arising from the clinical trial setting, that is also offering an interesting departure point for further analysis.

On a more strictly operative side, we plan a fine-tuning of the control variables with the inclusion of new control sets, such as other indicators of the investigator capabilities and sponsor related indicators and we plan to enlarge our sample including projects conducted in emerging countries (e.g. India, China, and Mexico) where clinical trials are increasingly taking place.

The route towards the enhancement of this firm's ability to scan, seize and reconfigure the environment to moderate regulatory constraints might require a change of the traditional managerial mindsets. The goal here is the development of a greater “mutual interest” (Williamson, 1985), as well as the development of a sense of “common destiny”. Leadership is a key ingredient in achieving this end (Fleming & Waguespack, 2007), as well as the use of interpersonal coordination mechanisms (Galbraith, 1973; March & Simon, 1958). A clear communication of goals, and an appropriate set of incentives to encourage actors in the knowledge network to share valuable knowledge with each other, will encourage them to set up idiosyncratic knowledge sharing routines, to further facilitate the learning of specified and agreed information and knowhow between them (Dyer & Nobeoka, 2000).

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